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► **To cite this version:**

Ilio Vitale, Federico Pietrocola, Emma Guilbaud, Stuart A Aaronson, John M Abrams, et al.. Apoptotic cell death in disease-Current understanding of the NCCD 2023. *Cell Death and Differentiation*, 2023, pp.1097-1154. 10.1038/s41418-023-01153-w . hal-04596448

HAL Id: hal-04596448

<https://hal.science/hal-04596448>

Submitted on 11 Jun 2024

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Apoptotic cell death in disease

– Current understanding of the NCCD 2023

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61 **Running Title:** Apoptosis in physiology and pathology

62 **Keywords:** BAX; BCL2; cancer; death receptors; ischemia; mitochondrial outer membrane
63 permeabilization; stroke.

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304 COI:

305 All the Editorial Board Members of Cell Death Differentiation, Cell Death Disease, or Cell Death Discovery are included
306 among the authors. A.D. is shareholder in Denali Therapeutics. A.D.G. has received remuneration, honorarium or consultancy
307 fees from Boehringer Ingelheim, Miltenyi Biotec or IsoPlexis. A.S. and P.E.C. are employees of the Walter and Eliza Hall
308 Institute, which has an agreement with Genentech and AbbVie and receives milestone and royalty payments related to
309 venetoclax. Employees of the Walter and Eliza Hall Institute may be eligible for financial benefits related to these payments.
310 P.E.C. receives such a financial benefit as a result of previous research related to venetoclax. B.D.S. has no COI with the
311 content of this paper. Possible perceived COI: B.D.S. is or has been a consultant for Eli Lilly, Biogen, Janssen Pharmaceutica,
312 Eisai, AbbVie and other companies. B.D.S. is also a scientific founder of Augustine Therapeutics and a scientific founder and
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315 Inc.; holds equity in Sonata Therapeutics, and serves as a consultant to Weatherwax Biotechnologies Corporation and Akin
316 Gump Strauss Hauer & Feld LLP, and receives research funding from Sumitomo Dainippon Pharma Oncology. C.M.T. has
317 the following patent applications US20200164026, US20190142915, US20150165061, US20140024597. US2020058683,
318 WO2018013519, WO/2020/223212. D.C.R. serves as a consultant for Alladdin Healthcare Technologies Ltd., Mindrank AI,
319 Nido Biosciences, Drishti Discoveries and PAQ Therapeutics. D.J.M receives funding from the Merck Group (Darmstadt,
320 Germany) & Puma Biotechnology (Los Angeles, CA, USA). D.O. is employed at SANOFI. J.T.O. serves as a consultant for
321 Anji Pharmaceuticals. J.T.O receives research funding from AbbVie. D.W.A. receives funding for research in apoptosis from
322 Amylyx. F.D.V. is Member of the Scientific Advisory Board (SAB) of Biosceptre Ltd (UK), and a consultant with Axxam
323 SpA (Italy). F.M. has financial interest in TLL, The Longevity Labs and Samsara Therapeutics. P.M. is founder and
324 shareholder of NETRIS Pharma. G.A.C. is the scientific founder of Ithax Pharmaceuticals. G.L.K. is an employee of the
325 Walter and Eliza Hall Institute which receives milestone and royalty payments related to venetoclax. G.L.K. has received
326 research funding from Servier. J.R.C.-R. is a scientific consultant for NextRNA Therapeutics, Inc. and Autoimmunity
327 Biologic Solutions, Inc.. K.R. is a founder and MD of KH Biotec GmbH. C.V.R is a scientific founder and member of the

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329 Roche Immunology Incubator. C.V.R has received grant support from Mirati Therapeutics. K.S. is a co-inventor on patent
330 applications for NLRP3 inhibitors which have been licensed to Inflazome Ltd, a company headquartered in Dublin, Ireland.
331 Inflazome is developing drugs that target the NLRP3 inflammasome to address unmet clinical needs in inflammatory disease.
332 K.S. served on the Scientific Advisory Board of Inflazome in 2016–2017, and serves as a consultant to Quench Bio, USA and
333 Novartis, Switzerland. L.A. receives funding for research from Merck and has shares in Epic SRL and CIRCE SRL. M.C.
334 (Michele Carbone) received donations from the UH Foundation through donations from: the Riviera United-4-a Cure, the
335 Melohn Family Endowment, the Honeywell International Inc., the Germaine Hope Brennan Foundation, and the Maurice and
336 Joanna Sullivan Family Foundation. M.C. (Michele Carbone) has a patent issued for BAPI. B.J. is cofounder of CERVO
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345 consulting or advisory role, received honoraria, research funding, and/or travel/accommodation expenses from: Ariad,
346 Abbvie, Bayer, Boehringer, Novartis, Pfizer, Servier, Roche, BMS and Celgene, Pierre Fabre, Janssen / Johnson&Johnson,
347 MSD. R.B.D is a scientific advisor for Immagine B.V., Amsterdam, Netherlands. R.I.A serves as consultant for Mahzi
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350 S.A.L. discloses that he is the named inventor on worldwide patents for the use of memantine and derivatives for the treatment
351 of neurodegenerative disorders. As per the rules of Harvard University, S.A.L. participates in a Royalty Sharing Agreement
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355 Ventus Therapeutics, Inc., Eisai, inc., and Takeda Pharmaceuticals, Inc.. S.G. has received grant support from Mirati
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357 BioPharma. S.v.K. is named inventor on patent applications covering some of the therapeutic concepts pertaining to TRAIL-
358 R blockade in disease. Y.H.C. is a member of the board of advisors for Amshenn Inc. and Binde Inc.. T.-D.K. is a consultant
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360 funding) of Oncoceutics/Chimerix, which is developing ONC201/TIC10 as cancer therapeutic. W.S.E-D. is founder and
361 shareholder (no research funding) of p53-Therapeutics, an early-stage company developing small molecules targeting mutant
362 p53. W.S.E-D. founder, and shareholder (no research funding) of SMURF-Therapeutics, an early-stage company developing
363 small molecules targeting hypoxia. W.S.E-D. is Co-Chair in the Executive Committee for Precision Oncology Alliance (no
364 research funding) of Caris Life Sciences. W.S.E-D. receives support from D&D Pharma and AACR-Novocure. W.S.E-D. is
365 the advisory board of Ocean Biomedical. W.S.E-D. is the advisory board of RAIN Therapeutics. G.K. has been holding
366 research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara
367 Therapeutics, Sanofi, Tollys, and Vascage. G.K. has been consulting for Reithera. G.K. is on the Board of Directors of the
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372 consulting/advisory honoraria from Boehringer Ingelheim, AstraZeneca, OmniSEQ, Onxeo, The Longevity Labs, Inzen,
373 Invax, Sotio, Promontory, Noxopharm, EduCom, and the Luke Heller TECPR2 Foundation, and holds Promontory stock
374 options. All other authors have no conflicts to declare.

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379 **Abstract**

380 Apoptosis is a form of regulated cell death (RCD) that involves proteases of the caspase family.
381 Pharmacological and genetic strategies that experimentally inhibit or delay apoptosis in mammalian
382 systems have elucidated the key contribution of this process not only to (post-)embryonic development
383 and adult tissue homeostasis but also to the etiology of multiple human disorders. Consistent with this
384 notion, while defects in the molecular machinery for apoptotic cell death impair organismal development
385 and promote oncogenesis, the unwarranted activation of apoptosis promotes cell loss and tissue damage
386 in the context of various neurological, cardiovascular, renal, hepatic, infectious, neoplastic and
387 inflammatory conditions. Here, the Nomenclature Committee on Cell Death (NCCD) gathered to
388 critically summarize abundant pre-clinical literature mechanistically linking the core apoptotic apparatus
389 to organismal homeostasis in the context of disease.

390

391 **Facts**

- 392 • Intrinsic and extrinsic apoptosis are forms of regulated cell death (RCD) promoting the cellular
393 demise along with the activation of proteases of the caspase family.
- 394 • In mammalian organisms, executioner caspases are activated after cells are already committed to
395 die.
- 396 • Apoptosis can be manipulated by genetic or pharmacological means, and multiple genetically
397 engineered animal models and pharmacological tools to modulate apoptosis have been developed.
- 398 • Apoptosis is intimately involved in both (post-)embryonic development and adult tissue
399 homeostasis.
- 400 • Apoptosis deregulation promotes oncogenesis and contributes to the etiology of multiple human
401 disorders, including cardiovascular, hepatic, inflammatory and neurological conditions.
- 402 • To date, venetoclax is the only apoptosis inducer that has received regulatory approval for use in
403 humans.

404 **Open Questions**

- 405 • Will inhibitors of apoptotic caspases with elevated target specificity become available?
- 406 • Will agents specifically conceived to modulate apoptosis enter the clinical practice to treat solid
407 tumors or other human disorders beyond hematological malignancies?
- 408 • Is it conceivable to design combinatorial strategies aimed at inhibiting apoptosis while
409 interrupting compensatory activation of other RCD signaling cascades?
- 410 • Will it be possible to specifically inhibit apoptotic signaling without impacting on other processes
411 dependent on apoptosis regulators such as differentiation, proliferation, and inflammatory
412 reactions?

413 **Introduction**

414 The health and homeostasis of multicellular organisms depend on the tight balance between cell
415 proliferation and cell death. In this context, a large body of experimental evidence has demonstrated the
416 existence of a form of regulated cell death (RCD) that is executed by a genetically programmed process,
417 and hence amenable to manipulation by genetic or pharmacological means ¹. Over the past decades,
418 multiple variants of RCD have been characterized at the genetic, biochemical, functional, and
419 immunological level ^{2, 3, 4, 5, 6, 7, 8}. For instance, programmed cell death (PCD) has been functionally
420 defined as a modality of RCD activated under purely physiological conditions (i.e., in the absence of
421 perturbations of extracellular or intracellular homeostasis) in the context of embryonic/post-embryonic
422 development or adult tissue homeostasis ^{1,9}. Conversely, pathological RCD is invariably initiated in the
423 context of failure to adapt to shifts in extra-cellular or intra-cellular homeostasis, constituting a *de facto*
424 organismal program for the elimination of excessively damaged and/or potentially harmful cells, such as
425 cells infected with pathogens ^{1, 10}. From a biochemical perspective, an increasing number of RCD
426 modalities have been defined by the Nomenclature Committee on Cell Death (NCCD) based on the
427 mechanistic involvement of specific molecular components ^{1, 11}. For instance, apoptotic cell death has
428 been defined as a form of RCD that is mainly executed by proteases of the caspase family, namely
429 caspase 3 (CASP3), CASP6 and CASP7 initiated by CASP8 and CASP9 ^{1, 12, 13}. However, in mammalian
430 organisms, with the exception of CASP8, apoptotic caspases simply accelerate RCD because their
431 activation occurs when cells are already committed to die ^{1, 14, 15, 16}. This means that contrarily to simpler
432 organisms (e.g., *C. elegans*), in which apoptotic caspase elimination fully rescues cells from death, in
433 mammals, apoptotic cell death can at most be retarded but not prevented by pharmacological or genetic
434 strategies inhibiting the activity of these caspases. Mitochondrial permeability transition (MPT)-driven
435 necrosis, necroptosis, ferroptosis, pyroptosis, parthanatos, entotic cell death, NETotic cell death,

436 lysosome-dependent cell death, and autophagy-dependent cell death represent forms of RCD that involve
437 precise molecular events and hence can also be manipulated with pharmacological or genetic
438 interventions ^{1, 2, 3, 4, 5, 6, 17, 18, 19}. Other RCD modalities have been recently identified, such as alkaliptosis
439 ²⁰, cuproptosis ²¹ and PANoptosis (involving the simultaneous activation of pyroptosis, apoptosis, and
440 necroptosis) ²², and their signal transduction modules are under investigation. The importance of several
441 of these forms of RCD in health and disease is not yet known.

442 Along with the identification of key RCD regulators and the advent of modern tools for genetic
443 manipulation, a great experimental effort has been devoted to elucidating the role of RCD in the
444 physiopathology of multi-cellular organisms ²³. Thus, various studies in animals (mostly rodents)
445 genetically altered to be deficient for or over-express components of the apoptotic apparatus (either at
446 the whole-body level or in selected cell/tissue types) have provided formal proof of the relevance, but
447 not always the exquisite requirement, of apoptosis for embryonic and fetal development or adult tissue
448 homeostasis ^{24, 25, 26}.

449 Along similar lines, pharmacological and genetic tools aimed at altering apoptotic signaling in pre-
450 clinical disease models revealed the mechanistic contribution of apoptosis to the etiology of various
451 conditions associated with the loss of post-mitotic or (in certain settings) non-post-mitotic cells, including
452 a panel of neurological, cardiovascular, renal, hepatic, and inflammatory disorders ²⁴. Extensive studies
453 over the last five decades highlighted the apoptotic machinery as a major target for the development of
454 new therapeutic interventions ²⁷, not only for the induction of cell death in the context of disrupted tissue
455 homeostasis (e.g., for neoplastic diseases) ²⁸, but also for the inhibition of cell death in the context of
456 ischemic, degenerative and inflammatory conditions ^{29, 30}. However, while at least one drug designed to
457 induce apoptosis is currently approved for use in humans, namely the BCL2 apoptosis regulator (BCL2)
458 inhibitor venetoclax ^{31, 32, 33, 34} which is used alone or in combinatorial regimens for the treatment of

459 chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma and acute myeloid leukemia (AML)
460 ^{31, 35, 36, 37, 38}, no other agents specifically conceived to inhibit the apoptotic apparatus have been licensed
461 for clinical practice so far. The broad-spectrum caspase inhibitor emricasan received fast-track
462 designation by the US Food and Drug Administration (FDA) for the treatment of non-alcoholic
463 steatohepatitis in 2016 but demonstrated inconsistent clinical efficacy ^{39, 40, 41}, and – as of now– is not
464 approved for therapy in humans.

465 The lack of clinically approved, selective apoptosis inhibitors and the inconclusive performance of
466 emricasan in recent trials reflect several aspects of (apoptotic and non-apoptotic) RCD that began to
467 emerge only recently (**Figure 1**). First, while detecting cell death as well as biomarkers of specific RCD
468 variants *in vitro* is relatively straightforward ⁴², precise quantification of cell death *in vivo* in adult tissue
469 remains challenging, at least in part because of rapid disposal of cell corpses by efferocytosis ^{43, 44, 45, 46}.
470 Thus, the actual contribution of cell death to the etiology of various human disorders is difficult to
471 quantify by observational approaches ^{47, 48}. Second, while for a long-time, specific forms of RCD were
472 considered virtually independent entities, recently it became clear that the molecular machinery for RCD
473 is composed of highly interconnected modules characterized by substantial redundancy, backup
474 pathways and feedback loops ^{10, 49, 50}. Thus, molecules that inhibit one specific form of RCD may
475 ultimately be unable to confer actual cyto- and tissue protection instead only altering the kinetic and
476 biochemical manifestations of death by allowing the engagement of a different RCD sub-routine. For
477 instance, while CASP8 is a major signal transducer in death receptor (DR)-driven apoptosis (see below),
478 it intrinsically inhibits necroptosis induced by DR and certain other signaling pathways, such as Toll-like
479 receptor (TLR) signaling ^{51, 52, 53}, suggesting that caspase inhibition in the context of DR signaling may
480 promote necroptotic cell death ^{54, 55, 56, 57}. Together with a low target specificity and selectivity within the
481 caspase family ⁵⁷, this can explain the inadequate efficacy of emricasan observed in pre-clinical and
482 clinical studies. Third, even in the hypothetical scenario of agents capable of simultaneous inhibition of

483 all (known and unknown) RCD pathways, loss of cellular homeostasis due to failing adaptation to stress
484 generally involve degenerative processes that at some stage cannot be reversed, such as widespread
485 mitochondrial permeabilization and loss of RNA and protein synthesis^{4, 58, 59, 60}, i.e., even if all RCD
486 modalities could be blocked effectively, cells might undergo uncontrolled necrotic death. In this setting,
487 cell death may occur as a consequence of an irremediable degeneration of cellular functions that can no
488 longer be rescued pharmacologically or even genetically⁶¹. Supporting these latter notions, accumulating
489 literature indicates that, at least in mammalian systems, perhaps with the exception of CASP8, so-called
490 apoptotic caspases mainly control the kinetics of apoptotic cell death and its immunological
491 manifestations, but not whether cell death ultimately occurs or not,^{15, 16}. This points to the caspase family
492 as a major regulator of organismal homeostasis via control of inflammatory responses^{62, 63}. The
493 simultaneous inhibition of multiple caspases, as for instance by emricasan, may thus also impact
494 inflammation, as was demonstrated for TNF-induced systemic inflammatory respiratory syndrome
495 (SIRS) in vivo for the pan caspase-inhibitor zVAD-fmk^{54, 64}. To complicate matters, multiple
496 components of the core apoptotic machinery, including caspases and multiple members of the BCL2
497 family have been reported to regulate a variety of non-apoptotic functions beyond inflammation, such as
498 mitochondrial energy production, Ca²⁺ signaling and terminal differentiation^{65, 66, 67, 68, 69, 70, 71, 72}.
499 Structurally, distinguishing between apoptotic and non-apoptotic functions of caspases and the BCL2
500 family remains challenging. Finally, there is a hitherto unclarified heterogeneity in the regulation of RCD
501 at distinct anatomical sites (possibly linked to micro-environmental features) at distinct stages of cellular
502 differentiation, and in the context of diverse patho-physiological states (*e.g.*, in young *vs.* adult and aged
503 individuals).

504 All these issues should also be kept under consideration in the context of the present review, in which
505 the NCCD aims at critically discussing a large amount of pre-clinical data in support of a key role for the
506 apoptotic machinery in mammalian diseases. Specifically, the interpretation of results of genetic and

507 pharmacological experiments presented herein should place particular attention on the aforementioned
508 connectivity amongst different RCD variants as well as on discriminating between essential vs. accessory
509 aspects of cell death¹⁴. Another issue to be considered is the fact that most conclusions are based on use
510 of knockout/congenic mice which often present other passenger mutations potentially influencing the
511 observed phenotype⁷³. Our objective is not only to provide a critical summary of the existing literature,
512 but also to offer an updated framework for interpretation of these findings in view of currently accepted
513 models of RCD signaling.

514

515 **Intrinsic apoptosis in disease**

516 There are substantive supporting data from genetic studies to demonstrate that the molecular machinery
517 for intrinsic apoptosis (described in **Box 1** and **Figure 2**) is involved in embryonic and fetal development
518 as well as in adult tissue homeostasis. Numerous preclinical studies in animal models of disease
519 demonstrate that intrinsic apoptosis contributes to etiology in various disorders involving the loss of not
520 only post-mitotic, but also non-post-mitotic tissues, including neurological, cardiac, renal, hepatic,
521 autoimmune/inflammatory, oncological, and infectious conditions. However, as discussed above, the
522 interpretation of these results should be taken with caution given the high interconnectivity of RCD
523 pathways and the crosstalk between RCD and inflammatory response. Moreover, the activation of
524 executioner caspases occurs after cells are already committed to intrinsic apoptosis^{15, 16}. Accordingly,
525 caspase inhibition only delays the execution of cell death. In this context, the phenotypes observed under
526 apoptotic caspase-deleted or inhibited conditions may reflect cell-extrinsic effects of caspase activity
527 such as the release of immunomodulatory and cytotoxic signals from dying/dead cells, including damage-
528 associated molecular patterns (DAMPs) or cytokines (this concept is extensively discussed in¹⁴). These
529 phenotypes may also stem from the lack of processes independent of intrinsic (or extrinsic) apoptosis,

530 as, for instance, the lack of CASP3-mediated cleavage of gasdermin E (GSDME) leading to impaired
531 pyroptosis and associated inflammatory response ^{74, 75}.

532 Below, we will provide details of the pro-apoptotic BCL2 proteins, the anti-apoptotic BCL2 proteins, the
533 components of the apoptosome - a platform for the activation of initiator caspases composed of
534 cytochrome c, somatic (CYCS), apoptotic peptidase activating factor 1 (APAF1) and pro-CASP9 - and
535 effector caspases in disease. The instances of involvement encompass participation in the pathogenic
536 mechanisms as well as experimental deletion or inhibition as a means of exploring potential utility as
537 treatment targets. The effects of these regulators and effectors of the intrinsic apoptosis pathway on health
538 are described in **Box 2**, **Box 3** and **Box 4**.

539 **Neurological disorders.** Intrinsic apoptotic factors are implicated in the pathophysiology of numerous
540 neurological diseases (**Figure 3**). In a mouse model of amyotrophic lateral sclerosis (ALS), deletion of
541 BCL2-associated X protein (*Bax*) reduces neuronal cell death coupled to attenuated motor dysfunction
542 and neuromuscular degeneration ⁷⁶. Additional ablation of BCL2-antagonist/killer 1 (*Bak1*) further
543 enhances neuroprotection, resulting in improved overall animal survival ⁷⁷. Similar protective effects
544 were observed in mice lacking the BH3-only proteins BCL2 like 11 (BCL2L11, best known as BIM) and
545 BCL2 binding component 3 (BBC3, best known as PUMA), as well as in transgenic mice overexpressing
546 BCL2, X-linked inhibitor of apoptosis (XIAP) ^{78, 79, 80, 81, 82}. Moreover, intra-cerebroventricular
547 administration of the broad-spectrum inhibitor Z-VAD-FMK protects mice from ALS ⁸³, although
548 whether such protection arises from the inhibition of intrinsic apoptosis was not proven. *Bax* deletion
549 also attenuates neuromuscular dysfunctions in a mouse model of congenital muscular dystrophy (another
550 neurodegenerative disease affecting motoneurons) ⁸⁴, while BCL2 overexpression limits neuromuscular
551 disease progression in some (but not all) mouse models of progressive motor neuronopathy and muscular
552 dystrophy ^{85, 86, 87}. Finally, genetic or pharmacological inhibition of poly (ADP-ribose) polymerase

553 family, member 1 (PARP1) and PARP2 halts axonal degeneration and improves related motor
554 phenotypes in *Caenorhabditis elegans* models of ALS⁸⁸.

555 Multiple components of the molecular machinery for intrinsic apoptosis, including BAX, PUMA, BH3
556 interacting domain death agonist (BID), Harakiri, BCL2 interacting protein (contains only BH3 domain)
557 (HRK), were shown to drive neuronal death in Alzheimer's disease (AD) and Parkinson's disease (PD)
558 models^{89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101}. Thus, overexpression of BCL2 decreases the appearance of
559 early pathological markers of AD, such as amyloid precursor protein (APP) and microtubule-associated
560 protein tau (MAPT, best known as tau) cleavage, which depend on caspases^{102, 103, 104}, resulting in
561 attenuated neurological defects^{105, 106}. Some findings indicate a role of apoptotic caspases in the
562 pathogenesis of AD. However, as discussed above, during intrinsic apoptosis, caspases simply accelerate
563 the course of cell death, and, so, such effects may be linked to the release of cytotoxic and pro-
564 inflammatory factors from dying cells. In more detail, pharmacological inhibition of CASP3 reduces
565 early synaptic failure in mouse models of AD, ultimately improving cognitive defects¹⁰⁷. Moreover,
566 expression of a mutated form of amyloid β (an APP cleavage product) or administration of broad-
567 spectrum caspase inhibitors attenuates synaptic defects in models of AD, an effect only partially
568 recapitulated by CASP3-specific inhibitors¹⁰⁸. Along similar lines, genetic deletion of *Casp2* was
569 reported to provide protection from synaptic loss and cognitive decline in a mouse model of AD¹⁰⁹. Such
570 protection may be linked to the generation of a specific cleavage product (Δ tau314) by CASP2, which is
571 reported to impair cognitive and synaptic function by promoting the missorting of tau to dendritic spines
572^{110, 111}. Accordingly, CASP2 inhibitors blocked tau truncation and restored excitatory neurotransmission
573 in mouse models of tauopathies, including AD^{112, 113}. Of note, a role for CASP4 in AD pathogenesis is
574 also reported^{114, 115}. Moreover, studies using senescence-accelerated OXY5 rat model of AD
575 demonstrated that the treatment with mitochondria-targeted antioxidant SkQ1 improved mitochondrial
576 fitness and slowed down the signs of Alzheimer's disease-like pathology in older rats¹¹⁶. Lack of BIM

577 (due to deletion of *Bcl2l1l*) also confers protection to dopaminergic neurons in experimental PD imposed
578 by inhibition of mitochondrial complex I, an effect that depends on BAX activation ¹¹⁷. In addition,
579 genetic deletion or down-regulation of *Casp3*, as well CASP3 inhibition by transgenic, neuron-restricted
580 expression of XIAP protects mice against pharmacologically induced PD, attenuating both dopaminergic
581 neuron alterations and behavioral deficits ^{118, 119, 120, 121}. Whether protection arises from the lack of cell-
582 intrinsic or cell-extrinsic processes dependent on apoptotic caspases has not been investigated. Finally,
583 pharmacological inhibition of CASP3 confers neuroprotection to rat model of Huntington's disease (HD)
584 ^{122, 123, 124}. That said, the precise mechanisms whereby components of the molecular apparatus for
585 intrinsic apoptosis influence neurodegeneration need to be further explored. Two studies in clear
586 contradiction to each other reported that at sublethal doses, pharmacological inhibition of myeloid cell
587 leukemia sequence 1 (MCL1) improved disease outcome in a mouse model of AD with a mechanism
588 independent of apoptosis induction and involving the stimulation of mitophagy ¹²⁵, but that Mcl1
589 haploinsufficiency accelerated the degeneration and dysfunctionality of motor neurons in mice ¹²⁶. Also,
590 there is evidence that necroptosis or ferroptosis rather than apoptosis can be the major contributor in
591 neuronal cell destruction during AD ^{127, 128}. Finally, although *Bax* deletion prevents the demise of
592 cerebellar granule neurons in a transgenic model of inherited prion disease ¹²⁹, the direct contribution of
593 BAX to neurotoxicity during prion disorders is a matter of controversy ¹³⁰.

594 BCL2 family proteins have also been reported to contribute to axonal degeneration and neuronal cell
595 death in animal models of brain trauma, degeneration, or neurotoxicity ^{131, 132, 133}. Thus, BAX- or BID-
596 deficient mice, as well as transgenic mice overexpressing BCL2, display increased survival of cortical
597 or hippocampal neurons after experimental traumatic brain injury, as compared to wild-type mice ^{134, 135,}
598 ^{136, 137}. Moreover, transgenic BCL2 overexpression protects mouse neurons against the detrimental
599 effects of transection of the sciatic nerve ¹³⁸. Likewise, BAX deficiency enhances the survival of
600 oligodendrocytes in mice subjected to spinal cord injury ¹³⁹. Both neuroprotection and functional

601 improvements were observed in rat or mouse models of traumatic spinal cord injury upon local
602 administration of Z-VAD-FMK) and other caspase inhibitors^{140, 141, 142}. However, these findings need to
603 be validated given the low selectivity of these inhibitors among caspases. Of note, in rats, post-traumatic
604 neuroprotection can further be improved by combined inactivation of PARP1 and CASP3¹⁴³, suggesting
605 a potential involvement for PARP1-dependent parthanatos in the process.

606 Deletion of *Bax* (but not of the genes encoding BIM, PUMA or BID), as well as *Bax* haploinsufficiency,
607 prevents the death or degeneration of retinal ganglion cells in mice subjected to optic nerve injury^{144, 145,}
608 ^{146, 147}. Moreover, the demise of injured retinal ganglion cells is exacerbated in mice with a conditional
609 loss of *Bcl2l1* (leading to lack of BCL-X_L)¹⁴⁸ and decreased in transgenic mice over-expressing XIAP
610 ¹⁴⁹ or BCL-X_L¹⁵⁰ in the eye, or in rodents treated with an XIAP-derived cell-permeant peptide targeting
611 CASP9¹⁵¹, or a CASP3-targeting small-interfering RNA (siRNA)^{152, 153}. Moreover, transgenic or
612 adenovirus-driven XIAP expression protects the retina in various animal models of retinal disease,
613 degeneration, or ischemia^{154, 155, 156, 157, 158, 159}, while a BCL-X_L inhibitor alleviated pathogenic neo-
614 vascularization during diabetic retinopathy¹⁶⁰. Genetic deletion of *Casp9* from endothelial cells protected
615 retinal ganglion cells from ischemic death, supporting non-cell autonomous functions of CASP9¹⁵¹. Of
616 note, CASP7 seems to play a crucial role in retinal ganglion cell death, as demonstrated in a model of
617 optic injury in *Casp7*^{-/-} mice¹⁶¹. However, both pro-survival (BCL2) and pro-apoptotic (BAK1, BAX
618 and BIM) BCL2 family members contribute to retinal neo-vascularization in response to experimental
619 ischemic retinopathy^{162, 163, 164}. In one of these papers, this effect is linked to an increased survival of
620 endothelial cells in the absence of BAX and BAK1¹⁶⁴. Persistent endothelial cells promote rapid tissue
621 re-vascularization, thus preventing the occurrence of a pathogenic excessive neovascularization.
622 Moreover, the inhibition of the intrinsic apoptotic pathway by genetic inhibition of c-Jun N-terminal
623 kinase 1 (*Jnk1*) or the administration of a broad-spectrum caspase inhibitor led to reduced choroidal neo-
624 vascularization in the murine model of wet age-related macular degeneration (AMD)¹⁶⁵. These

625 observations may indicate that factors released by dying cells regulate neo-vascularization in the retina
626 or other eye tissues.

627 Deletion of *Bax*, *Hrk* or *Casp3* as well as transgenic overexpression of XIAP prevents neuronal loss
628 and/or axon degeneration in mouse models of trophic factor deprivation including nerve growth factor
629 (NGF) withdrawal^{166, 167, 168}. Conversely, lack of BIM or PUMA does not limit hippocampal neuronal
630 injury upon experimental excitotoxicity^{169, 170}. Moreover, while *in vivo* delivery of an XIAP fusion
631 protein protects neurons against death induced by glutamate or kainic acid¹⁷¹, kainic acid-mediated
632 neurodegeneration cannot be rescued by the CASP3 inhibitor DEVD-CHO¹⁷². Conversely, BIM appears
633 to be activated during excitotoxicity¹⁷³, and *Bcl2l1l1*^{-/-} mice (which lack BIM) display attenuated neuro-
634 degeneration after experimental seizures induced by administration of kainic acid into the amygdala, at
635 least in part because of decreased neuronal cell death in the hippocampus (but not in the neocortex)¹⁷⁴.
636 Moreover, data from knockout mice suggest that experimental seizure-induced neuronal death involves
637 BCL2-associated agonist of cell death (BAD), BCL2 interacting killer (BIK), BCL2 modifying factor
638 (BMF), or PUMA^{175, 176, 177, 178} and that BCL2-like 2 (BCL2L2; best known as BCL-W) may provide
639 neuroprotective, seizure-suppressive functions¹⁷⁹. Confirming a certain degree of functional redundancy,
640 phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1, best known as NOXA) and BID seem
641 dispensable for RCD driven by excitotoxicity, as shown in kainic acid-treated animals^{180, 181}.

642 Intrinsic apoptosis is also involved in neuronal apoptosis post-ischemic injury in both developing and
643 adult brains. In a mouse model of neonatal hypoxia-ischemia, neuroprotection was documented upon
644 deletion of *Bax*¹⁸², simultaneous absence of BIM and BAD¹⁸³, or transgenic overexpression of XIAP
645¹⁸⁴. Conversely, *Xiap*^{-/-} mice are sensitized to neonatal hypoxia-ischemia injury¹⁸⁵. Apparently at odds
646 with these findings, *Casp3*^{-/-} mice display increased vulnerability to such experimental perturbation,
647 possibly due to complementary over-activation of CASP3-independent pathways¹⁸⁶. Of note, the

648 absence of CASP3, BAX, or PUMA (but not the absence of NOXA, BIM or HRK) also confers neuro-
649 protection to newborn mice acutely exposed to ethanol^{187, 188, 189}, while loss of BAX is neuroprotective
650 in newborn mice exposed to isoflurane¹⁹⁰ as well as ionizing radiation^{133, 191}. At the same time, it is
651 interesting to note that BAX-dependent neuronal RCD also contributes to reactive microgliosis during
652 the recovery of the developing brain from acute alcohol exposure¹⁹², pointing to an etiological role for
653 activation of microglial cells by dead neurons.

654 *Bax*^{-/-} mice displayed pronounced neuroprotection when subjected to distinct experimental brain injuries,
655 including middle cerebral artery occlusion¹⁹³. A similar protection against experimental ischemic insults
656 has been observed in mice deficient for BMF¹⁹⁴, or BID^{195, 196, 197}. Conversely, NOXA seems to be
657 dispensable for neuronal damage induced by experimental ischemic stroke¹⁹⁴. Moreover, the absence of
658 BID fails to protect mice from ischemia-reperfusion, although it limits the associated inflammatory
659 response¹⁹⁸. Transgenic over-expression of BCL2, BCL-X_L or XIAP as well as inhibition of apoptotic
660 caspases or genetic deletion of *CASP6* ameliorates neuronal survival upon global ischemia, focal
661 ischemia or stroke^{199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215}. It should be noted, however,
662 that in these settings, neuroprotection by inhibition or deletion of caspases may be related to the lack of
663 cell-extrinsic or apoptotic-unrelated roles of caspases. Moreover, various examples of caspase-
664 independent neuronal death after cerebral ischemia have been reported^{216, 217, 218, 219}. In this context, it is
665 important to note that apoptosis is dynamically regulated during lifespan in the brain²⁴. Indeed, while
666 immature brain cells express high levels of many BCL2 proteins^{133, 220, 221}, most of these proteins are
667 downregulated in the adult brain, when most post-mitotic neural cells become resistant to apoptosis^{131,}
668²²². This may help explain the divergent findings on the mechanisms of neural cell death reported above.

669 **Cardiovascular conditions.** While a role for RCD in non-reperfused myocardial infarction remains
670 questionable, apoptosis and other cell death programs including necroptosis, MPT-driven necrosis,

671 ferroptosis, pyroptosis and autosis appear to contribute to cardiomyocyte death and tissue damage during
672 myocardial infarction with reperfusion (also referred to as myocardial ischemia-reperfusion injury).
673 However, the relative importance of the RCD and how they interconnect mechanistically and
674 functionally to produce an integrated response remains poorly understood. For example, *Bak1*^{-/-} mice with
675 a cardiomyocyte-specific deletion of *Bax* displayed considerably reduced infarct size as compared to
676 their wild-type littermates when subjected to experimental myocardial ischemia-reperfusion, although it
677 remains unclear whether these effects are attributable to reductions in apoptosis or MPT-driven necrosis
678 ^{223, 224, 225}, a RCD variant shown to participate in the pathogenesis of ischemic stroke ²²⁶. Protection
679 against myocardial ischemia-reperfusion has also been reported in transgenic mice overexpressing BCL2
680 ^{227, 228, 229} or a BCL-X_L-derived peptide ²³⁰. Likewise, deletion of *Bbc3* (leading to lack of PUMA)
681 ameliorates myocardial ischemia-reperfusion injury ²³¹, ultimately translating into increased survival ²³².
682 Moreover, neurotrophin-3 was reported to confer cardioprotection from ischemic and reperfusion injuries
683 by reducing BIM levels ²³³. Broad spectrum caspase inhibition ^{234, 235, 236} and XIAP mimicking peptides
684 ²³⁷ were shown to modestly reduce myocardial infarct size. Finally, simultaneous deletion of *Casp3* and
685 *Casp7* had no cardioprotective effect during reperfused myocardial infarction ²³⁸, in line with the notion
686 that the absence of caspase only delays cell death.

687 In contrast to the large burst of cell death over several hours characterizing myocardial infarction,
688 cardiomyocytes are lost gradually over months to years during heart failure with reduced ejection fraction
689 ³. The role of intrinsic apoptosis in these heart conditions is, however, debated. In a mouse model of
690 cardiomyopathy based on the deletion of desmin (*Des*), the cardiomyocyte-specific over-expression of
691 BCL2 reduces cardiac lesions and hypertrophy coupled to ameliorated cardiac functionality ²³⁹.
692 However, despite improved survival, these mice show increased levels of necrosis due to the activation
693 of alternative cell death pathways ²⁴⁰. Moreover, *Casp3*^{-/-} mice display enhanced vulnerability to
694 experimental cardiomyopathy, at least in part reflecting the inefficient activation of pro-survival AKT

695 serine/threonine kinase 1 (AKT1) signaling²⁴¹. As an alternative explanation, the absence of CASP3
696 may foster RCD-driven inflammation as a consequence of increased type I interferon (IFN) release²⁴²,
697 ^{243, 244}. Indeed, experimental data linking dysregulated type I IFN release and cardiac conditions have
698 recently emerged²⁴⁵.

699 As for therapeutic interventions, cardioprotective effects have been achieved by inhibition of CASP3 in
700 rodent models of myocardial dysfunction induced by endotoxin²⁴⁶, burn injury²⁴⁷ or hypoxia²⁴⁸,
701 although perhaps such effects can be attributed to the lack of cell-extrinsic or apoptosis-unrelated effects
702 of caspase activity. Moreover, inhibition of BAX prevents cardiotoxicity induced by doxorubicin in
703 zebrafish and mice without affecting the anti-neoplastic activity of doxorubicin²⁴⁹. Similarly, the
704 endothelial cell-specific expression of B cell leukemia/lymphoma 2 related protein A1a (BCL2A1A)
705 promotes survival in a model of allogeneic heart transplantation²⁵⁰.

706 Finally, the mechanistic links between intrinsic apoptosis and atherosclerosis remain a matter of debate.
707 Indeed, while *Casp3* deletion favors plaque development in mouse models of atherosclerosis²⁵¹, the
708 absence of DNA fragmentation factor subunit beta (DFFB, best known as CAD))²⁵² protects mice against
709 the disease. Likewise, while conditional deletion of *Mcl1* in myeloid cells is pro-atherogenic²⁵³, genetic
710 or pharmacological inhibition of BCL-X_L reduces atherosclerosis via a mechanism involving the
711 depletion of platelets²⁵⁴. Moreover, the macrophage or leukocyte-specific deletion of the gene encoding
712 BIM in mice has modest effects on plaque development, especially in the early phase of atherosclerosis
713 ^{255, 256}. As the etiology of atherosclerosis involves a major inflammatory component, these apparently
714 discrepant results may reflect (at least in part) the key role of some components of the apoptotic
715 machinery in the control of inflammatory responses.

716 **Renal disorders.** Germline or kidney-specific deletion of *Bax* attenuates acute kidney damage in mice
717 subjected to experimental renal ischemia/reperfusion²⁵⁷. A similar nephron-protection has been observed

718 in *Bid*^{-/-} mice ²⁵⁸, as well as in transgenic mice specifically expressing BCL-X_L in the kidney ²⁵⁹.
719 Moreover, the simultaneous deletion of *Bax* and *Bak1* in kidney proximal tubules limits tubular apoptosis
720 and ameliorates kidney inflammation and fibrosis in a mouse model of renal fibrosis based on unilateral
721 ureteral obstruction ^{260, 261}. Apoptotic caspases also appear to contribute to the etiology of renal
722 conditions, although, perhaps, this reflects cell-extrinsic effects of caspase activity. *Casp3* deletion
723 reduces microvascular rarefaction and renal fibrosis in mice subjected to experimental ischemia-
724 reperfusion injury ²⁶², resulting in better long-term outcomes ²⁶³. Moreover, the lack of CASP3 increases
725 the survival of mice with chronic kidney disease caused by a congenital mutation in cystin 1 (*Cys1*) ²⁶⁴.
726 In this setting, CASP3-deficient mice display increased CASP7 and decreased BCL2 expression, which
727 is in line with recent clinical evidence of constitutive BCL2 down-regulation in patients with polycystic
728 kidney disease ²⁶⁵. Administration of broad-spectrum caspase inhibitors limits kidney damage and
729 improves renal functionality after a variety of experimental insults to kidneys, as observed in animal
730 models of renal ischemia ^{266, 267}, polycystic kidney disease ²⁶⁸, glomerulonephritis ²⁶⁹, lupus nephritis ²⁷⁰
731 and diabetic renal disease ²⁷¹. Nonetheless, the specific targeting of apoptotic caspases will reveal
732 whether this effect reflects the inhibition of intrinsic apoptosis. Indeed, these studies do not rule out the
733 involvement of non-apoptotic RCD pathways in the etiology of acute and chronic kidney injury ^{272, 273}.
734 Moreover, some of the nephron-protective effects of broad-spectrum caspase inhibitors have been linked
735 to decreased post-RCD inflammation rather than the sole inhibition of apoptosis ^{266, 274}. In this context,
736 Z-VAD-FMK aggravates (rather than ameliorates) renal dysfunction in a mouse model of cisplatin
737 nephrotoxicity, by a mechanism involving the abrogation of cyto-protective autophagy ²⁷⁵. Similarly, Z-
738 VAD-FMK is ineffective in mouse models of osmotic nephrosis and contrast-induced acute kidney injury
739 ²⁷⁶, and this may be linked to the ability of Z-VAD-FMK to inhibit CASP8 (and hence promote
740 necroptosis). Finally, acute loss of BCL-X_L in all tissues of adult mice, except for hematopoietic cells,

741 caused severe renal tubular degeneration leading to fatal anemia due to the loss of erythropoietin
742 production²⁷⁷.

743 **Hepatic diseases.** Abundant evidence highlights pathogenic roles of apoptosis in acute liver injuries, as
744 well as in alcohol-related and alcohol-unrelated chronic liver disorders. Hepatocytes express high levels
745 of BID, which connects DR signaling to mitochondrial outer membrane permeabilization (MOMP) upon
746 CASP8-dependent cleavage²⁷⁸, and this complicates distinguishing between the intrinsic and extrinsic
747 pathways. Here, we shall discuss studies performed on animal models of liver injury unrelated to overt
748 signaling engaged by the Fas cell surface death receptor (FAS; also known as CD95 or APO-1) or the
749 TNF receptor superfamily member 1A (TNFRSF1A, best known as TNF-R1) (which instead will be
750 discussed in the next section).

751 Distinct preclinical models of hepatic ischemia-reperfusion injury demonstrated that deletion of *Bcl2l1l*
752 (leading to lack of BIM) and/or *Bid* as well as over-expression of *BCL2* or administration of
753 pharmacological broad-spectrum caspase inhibition mediate robust hepatoprotective effects^{279, 280, 281,}
754²⁸². A similar improvement of hepatocyte survival and liver functionality was observed in rodents
755 specifically expressing a mutated variant of BID in the liver and subjected to warm ischemia/reperfusion
756 injury²⁸³. As for other models of liver injury, BIM-deficient mice are protected against viral hepatitis²⁸⁴.
757 Moreover, deletion of the genes encoding BIM or PUMA, but not that of BCL2-related ovarian killer
758 (*Bok*) limits liver injury in mice exposed to the hepatotoxic agent acetaminophen^{285, 286, 287}. Moreover,
759 pre-treatment with Z-VAD-FMK improves the survival of mice subjected to extensive hepatectomy²⁸⁸.

760 There is contrasting evidence on the role of BID in the etiology of liver conditions unrelated to overt
761 FAS and TNF-R1 signaling. In a model of alcohol-related liver disease, the lack of BID confers some
762 protection against ethanol-induced fibrosis, although mice display persisting signs of inflammation and
763 steatosis²⁸⁹. Moreover, mice with a hepatocyte-specific deletion of *Bid* present reduced liver

764 inflammation and fibrosis when subjected to a choline-deficient diet to cause non-alcoholic
765 steatohepatitis (NASH) ²⁹⁰. Also, administration of BID-targeting antisense oligonucleotides exerted
766 significant hepatoprotective effects ²⁹¹. However, BID deficiency fails to ameliorate liver injury and
767 fibrosis upon bile duct ligation (as a model of obstructive cholestasis and chronic liver disease) ²⁹². Of
768 note, in the same experimental model, the liver-specific overexpression of MCL1 but not BCL2 protects
769 animals from hepatic damage ^{293, 294}, suggesting some specificity for MCL1. To add a layer of
770 complexity, conditional deletion of *Xiap* in hepatocytes does not result in liver injury, steatosis, or
771 fibrosis, possibly due to compensatory effects of other inhibitor of apoptosis protein (IAPs) isoforms ²⁹⁵.
772 That said, *Xiap*^{-/-} and *Casp3*^{-/-} mice subjected to diet-induced hepatic steatosis and/or fibrosis, display
773 exacerbated and attenuated liver damage, respectively ^{296, 297}. These effects have been linked to the
774 modulation of the inflammatory response rather than apoptosis. Finally, genetic co-deletion of *Mcl1* and
775 transformation-related protein 53 (*Trp53*, best known as p53) ²⁹⁸ as well as conditional deletion of the
776 genes encoding BCL-X_L or MCL1 promote fibrosis and/or carcinogenesis, two common final stages of
777 liver disease ²⁹⁹. In this latter study, the additional deletion of *Bak1* limited hepatotoxicity, which is in
778 line with evidence indicating that deletion of *Bid* and/or *Bok* protects mice against experimentally
779 induced hepatocarcinogenesis ^{300, 301, 302}.

780 CASP2 was found upregulated in mouse model of NASH and in NASH patients and was implicated in
781 driving lipogenesis and steatohepatitis with a mechanism involving the cleavage of the site-1-protease
782 (S1) followed by the activation of sterol regulatory element binding proteins (SREBP) ³⁰³. In this study,
783 the ablation or pharmacological inhibition of CASP2 prevented diet-induced steatosis and NASH
784 progression. Of note, CASP2 deficiency was also reported to protect mice from diet-induced obesity and
785 metabolic syndrome ³⁰⁴. Supporting the etiological contribution of caspase activation to liver disease, the
786 administration of broad-spectrum caspase inhibitors (e.g., emricasan, VX-166) reduced liver injury,
787 inflammation and fibrosis in mice fed a diet rich in fat or deficient in methionine and choline ^{305, 306}.

788 Along similar lines, emricasan reportedly decreased portal pressure, fibrogenesis and hepatic
789 inflammation, and preserved liver function in rodent models of chronic carbon tetrachloride (CCl₄)-
790 mediated cirrhosis or cholestasis driven by bile duct ligation^{307, 308, 309}. Preliminary anti-inflammatory
791 effects coupled with improved liver function have also been observed in patients with NASH-related
792 cirrhosis treated with emricasan^{39, 310}. However, follow-up, randomized clinical studies failed to observe
793 beneficial effects of this agent on portal pressure and clinical outcome^{40, 41, 311}. At least in part, these
794 findings may reflect the complex interconnection between multiple RCD variants involved in the
795 pathogenesis of NASH. Supporting this possibility, the administration of CASP3-specific inhibitors that
796 abrogate both pro-apoptotic and pro-pyrototic activities of CASP3 protected mice against acute liver
797 injury caused by bile duct ligation³¹². Additional pharmacological and genetic studies specifically
798 targeting intrinsic apoptosis (over other RCD pathways controlled by caspases) are needed to formally
799 ascertain the involvement of this pathway in the etiology of hepatic disorders.

800 **Hematological malignancies and solid cancers.** The role of the intrinsic apoptosis pathway in
801 preventing oncogenesis has been demonstrated in multiple animal models of induced hematological and
802 solid tumors. In particular, a wide range of evidence demonstrates that over-expression of BCL2, BCL-
803 X_L or MCL-1 accelerates the onset of leukemia and lymphoma induced by over-expression of the MYC
804 proto-oncogene, bHLH transcription factor (MYC)^{313, 314, 315, 316, 317}. Accordingly, the pharmacological
805 inhibition of anti-apoptotic BCL2 proteins is effective against MYC-driven tumors, even when they lack
806 p53 function^{318, 319, 320, 321}. In this context p53 has been shown to exert multiple roles in RCD (e.g.,^{322,}
807^{323, 324}). In particular, it acts as a direct or indirect regulator of the expression of several apoptotic genes
808^{325, 326, 327, 328} and connects apoptosis induction and cell cycle arrest³²⁹. One main target of p53 in this
809 context is cyclin dependent kinase inhibitor 1A (*CDKN1A*, best known as p21). p53-induced expression
810 of *CDKN1A* leads to the activation of DREAM and RB/E2F transcriptional repressor complexes, in turn
811 promoting cell cycle arrest by downregulating crucial cell cycle regulators such as cyclins and cyclin-

812 dependent kinases^{326, 327, 330}. However, recent finding indicates that the p53-p21-DREAM or p53-p21-
813 RB/E2F axis can also downregulate *CASP2* and CASP8-associated protein 2/FLASH (*CASP8AP2*),
814 generating a feedback loop centered on p53 that limits rather than promoting the induction of apoptosis
815^{326, 327}. Of note, when analyzing the impact of endogenous proteins, it was shown that the absence of
816 BCL-X_L but not BCL2 limits the development of lymphoma in transgenic mice expressing MYC under
817 the IgH enhancer (E μ -myc mice)^{331, 332}, thus supporting the therapeutic use of BCL-X_L inhibitors against
818 these blood cancers. Along similar lines, MCL1 overexpression³¹⁷ or *Mcl1* ablation^{318, 333, 334},
819 respectively, accelerates and suppresses MYC-driven lymphomagenesis. Lending further support to the
820 relevance of MCL1, prevalence and onset of MYC-driven lymphoma development were reduced by *Mcl1*
821 haploinsufficiency^{318, 334}, or B cell-specific deletion of *Mcl1*³³⁵. Of note, loss of one allele of *Mcl1* (but
822 not complete loss of the gene encoding BCL-X_L) also impairs the development of thymic lymphoma in
823 p53-deficient mice³³⁶, which possibly explains the limited effect of the BCL-X_L + BCL2 + BCL-W
824 inhibitor ABT-737 in these models of tumorigenesis³³⁷. The contribution of pro-survival BCL2 proteins
825 in the development of AML has been demonstrated by using mice reconstituted with genetically modified
826 bone marrow cells overexpressing MYC³³⁸ and in human Burkitt lymphomas and diffuse large B-cell
827 lymphomas (Diepstraten, 2020,31985804). Notably, the acute genetic removal of *Mcl1* prevents the
828 sustained survival and proliferation of AML driven by diverse oncogenic fusion proteins³³⁹.
829 Accordingly, MCL-1 specific BH3 mimetic drugs, such as S63845, are able to potently kill a diverse
830 range of lymphoid and myeloid malignant cells in culture and even in tumor transplanted mice³⁴⁰.
831 Finally, ablation of *Bcl2l2* (leading to lack of BCL-W) limits the development of MYC-mediated B cell
832 lymphoma³⁴¹.

833 In support of the relevance of the intrinsic apoptosis pathway in tumorigenesis, several studies
834 demonstrated that the development of MYC-driven lymphoma and leukemia is accelerated in mice
835 lacking the genes encoding BAX³⁴², BIM^{343, 344}, BAD³⁴⁵, BMF³⁴⁵ or PUMA^{346, 347, 348}. In particular,

836 these studies report that loss of only a single allele of *Bcl2l1l* (encoding BIM) accelerates the
837 development of lymphoma and this effect was reversed following full ablation of *Bcl2l1* (leading to lack
838 of BCL-X_L)³⁴⁴. In this context, the presence of all prosurvival BCL2 proteins is shown to limit the impact
839 of BIM in *Eμ-Myc* transgenic mice³⁴⁹. Instead, the combined ablation of the genes encoding BIM and
840 p53 or PUMA and p53 accelerates MYC-driven lymphomagenesis³⁵⁰. This is in line with the evidence
841 that loss of the genes encoding BAX or BIM augmented lymphomagenesis in p53-deficient mice^{351, 352}.
842 Of note, PUMA seems to exert a strong tumor-suppressive role in blood cancers, as shown by the
843 evidence that *Bbc3* deletion accelerates the development of MYC-driven B-cell lymphomas and that *Eμ-*
844 *Myc* lymphomas developing in PUMA-proficient mice display downregulated expression of PUMA^{347,}
845 ^{348, 353}. On the contrary, the loss of the gene encoding NOXA does not accelerate MYC-driven
846 lymphomagenesis, and the role of BIK in this murine lymphoma model is debated^{347, 354}. Along similar
847 lines, while CASP2 suppresses MYC-induced lymphomagenesis in mice³⁵⁵, the tumor suppressive role
848 of apoptosome components (**Box 1**) is questioned, as shown in lethally irradiated mice reconstituted with
849 *Eμ-Myc* transgenic APAF1-deficient or CASP9-deficient fetal liver cells which showed no difference in
850 the incidence of lymphoma compared to their wild-type counterparts³⁵⁶. This is consistent with the
851 notion that APAF1 and caspase-9 function downstream of the commitment to cell death (MOMP) and
852 therefore do not act as tumor suppressors¹⁵.

853 Concerning other experimental animal models of induced hematological malignancies, the absence of
854 PUMA (due to ablation of *Bbc3*) abrogated the development of both myelodysplasia, as shown in
855 transgenic mice expressing a nucleoporin 98 (Nup98)-homeobox D13 (Hoxd13) fusion gene³⁵⁷, and
856 thymic T cell lymphoma induced by gamma radiation^{358, 359}. The explanation for these surprising
857 findings is based on the fact that the absence of PUMA prevents the extensive death of hematopoietic
858 cells caused by gamma radiation, which causes mobilization and extensive proliferation of hematopoietic
859 stem and progenitor cells, resulting in elevated replication stress and genetic instability and

860 lymphomagenesis. These findings show that inhibition of apoptosis does not only promote the
861 development of hematological malignancies, but in certain conditions can do the exact opposite and
862 prevent lymphoma development. The absence of NOXA, augments the development of chronic
863 lymphocytic leukemia in T cell lymphoma breakpoint 1 (TCL1) transgenic mice ³⁶⁰ and accelerated the
864 development of thymic T lymphoma induced by gamma radiation ³⁵⁸. Moreover, conditional deletion of
865 *Bcl2l1l* in B cells (leading to the absence of BIM) accelerates the development of mantle cell lymphoma
866 in mice driven by cyclin D1 (CCND1) over-expression ³⁶¹. Over-expression of MCL1 and/or BCL2
867 promotes the development of acute myeloid leukemia driven by lysine (K)-specific methyltransferase
868 2A (KMT2A, best known as MLL) fusion proteins ^{339, 362} and plasmacytoma driven by ABL proto-
869 oncogene 1, non-receptor tyrosine kinase (ABL1) ³⁶³. Conversely, the loss of one *Mcl1* allele suppresses
870 the development of T cell lymphoma, as shown in models based on sequential low-dose irradiation or
871 the expression of a transgene encoding an IL2 inducible T cell kinase (ITK)-spleen tyrosine kinase (SYK)
872 fusion protein ³⁶⁴. Finally, the absence of CASP2 accelerates lymphomagenesis in ataxia telangiectasia
873 mutated (ATM)-deficient mice ³⁶⁵, but this may be due to the loss of the function of caspase-2 in mitotic
874 cell division ³⁶⁶. Lending support to the role of intrinsic apoptosis in hematologic malignancies, the BCL2
875 inhibitor venetoclax has entered clinical practice for the treatment of CLL as single agent or more
876 effectively in combination with other therapeutic agents ^{31, 35, 36, 37}. Combinatorial regimens of BCL2
877 inhibition with epigenetic modulation have entered center stage in certain settings of AML ^{38, 367}.
878 However, mechanisms of resistance of CLL and AML to venetoclax related to defects in p53 and the
879 apoptotic network or deregulated energy metabolism have been described ^{368, 369, 370, 371}. Venetoclax-
880 based regimens also display effectiveness in patients with high-risk myelodysplastic syndromes ³⁷², thus
881 suggesting a potential application in these syndromes ^{373, 374}.

882 Significant work demonstrated a tumor suppressor role of the intrinsic apoptotic pathway in many
883 cancers. For example, BCL2 overexpression accelerates the development of MYC-induced mammary

884 tumorigenesis³⁷⁵. A similar acceleration of tumor development has been described for the loss of genes
885 encoding BAX, BIM, CASP2 or PUMA in distinct models of breast cancer induced by expression or
886 overexpression of C3(1)/SV40 T-antigen, MYC, or erb-b2 receptor tyrosine kinase 2 (ERBB2, best
887 known as HER2)^{376, 377, 378, 379}. At odds with these results, BCL2 overexpression in the mammary gland
888 suppresses the development of breast tumors driven by the administration of dimethylbenz(a)anthracene
889³⁸⁰. This latter finding may be explained in a similar way as was mentioned for the suppression of
890 radiation-induced thymic T cell lymphoma development by over-expression of BCL-2 or loss of PUMA
891 (see above). Conditional deletion of the genes encoding BCL2 or BCL-X_L in intestinal epithelial cells
892 delays the development of colorectal cancer driven by inflammation^{381, 382}, which is in line with the
893 evidence that the absence of PUMA (due to *Bbc3* deletion) exacerbates colorectal tumorigenesis as
894 shown in a mouse model of intestinal oncogenesis driven by colitis or APC, WNT signaling pathway
895 regulator (APC)³⁸³. Interestingly, doxorubicin-induced intestinal cytotoxicity requires PUMA but not
896 BIM, whereas the reverse is true for MYC-driven apoptosis in the gut, indicative of differential roles for
897 different BH3-only proteins in this tissue³⁸⁴. Intriguingly, treatment with BCL-X_L, but not BCL2-
898 targeting BH3 mimetics is sufficient to prevent intestinal tumorigenesis, suggesting that BCL-X_L is the
899 crucial mediator of protection of early neoplastic cells in this model³⁸⁵. In agreement, earlier work
900 showed BCL-X_L dependency in cell cultures derived from both colorectal and non-small cell lung
901 cancers^{386, 387}. Moreover, a tumor suppressive effect is ascribed to BAX and CASP2 respectively in
902 murine models of brain cancer^{388, 389} and lung cancer³⁹⁰ development. In line with this evidence,
903 pharmacologic/genetic inhibition of MCL1 delayed tumor development in a mouse model of mutant
904 KRas-driven adenoma/adenocarcinoma³⁹¹. In the same model, tumor progression was promoted by the
905 ablation of pro-apoptotic *Bok*³⁹². Of note, there is evidence of a certain tissue-specificity in the epigenetic
906 regulation of *Bcl2* and *Mcl1*, such as the epigenetic mechanism centered on the deubiquitinase BRCA1
907 associated protein 1 (BAP1)³⁹³ a tumor suppressor that is frequently mutated in certain cancers³⁹⁴ and

908 has been associated with tumor aggressiveness and therapy resistance^{395, 396}. Finally, age-related
909 differences in the expression of pro-apoptotic members of the BCL2 family have been linked to the
910 increased sensitivity of neonatal/childhood tissues, relative to adult counterparts, to chemotherapy and
911 radiotherapy. This was causally linked to MYC-dependent expression of genes encoding BAX, BID and
912 BIM, both in mice and humans¹³³.

913 Cancer-specific contributions were attributed to particular BCL2 protein family members. For example,
914 deletion of *Bax* accelerates the development of MYC-induced pancreatic tumors³⁹⁷ which was not seen
915 with ablation of *Bak1* or *Casp3*^{397, 398} but was achieved by BCL-X_L overexpression^{314, 399}. Likewise,
916 BOK seems to be crucial in hepatocarcinogenesis, as demonstrated in a mouse model of
917 diethylnitrosamine-induced liver cancer which was accelerated on a *Bok*^{-/-} genetic background³⁰⁰. Using
918 the same mouse model, enhanced hepatic cancer development was also demonstrated for the deletion of
919 the genes encoding PUMA or CASP2^{400, 401}. Conversely, overexpression of BCL2 was shown to limit
920 transforming growth factor- α (TGFA)-driven hepatic tumorigenesis^{402, 403}, perhaps because the death of
921 certain cells in the liver causes massive mobilization and proliferation of progenitor cells, leading to
922 acquisition of oncogenic lesions that drive tumorigenesis in a manner similar to radiation-induced thymic
923 lymphoma development (see above). Finally, the transgenic overexpression of BCL-X_L (but not BCL2)
924 and the keratinocyte-specific deletion of *Bcl2l1* (leading to lack of BCL-X_L) respectively accelerates or
925 limits chemically- and/or ultraviolet B (UVB)-induced skin tumorigenesis^{404, 405, 406, 407}. It will be
926 important to investigate and better understand why in certain settings inhibition of apoptotic cell death
927 promotes tumorigenesis whereas it inhibits tumorigenesis in others.

928 **Autoimmune and inflammatory diseases.** There is substantial evidence linking intrinsic apoptosis to
929 the development and progression of autoimmune diseases. However, the interpretation of these findings

930 should take into consideration the crosstalk between the apoptotic and inflammatory pathways and the
931 fact that apoptotic caspases accelerate cell death and regulate its immunological manifestation.

932 The first evidence that defects in the intrinsic apoptosis pathway can cause the development of
933 autoimmune disease was reported when over-expression of BCL-2 in B lymphocytes⁴⁰⁸ or loss of BIM
934 in all tissues⁴⁰⁹ was shown to cause fatal systemic lupus erythematosus (SLE)-like disease. Consistent
935 with a critical role for the intrinsic apoptotic pathway in preventing autoimmune disease, the combined
936 loss of the genes encoding BAX and BAK1 in hematopoietic cells, achieved by transplantation of lethally
937 irradiated wild-type mice with hematopoietic stem/progenitor cells from the livers of E14.5 *Bax*^{-/-}*Bak1*^{-/-}
938 embryos also causes fatal SLE-like disease⁴¹⁰. In mouse models of rheumatoid arthritis, ablation of the
939 genes encoding BIM, BID or BAD, but not the loss of *Bax* and *Bak1*, accelerated the emergence and
940 increased the duration and severity of this disease^{411, 412, 413}. Consistent with these findings,
941 administration of a BIM mimetic suppressed inflammatory arthritis in mice⁴¹⁴. Mice deficient for BAX
942 as well as transgenic mice expressing XIAP display increased severity of autoimmune encephalomyelitis
943 induced by immunization with myelin oligodendrocyte glycoprotein (MOG)^{415, 416}. Similar results have
944 been obtained in mouse models of autoimmune encephalomyelitis genetically engineered for
945 hematopoietic cell-specific deletion of *Bcl2l1l* (leading to BIM deficiency), or the neuron-specific
946 overexpression of BCL2^{417, 418}. Consistent with the notion that inhibition of apoptosis can promote the
947 development of auto-immune disease, inhibition of BCL-2, BCL-XL and BCL-W using the BH3 mimetic
948 drug ABT-263 substantially reduced pathology in several mouse models of autoimmune disease,
949 including scleroderma⁴¹⁹. In apparent contrast with these results, studies using models of type 1
950 (autoimmune) or type 2 (non-autoimmune) diabetes revealed that deletion of *Bax* alone or combined loss
951 of *Bax* and *Bak1*^{420, 421}, deletion of the gene encoding BIM, alone or together with the gene encoding
952 PUMA^{417, 422, 423, 424} or loss of BMF⁴²⁵ protect pancreatic β cells from autoimmune destruction.
953 Moreover, the absence of BIM prevented the emergence of type 1 diabetes in non-obese diabetic (NOD)

954 mice^{417, 422}, while ablation of *Trp53* in pancreatic β cells failed to halt cell death in multiple experimental
955 models of diabetes⁴²⁶.

956 Based on the studies described above, inhibiting or deleting pro-apoptotic proteins or genes can have
957 conflicting effects on autoimmune disease progression. This may depend on the cell type in which the
958 major effect on apoptosis occurs, e.g., the immune cells (attacking the target cell) or the target cell.
959 Inhibiting cell death in the target cells would provide protection and may improve disease outcome,
960 whereas inhibiting cell death in the immune cell may lead to an accumulation of immune cells and
961 aggravation of the autoimmune disease. The distinction could be explored by studying tissue-specific
962 deletion of apoptosis regulator genes.

963 In this context, there is evidence that inflammatory and autoimmune disorders may derive from increased
964 survival of specific immune cell population. For instance, elevated levels of cytokines, such as GM-CSF,
965 IL-3 and IL-5 in immune disorders have been associated with prolonged survival of neutrophils,
966 eosinophils or basophils with a mechanism involving the upregulation of anti-apoptotic proteins MCL1,
967 BCL-X_L and Baculoviral IAP Repeat Containing 2 (BIRC2, best known as cIAP2) promoted by^{427, 428,}
968^{429, 430, 431, 432, 433, 434}. Apoptosis also plays a relevant role in certain hemopathies, including beta
969 thalassemia⁴³⁵, Diamond-Blackfand anemia⁴³⁶, and in the Cohen syndrome neutropenia⁴³⁷. BIM, BID
970 and BAD have all been shown to influence survival in mouse models of septic shock, as their targeting
971 confer protective effects from tissue damage of multiple organs^{438, 439, 440}, as well as in patients with
972 severe sepsis⁴⁴¹. On the contrary, the role of apoptotic caspase in septic shock is contentious^{54, 73, 442, 443}.
973 The precise impact of apoptosis in widespread inflammation during sepsis requires further investigation.
974 Concerning other inflammatory disease, while broad-spectrum caspase inhibition reportedly protected
975 rats against severe acute pancreatitis⁴⁴⁴, activation of intrinsic apoptosis appears to attenuate the severity
976 of this disease by limiting inflammation, as shown *in vivo* in a pancreatitis mouse model lacking XIAP

977 ⁴⁴⁵. These data reinforce the notion that inhibiting (apoptotic) cell death may exacerbate unwarranted
978 inflammatory reactions that contribute to the pathology of various autoimmune and inflammatory
979 disorders. In line with this notion, chronic colitis driven by dextran sulfate sodium in mice manifests with
980 increased (rather than decreased) severity in BID- or BIM-deficient hosts as compared to their wild-type
981 littermates, at least in part owing to immune dysregulation ^{446, 447}. Similarly, inhibition of BCL2 and/or
982 BCL-X_L reduces inflammation and ameliorates experimental colitis ^{448, 449}, an effect that was abrogated
983 by concomitant deletion of the gene encoding BIM ⁴⁴⁹. PUMA-deficient mice displayed reduced levels
984 of apoptosis amongst intestinal epithelial cells but not reduced inflammation in an experimental model
985 of colitis ⁴⁵⁰. Corroborating the specific relevance of PUMA for intestinal homeostasis, mice deficient
986 for PUMA but not *Bax*^{-/-}*Bak1*^{-/-} mice were protected against the gastrointestinal side effects of
987 radiotherapy, at least in part due to increased survival of intestinal stem/progenitor cells ^{451, 452}. Moreover,
988 the absence of PUMA conferred protection to intestinal epithelial cells in mouse models of hypertensive
989 gastropathy ⁴⁵³, ulcerative colitis (UC) ⁴⁵⁴ and intestinal ischemia/reperfusion ⁴⁵⁵. In the latter model,
990 transgenic BCL2 expression limited intestinal epithelial cell death ⁴⁵⁶. On the other hand, deficiency in
991 XIAP, an inhibitor of CASP3, CASP7, CASP9, causes X-linked lymphoproliferative syndrome 2 with
992 one-third of these patients suffering from severe and therapy-refractory inflammatory bowel disease ⁴⁵⁷,
993 ^{458, 459, 460}. Absence of XIAP also results in enhanced TNF production and TNF-R1/TNF-R2 targeting of
994 TLR5-expressing Paneth cells and dendritic cells, leading to ileitis and dysbiosis ⁴⁶¹. In this context, it is
995 interesting to note that CASP3- or CASP7-deficient mice display an altered gut microbiome ⁴⁶², which
996 may play a hitherto unexplored role in multiple autoimmune and inflammatory disorders beyond
997 intestinal conditions. However, recently it was found that under steady state conditions absence of
998 CASP3 and CASP7 in the intestinal epithelial cells apparently does not affect the microbiome neither
999 cause spontaneous inflammation, suggesting that apoptosis may be dispensable for intestinal epithelium
1000 turnover and homeostasis at steady state ⁴⁶³.

1001 **Infectious diseases.** Activation of RCD constitutes a protective mechanism against many microbial
1002 infections by eliminating infected cells and potentiating the anti-infective immune response. Accordingly,
1003 both viruses and bacteria have developed multiple strategies to overcome or disable host intrinsic
1004 apoptosis thus improving survival of both the host cells and the infectious organisms^{464, 465} Waguia Kontchou,
1005 2022 35397654 Waguia Kontchou, 2022 35397654 Waguia Kontchou, 2022 35397654 Waguia Kontchou, 2022 35397654. Mice with loss of one
1006 allele of the genes encoding BCL-X_L displayed reduced pathology and had improved survival rates when
1007 challenged with Japanese encephalitis virus (JEV), as compared with wild-type mice. This was attributed
1008 to compromised viral propagation within JEV-infected cells succumbing to intrinsic apoptosis⁴⁶⁶. There
1009 is also evidence of a contribution of BAX and BAK1 to the response to murine cytomegalovirus (MCMV)
1010 infection. In particular, the MCMV genome encodes inhibitors of BAK1 (m41.1 protein) and BAX
1011 (m38.5 protein), promoting viral replication by inhibiting the induction of intrinsic apoptosis in infected
1012 cells⁴⁶⁷ Fleming, 2013, 23468630 Fleming, 2013, 23468630 Fleming, 2013, 23468630 Fleming, 2013, 23468630, 468 Manzur, 2009, 18949000 Manzur,
1013 2009, 18949000 Manzur, 2009, 18949000 Manzur, 2009, 18949000. Supporting the requirement of the inhibition of intrinsic
1014 apoptosis for optimal *in vivo* MCMV dissemination, the titers of m41.1-deficient viruses were higher in
1015 salivary glands and other organs in *Bak1*^{-/-} mice as compared to wild-type animals⁴⁶⁷ Fleming, 2013, 23468630
1016 Fleming, 2013, 23468630 Fleming, 2013, 23468630 Fleming, 2013, 23468630. Intrinsic apoptosis also protects against bacterial
1017 infections, as demonstrated by the lethal course of disease in *Bbc3*^{-/-} mice (which lack PUMA) after
1018 *Streptococcus pneumoniae* infection⁴⁶⁹. Such an effect has been attributed to insufficient immune-
1019 mediated bacterial clearance because of an increased neutrophil lifespan in the absence of PUMA-
1020 mediated apoptosis.

1021 However, in certain other contexts, excessive activation of the intrinsic apoptosis pathway has been
1022 reported to drive, rather than prevent, microbial disease pathogenesis and lethality. For example, loss of
1023 *Xiap* increased the susceptibility of mice to *Shigella* infection, manifested with coalescing necrotic areas
1024 and a high bacterial burden in the liver and this was associated with an inefficient immune-mediated

1025 resolution of the bacterial infection⁴⁷⁰. Although at least part of this effect may be due to the requirement
1026 for XIAP to activate NOD signaling, rather than its ability to inhibit caspases^{458, 470, 471}. Moreover, mice
1027 lacking the genes encoding BIM and NOXA (*i.e.*, *Bcl2l1l^{-/-}Pmaip1^{-/-}* mice) displayed high resistance
1028 to the challenge with high doses of *Listeria monocytogenes*, as shown by a decreased bacterial burden
1029 and low apoptosis induction in the spleen⁴⁷². The overexpression of BCL2 in the hematopoietic
1030 compartment increased the survival of mice infected with Ebola virus⁴⁷³, while deletion of *Bok* increased
1031 resistance of lung epithelial cells to apoptosis induced by SARS-CoV-2 virus membrane (M) protein⁴⁷⁴.
1032 Intriguingly, this study showed that the SARS-CoV-2 M protein, induced BOK to trigger apoptosis in
1033 the absence of BAX and BAK1⁴⁷⁴. In another example, conditional deletion of *Casp3* in the murine
1034 intestinal epithelium conferred protection from pathogenic *Salmonella enterica*, and this was attributed
1035 to a reduction in cell death-induced nutrients that are critical for sustaining bacterial growth⁴⁷⁵. Finally,
1036 *Casp3^{-/-}* mice subjected to intracranial inoculation of reovirus type 3 (strain Dearing) displayed limited
1037 injuries in the central nervous system (CNS) and enhanced survival compared to wild-type mice⁴⁷⁶. As
1038 discussed above, the interpretation of the infection phenotypes using CASP3-, CASP7- and/or CASP9-
1039 deficient mice needs particular caution because of the crucial roles of these caspases in modulating
1040 immune and inflammatory responses^{242, 243, 244}. Notably, there is evidence for a role of specific regulators
1041 of apoptosis in the response to infection with human herpes simplex virus 1 (HSV-1). Thus, on the one
1042 hand, a significant accumulation in total leukocyte and CD8⁺ T cells was observed in mice deficient for
1043 BIM and PUMA upon infection with HSV-1⁴⁷⁷, which is in line with a role of these BH3-only proteins
1044 in controlling the survival of lymphoid and myeloid cells^{409, 478, 479}. On the other hand, mice deficient
1045 for NOXA, BAD or BID were reported to mount a normal CD8⁺ T cell immune response to HSV-1
1046 infection⁴⁷⁷. Some of the contradictory results reported may arise from the divergent effects of inhibition
1047 or promotion of apoptosis on immune cells versus other cell types affected by the infectious disease, a
1048 distinction that cannot be addressed using mice in which apoptotic regulators have been deleted in the

1049 germline. In this context it is noteworthy that myeloid cell-specific deletion of the gene encoding BCL-
1050 X_L or its inhibition using BH3 mimetic drugs massively reduced bacterial burden in the lung and
1051 extended the survival of mice infected with *Legionella* bacteria⁴⁸⁰. This indicates that BH3 mimetic
1052 drugs might be effective for the treatment of intra-cellular bacterial infections.

1053 **Other diseases.** Pro-apoptotic BCL2 proteins and caspases have also been implicated in disorders
1054 affecting other tissues/organs, such as skeletal muscle and lungs. For instance, the conditional ablation
1055 of *Bax* and *Bak1* protected mouse skeletal muscles against pressure-induced injury⁴⁸¹. Similar results
1056 have been obtained in rats receiving Z-VAD-FMK after being subjected to muscular compression or
1057 blunt injury^{482, 483}. Moreover, deletion of *Casp3* or CASP3 inhibition with Ac-DEVD-CHO limited
1058 muscular damage and atrophy in experimental models of plaster-mediated immobilization^{484, 485}. In
1059 mouse models of catabolic disorders, muscle wasting due to protein degradation was decreased by
1060 lentiviral expression of XIAP^{486, 487}, although whether this effect reflects the inhibition of intrinsic
1061 apoptosis needs further confirmation. Finally, *Casp3*^{-/-} mice were protected against denervation-induced
1062 muscular atrophy⁴⁸⁸, while expression of a dominant-negative variant of CASP9 improved the
1063 neuromuscular activity in a transgenic mouse model of slow-channel syndrome⁴⁸⁹.

1064 In a mouse model of oxidant-induced lung injury, the tissue-specific ablation of *Bax* and *Bak1* but not
1065 that of the genes encoding BID, BIM, NOXA or PUMA protected lung epithelial cells from degeneration
1066⁴⁹⁰. Among the anti-apoptotic BCL2 proteins, BCL2A1 (best known as A1) seems to exert a crucial role
1067 in this setting, as *Bcl2a1* deletion aggravated lung injury in mice subjected to hyperoxia⁴⁹¹, while lung-
1068 specific overexpression of BCL2 did not confer protection to mice exposed to excessive oxygen supply
1069⁴⁹². That said, no critical cytoprotective effect of A1 was seen in acute lung inflammation and peritonitis
1070⁴⁹³. Intrinsic apoptosis has also been reported to be involved in pulmonary fibrosis⁴⁹⁴. *Bid*^{-/-} mice
1071 displayed decreased levels of pulmonary fibrosis after intra-tracheal bleomycin administration⁴⁹⁵. In

1072 apparent contradiction, in the same model of fibrotic pulmonary damage, similar protection was reported
1073 in mice deleted for *Bcl2*⁴⁹⁶ or in animals treated with inhibitors of BCL2⁴⁹⁶ or caspases^{497, 498}. Along
1074 similar lines, ablation of *Bid* limited acute lung injury in mice induced by exposure to lipopolysaccharide
1075⁴⁹⁹. Moreover, CASP3 depletion using short-hairpin RNAs (shRNAs) protected the lungs of mice
1076 subjected to pulmonary ischemia/reperfusion⁵⁰⁰, a protection further strengthened when necroptosis was
1077 concomitantly also suppressed⁵⁰¹. BCL2 overexpression or caspase inhibition protected rodents
1078 subjected to lung transplantation^{502, 503}. This is in line with the notion that delivery of the caspase
1079 inhibitor Z-VAD-FMK to rodents ameliorated lung injury developing as a consequence of severe acute
1080 pancreatitis or lipopolysaccharide administration^{504, 505} but not as a result of pneumovirus infection⁵⁰⁶.
1081 In the latter case, lung damage was exacerbated by Z-VAD-FMK, perhaps due to increased inflammation
1082 downstream of necroptotic RCD⁵⁰⁶.

1083 The studies briefly summarized above illustrate that components of the intrinsic apoptosis pathway can
1084 be part of the pathogenic mechanism of disease, and, in certain cases, this may offer the opportunity for
1085 therapeutic intervention. It is important to note though that in many pathogenic processes intrinsic
1086 apoptotic cell death is the endpoint, and simply inhibiting it will not be curative. If the cells continue
1087 being exposed to the initiating insult, they will likely undergo less regulated forms of cell death.
1088 However, inhibiting the intrinsic apoptotic cell death may buy time to remediate the factors that are
1089 damaging the cells in first place. Ischemia and hypoxia, in cases where the ensuing cell death has a
1090 substantial intrinsic apoptotic component, are examples. If cells in the ischemic region were kept alive
1091 until adequate circulation was restored, therapeutic benefits might be achieved. Other examples include
1092 metabolic disorders, which may be amenable to correction, and traumatic injury, where healing might be
1093 supported by inhibiting apoptosis. It would be worth concentrating on inhibiting intrinsic apoptotic cell
1094 death in conditions where the initiating tissue insults can be (at least partially) reversed. In contrast,
1095 failure to undergo intrinsic apoptosis is the initial pathogenic step or a contributing factor in certain

1096 malignancies. Here, the induction of apoptosis, for example by using BH3 mimetic drugs^{33, 34}, targets
1097 the pathogenesis directly.

1098

1099 **Extrinsic apoptosis in disease**

1100 The molecular apparatus for extrinsic apoptosis is described in **Box 5** and illustrated in **Figure 4**. Unlike
1101 the intrinsic apoptotic pathway, DR-induced apoptosis is not required for embryonic or fetal development
1102 but plays a critical role in adult tissue homeostasis, as detailed in **Box 6** and **Box 7**. Of note, various
1103 components of the extrinsic pathway of apoptosis are involved in the etiology of multiple human
1104 disorders, although (1) with a considerable degree of context-dependency, and (2) with an effect not
1105 necessarily linked to the activation of apoptosis but often due to the role of DR signaling in necroptosis
1106 and inflammation, as outlined below.

1107 **Neurological diseases.** Although numerous studies investigated FAS and TNF-R1 signaling in the
1108 pathogenesis of multiple neurological diseases, the precise role of extrinsic apoptosis remains unclear
1109 (**Figure 5**). Loss-of-function mutations of FAS ligand (*Fasl*) as well as *Fas* silencing prevented moto-
1110 neuron loss in mouse models of ALS driven by defect in superoxide dismutase 1, soluble (SOD1)^{507, 508}.
1111 Moreover, the lack of TNF did not affect motor neuron loss and mouse survival in this model⁵⁰⁹, while
1112 binding of the TNF receptor superfamily member 1B (TNFRSF1B, best known as TNF-R2) appeared to
1113 mediate neuroprotective effects⁵¹⁰. As an additional layer of complexity, TNF mediates neuroprotective
1114 functions in wobbler mice - another mouse model of ALS that carries a point mutation in VPS54 GARP
1115 complex subunit (*Vps54*), at least in part by promoting the upregulation of ADAM metallopeptidase
1116 domain 8 (ADAM8)⁵¹¹. CASP8 has not yet been implicated in the pathogenesis of ALS, and non-
1117 apoptotic forms of FAS-driven RCD may play a predominant role in this context. For example, FAS

1118 stimulation reportedly triggered the demise of motoneurons in mouse models of ALS by aggravating
1119 endoplasmic reticulum stress⁵¹². Similarly, cleavage of BID by CASP1 (and not CASP8) appears to
1120 contribute to neurodegeneration in transgenic mice expressing a mutant form of human *SOD1*⁵¹³.
1121 However, the precise contributions of endoplasmic reticulum stress and CASP1 in ALS and other
1122 motoneuron disorders remain to be elucidated.

1123 The ability of TNF-R1 signaling to influence neurodegenerative conditions involves not only the
1124 induction of extrinsic apoptosis but also the activation of an inflammatory response. In distinct murine
1125 models of AD, deletion of *Tnf*, modification of its untranslated region (UTR) as well as pharmacological
1126 or genetic removal of TNF reduced plaque formation, resulting in attenuated neurological deficits^{514, 515,}
1127 ^{516, 517, 518, 519, 520, 521}. Mechanistic studies in mice and monkeys revealed that TNF-R1 activation stimulates
1128 the protein activator of interferon-induced protein kinase EIF2AK2 (PRKRA) network⁵²², which is
1129 linked to PD in humans⁵²³. Moreover, TNF-R1 signaling has been shown to favor microglial reactivity
1130 during neurodegeneration, culminating in neuronal loss⁵²⁴. Amelioration of disease was seen in mouse
1131 models of AD upon genetic or pharmacological inhibition of TNF-R1^{525, 526}. AD-associated
1132 neuroinflammation seems to depend on TNF-induced necroptosis rather than extrinsic apoptosis^{527, 528}.
1133 Unexpectedly, AD pathogenesis was shown to be enhanced in mice bearing a co-deletion of the TNF
1134 receptor superfamily member genes *Tnfrsf1a* and *Tnfrsf1b*⁵²⁹, a phenotype that appears to impinge on a
1135 complex network of mutual interactions between TNF-R1 and TNF-R2 signaling⁵³⁰. Such a network
1136 may also contribute to PD pathogenesis. Genetic ablation of *Tnf* or *Tnfrsf1a* plus *Tnfrsf1b* (leading to the
1137 lack of both TNF receptors), as well as pharmacological inhibition of TNF, were reported to protect
1138 dopaminergic neurons in murine models of PD following the administration of 1-metil 4-phenyl 1,2,3,6-
1139 tetrahydro-piridina (MPTP) or 6-hydroxydopamine^{531, 532, 533, 534}. Notably, in the above-mentioned
1140 experimental settings, TNF is thought to induce neuronal death *in vivo* by promoting microglia reactivity

1141 ⁵³⁵ with a complex interaction between TNF-R1 and TNF-R2 signaling ⁵³⁶. Importantly, clinical evidence
1142 from AD patients subjected to perispinal administration of the TNF blockers infliximab or etanercept
1143 suggests that the inhibition of TNF can ameliorate AD ^{537, 538}. In contrast, a dominant-negative variant of
1144 TNF failed to protect mice against neuronal degeneration in a model of HD ⁵³⁹, suggesting that this
1145 approach may not be viable in patients with HD.

1146 TRAIL/TRAIL-R signaling has also been implicated in the onset and progression of AD ^{540, 541}.
1147 Specifically, in a mouse model of AD, neutralization of TNF superfamily member 10 (*TNFSF10*, best
1148 known as TRAIL) with a monoclonal antibody resulted in decreased neuroinflammation and a reduction
1149 in cognitive defects ⁵⁴⁰. However, these findings were not extensively validated. Similarly, the impact of
1150 FASL-FAS signaling on neurodegenerative conditions is debated. Indeed, lymphoproliferative (*lpr/lpr*)
1151 mice, which lack FAS ⁵⁴² and to a lesser extent generalized lymphoproliferative disease (*gld/gld*) mice,
1152 which lack FASL ⁵⁴², are particularly susceptible to neuronal degeneration driven by MPTP ⁵⁴³. However,
1153 contrasting results have been obtained in another study of MPTP-treated mice with FAS deficiency ⁵⁴⁴,
1154 ⁵⁴⁵. In this context, FAS-associated factor 1 (*Faf1*, a FAS binding protein that can initiate or enhance
1155 apoptosis) was found increased in midbrain in murine models of PD ⁵⁴⁶. Moreover, a reduction in *Faf1*
1156 expression reduced MPTP-induced dopaminergic cell loss ⁵⁴⁷. Such an apparent discrepancy in results
1157 may originate from the pleiotropic role of FAS in apoptosis and inflammation and other pro-
1158 survival/regenerative signals.

1159 CASP8 activation has been detected in the brain of both AD ⁵⁴⁸ and HD ⁵⁴⁹ patients as well as in
1160 dopaminergic neurons of MPTP-treated mice and PD patients, a setting in which BID cleavage has also
1161 been documented ¹¹⁹. This is in line with the ability of the broad-spectrum caspase inhibitor Q-VD-OPH
1162 to inhibit BID cleavage and mediate neuroprotection in MPTP-treated mice and rats ⁵⁵⁰. Of note, CASP8
1163 was also reported to promote microglia reactivity potentially leading to neuronal loss ^{551, 552, 553}. In this

1164 context, genetic loss or pharmacological inhibition of CASP8 attenuated neurotoxicity by reducing
1165 microglial reactivity, thus extending survival of neurons, at least in part by stimulating the necroptotic
1166 death of activated microglial cells ^{551, 552, 553}. Consistent with this notion, *Casp8* deletion in myeloid cells
1167 protected mice from MPTP-mediated neurotoxicity ⁵⁵⁴, suggesting that CASP8 inhibitors may be
1168 harnessed for the treatment of neurodegenerative conditions. Corroborating this idea, a pharmacological
1169 inhibitor of TNF-R1-associated death domain protein (TRADD) protected mice from disease in a model
1170 of AD-like proteinopathy driven by mutant tau ⁵⁵⁵. However, pharmacological inhibition of CASP8 only
1171 partially prevented neuronal alterations in other models of AD ¹⁰⁸ and even exacerbated dopaminergic
1172 neuronal necrosis in mice developing PD upon MPTP administration ⁵⁵⁶. Moreover, rare *CASP8* loss-of-
1173 function variants have been associated with AD in a large cohort of patients ⁵⁵⁷. Thus, the precise
1174 contribution of CASP8 signaling to neurodegenerative disorders and whether this relates to its function
1175 in driving extrinsic apoptosis, inhibiting necroptosis or promoting inflammatory cytokine production
1176 remains to be formally defined. Concerning dependence receptors, Netrin 1 (NTN1) upregulation was
1177 shown to confer neuroprotection in murine models of PD, suggesting a potential role of dependence
1178 receptors in neurodegenerative disease ⁵⁵⁸.

1179 DR signaling has also been shown to contribute to neuronal death and inflammation in preclinical models
1180 of CNS trauma. In a compression model of spinal cord injury, mice with loss of FAS (i.e., *lpr/lpr* mice)
1181 as well as mice treated with FASL blockers displayed reduced post-traumatic neuronal degeneration and
1182 inflammation coupled to considerable functional improvement ^{559, 560, 561}. This beneficial effect also
1183 involved reduced engagement of the intrinsic apoptosis pathway ⁵⁶². Myeloid cell-specific deletion of
1184 *Fasl* promoted neuronal regeneration and functional recovery in mice subjected to spinal cord injury ⁵⁶³.
1185 A similar functional improvement after spinal injury was observed in mice with conditional deletion of
1186 *Tnf* in macrophages and neutrophils but not in microglia ⁵⁶⁴. Moreover, neuroprotection and limited
1187 neuroinflammation have been documented in FAS-deficient *lpr/ lpr* mice subjected to traumatic brain

1188 injury⁵⁶⁵ as well as in mice subjected to experimental spondylotic myelopathy and exposed to FASL-
1189 neutralizing antibodies⁵⁶⁶. Studies on mice with loss of *Fas* and *Tnfrsf1a* revealed at least some
1190 redundancy between FAS and TNF-R1 signaling in the context of experimental brain trauma^{567, 568, 569,}
1191 ^{570, 571}. Furthermore, TNF inhibition reduced damage in mice or rats experiencing spinal cord injury^{572,}
1192 ^{573, 574}, and also reduced the appearance of signs of autonomic dysreflexia, a cardiovascular disease
1193 associated with high-level spinal cord injury^{572, 575}. Interestingly, some of these studies point to a
1194 neuroprotective function for TNF-R2^{567, 569, 571}, which is in line with at least some results from models
1195 of ALS^{510, 530}. Moreover, several studies question a purely detrimental effect of TNF signaling in these
1196 experimental settings^{576, 577, 578, 579}. In particular, TNF was reported to support, at least in part,
1197 regeneration and long-term functional recovery in mice exposed to traumatic brain injury^{577, 578, 579}.
1198 Conversely, TRAIL neutralization stands out as a promising strategy to promote neuronal regeneration
1199 and functional recovery based on mice with spinal cord injuries^{580, 581}. In this context, injured neurons
1200 seem to undergo Fas-associated via death domain (FADD)- and CASP8-dependent RCD⁵⁸².
1201 Accordingly, *Casp8* deletion or transgenic expression of a FADD inhibitor (the glycoprotein P45)
1202 protected mice after spinal cord injury^{583, 584}. Similarly, transgenic expression of a dominant negative
1203 mutant of FADD (FADD-DN) limited motoneuron loss in mice undergoing axotomy⁵⁸⁵.

1204 Components of the molecular apparatus for the extrinsic pathway are associated with disorders of the
1205 visual system, again in the context of both exacerbated cell death and inflammation. Thus, in mouse and
1206 rat models of optic nerve injury, deletion of *Tnfrsf1a* (encoding TNF-R1) or inhibition of CASP8 with
1207 Z-IETD-FMK inhibited the degeneration of retinal ganglion cells^{586, 587}. Moreover, the absence of TNF-
1208 R1 (but not the absence of TNF-R2) attenuated neurodegeneration in a mouse model of retinal ischemia,
1209 despite neuronal survival not being improved⁵⁸⁸. Along similar lines, deletion of *Tnf*⁵⁸⁹ as well as
1210 inhibition of FAS⁵⁹⁰ or TNF^{591, 592} protected mice against retinal ganglion cell death in a model of
1211 glaucoma. Similar neuroprotective effects were documented for the conditional deletion of *Casp8* in

1212 astrocytes or intra-ocular Z-IETD-FMK administration ⁵⁹³. In this context, the conditional inducible
1213 ablation of *Casp8* from endothelial cells reduced postnatal retinal angiogenesis and pathological
1214 neovascularization in a mouse model of oxygen-induced retinopathy ⁵⁹⁴ (note that ablation of *Casp8* in
1215 endothelial cells is embryonically lethal ⁵⁹⁵; see **Box 7**). Moreover, CASP8 inhibition could prevent
1216 experimental neovascularization of the cornea ⁵⁹⁶. Finally, TRAIL neutralization protected the retinal
1217 tissue from damage associated with AD in a mouse model ⁵⁹⁷.

1218 Experimental models of ischemic stroke and hemorrhage revealed a role of DR signaling in the
1219 pathophysiology of brain damage. In models of focal ischemia induced by middle cerebral artery
1220 occlusion, *lpr/lpr* as well as *gld/gld* mice (deficient for FAS or FAS ligand, respectively) displayed
1221 decreased infarct size and neuroinflammation ^{598, 599, 600}. Robust neuroprotection was also observed in
1222 *lpr/lpr* mice subjected to neonatal hypoxia-ischemia ⁶⁰¹, as well as in *lpr/lpr* and *gld/gld* mice subjected
1223 to hyperoxia ⁶⁰². Accordingly, inhibition of FAS or FASL exerted neuroprotective effects in an
1224 experimental murine model of stroke ^{603, 604}. Likewise, TRAIL neutralization limited brain injury in rats
1225 and mice subjected to middle cerebral artery occlusion ^{600, 605} or transient ischemia-reperfusion ⁶⁰⁶.
1226 Moreover, despite some contention in this respect ^{607, 608, 609, 610}, abrogation of TNF/TNF-R1 signaling
1227 by genetic or pharmacological means prevented brain injury in rodent models of intracerebral
1228 hemorrhage ⁶¹¹ and focal cerebral ischemia ^{612, 613, 614, 615, 616, 617, 618, 619, 620}. Further corroborating a
1229 pathogenic role of DR signaling, transgene-driven expression of dominant-negative CASP8 mutant and
1230 of FADD-like apoptosis regulator (CFLAR; best known as c-FLIP) attenuated brain damage after middle
1231 cerebral artery occlusion ^{621, 622}. This is in line with the ability of CASP8 to drive BID activation upon
1232 focal cerebral ischemia ¹⁹⁶, as well as with the neuroprotective effects afforded by pharmacological
1233 CASP8 inhibitors seen in mice experiencing subarachnoid hemorrhage ⁶²³ or mice and rats subjected to
1234 focal cerebral ischemia ^{624, 625}. Importantly, FADD and CASP8 expression and/or activation have also
1235 been associated with ischemic stroke in humans ^{626, 627}.

1236 Perhaps surprisingly, TNF appears to protect mice against experimental seizures, not only through the
1237 engagement of TNF-R2 but also through TNF-R1 signaling^{610, 628, 629, 630, 631, 632, 633} and consequent
1238 modulation of NF- κ B^{634, 635}. Conversely, *lpr/lpr* mice⁶³⁶, mice with neuron-specific deletion of the gene
1239 encoding TNF-R1⁶³⁷ as well as mice and rats treated with Z-IETD-FMK^{584, 638, 639} displayed a reduced
1240 sensitivity to experimental seizures, pointing to a detrimental role for apoptotic DR signaling in this
1241 condition. Precise mechanisms through which TNF-R1 signaling promotes anti-apoptotic and anti-
1242 inflammatory effects in the context of excitotoxic insults remain unclear.

1243 **Cardiovascular disorders.** Data from preclinical models of ischemic and non-ischemic conditions
1244 indicate the involvement of FASL, TRAIL and TNF in the onset and progression of myocardial infarction
1245 with reperfusion and other heart diseases. In particular, both *lpr/lpr* mice (lacking FAS), as well as hearts
1246 isolated from these animals, displayed reduced cardiomyocyte death and infarct area upon experimental
1247 ischemia-reperfusion^{640, 641}. Nonetheless, no protection against ischemia-reperfusion was found in hearts
1248 from *Fas*^{-/-} or *Fasl*^{-/-} mice⁶⁴². However, supporting the therapeutic potential of the inhibition of DR
1249 signaling for the management of myocardial infarction, FASL-neutralizing antibodies conferred
1250 cardioprotection, limited inflammation, and improved cardiac function in mice experiencing cardiac
1251 ischemia-reperfusion^{643, 644, 645}. Likewise, TRAIL blockade protected monkeys, pigs, and rats against
1252 experimental infarction by increasing cardiomyocyte survival and reducing inflammation⁶⁴⁶. This is in
1253 line with the predictive value of the levels of TRAIL as a biomarker for heart failure in patients^{647, 648}.
1254 Of note, TRAIL has also been reported to exert apoptosis-independent roles in cardiomyocyte growth
1255 and heart hypertrophy⁶⁴⁹ as well as in angiogenesis and neovascularization upon experimental hindlimb
1256 ischemia⁶⁵⁰. Similar to neurological conditions, while TNF-R2 signaling appears to exert
1257 cardioprotective effects, the engagement of TNF-R1 drives cardiac hypertrophy, inflammation and
1258 cardiomyocyte loss^{651, 652, 653, 654, 655, 656, 657, 658}. The opposite outcome of TNF-R1 vs TNF-R2 signaling
1259 has been invoked to explain the clinical failure of TNF blocking agents in patients with chronic heart

1260 failure⁶⁵⁹, despite encouraging preliminary findings^{660, 661}, as well as cardiotoxic effects associated with
1261 the use of TNF blockers in patients with rheumatoid arthritis⁶⁶². Confirming the involvement of extrinsic
1262 apoptosis in cardiac diseases, cardiomyocyte-specific deletion of *Fadd* in mice improved cardiomyocyte
1263 survival and heart function after ischemia/reperfusion⁶⁶³. Accordingly, haploinsufficiency of the gene
1264 encoding c-FLIP increased infarct area and aggravated cardiac dysfunction in mice subjected to
1265 myocardial infarction, while the cardiomyocyte-specific overexpression of c-FLIP attenuated pathology
1266^{664, 665}. Cardioprotection has been observed in a mouse model of ischemia/reperfusion upon shRNA-
1267 mediated CASP8 depletion⁶⁶⁶ or treatment with the CASP8 inhibitor Q-LETD-Oph⁶⁶⁷. Moreover,
1268 transplantation of *CASP8*^{-/-} cells did not increase neovascularization in wild-type mice subjected to
1269 hindlimb ischemia⁶⁶⁸, in line with a crucial role of CASP8 in the maintenance of endothelia in healthy
1270 conditions⁵⁹⁵ (see **Box 7**). That said, combined pharmacological inhibition of apoptosis and necroptosis
1271 exerted greater cardioprotection than monotherapy in myocardial ischemia-reperfusion injury⁶⁶⁹,
1272 suggesting the involvement of multiple RCD pathways in cardiovascular disorders.

1273 FASL neutralization has been reported to improve cardiomyocyte survival and cardiac function in a
1274 model of cirrhotic cardiomyopathy⁶⁷⁰. Conversely, a cardioprotective effect of TRAIL and TNF was
1275 observed in mice developing cardiomyopathy upon the deletion of apolipoprotein E (*ApoE*)⁶⁷¹ or desmin
1276 (*Des*)⁶⁷², respectively. Both FASL deficiency and administration of CASP8 inhibitors decrease tissue
1277 inflammation and aneurysm formation in mice subjected to CaCl₂-induced abdominal aortic aneurysms
1278⁶⁷³. A potential role of extrinsic apoptosis in gradual cardiomyocyte attrition during heart failure with
1279 reduced fraction was also reported in a transgenic mouse model of inducible CASP8 overexpression⁶⁷⁴.
1280 Concerning TNF receptors, deletion of *Tnfrsf1b* resulted in increased cardiomyocyte death and
1281 hypertrophy induced by isoproterenol⁶⁷⁵. In contrast, deletion of *Tnfrsf1a* (but not *Tnfrsf1b*) was shown
1282 to be cardioprotective in murine models of vascular thrombosis⁶⁷⁶, and heart failure based on angiotensin
1283 II administration⁶⁷⁷. Similar cardioprotection to angiotensin II was reported after silencing of *Tnfrsf1a*

1284 ⁶⁷⁸. In line with these findings, *Cflar*^{+/-} mice (which lack c-FLIP) displayed increased sensitivity to
1285 cardiac injury upon angiotensin II administration ⁶⁷⁹.

1286 FASL and TNF have also been reported to promote cardiac maladaptation and hypertrophy in models of
1287 pressure overload ^{680, 681, 682, 683, 684}. Consistent with this notion, TNF inhibition ⁶⁸⁵ or transgenic c-FLIP
1288 overexpression ⁶⁸⁶ limited experimental heart hypertrophy driven by hypertension. Moreover, treatment
1289 with etanercept reduced cardiac fibrosis in a diet-induced mouse model of obesity ⁶⁸⁷. Conversely, both
1290 FAS and TNF receptor superfamily member 10b (TNFRSF10B, best known as TRAIL-R2 or mTRAIL-
1291 R) were reported to protect mice against atherosclerosis, at least in part, by modulating TNF superfamily
1292 member 11 (TNFSF11, best known as RANKL) signaling ^{688, 689, 690, 691, 692}, while the impact of TNF on
1293 experimental atherosclerosis remains a matter of debate ^{693, 694, 695, 696}. Finally, pharmacological inhibition
1294 of TNF prevented cardiotoxicity induced by doxorubicin in mice ^{697, 698, 699}

1295 **Renal conditions.** FASL, TNF and TRAIL have all been implicated in the development of acute kidney
1296 injury by driving the activation of both extrinsic apoptosis and inflammation. Loss-of-function mutations
1297 in *Fasl*, inhibition or depletion of FASL ^{700, 701, 702} as well as *Fas* ⁷⁰³ or *Tnf* ⁷⁰⁴ silencing, TNF
1298 neutralization ^{705, 706}, or TRAIL blockade ⁷⁰⁷ exerted nephron-protective effects in mouse models of renal
1299 ischemia/reperfusion. Generation of chimeric mice reconstituted with spleen cells from *gld/gld* mice
1300 (lacking FAS ligand) revealed a particular impact of FASL signaling in the hematopoietic compartment
1301 on ischemic acute kidney injury ⁷⁰¹. However, some functional overlap between DRs has also been
1302 reported. Indeed, while one study suggested that FASL neutralization was more effective than *Tnfrsf1a*
1303 deletion (leading to lack of TNF-R1) in preventing renal inflammation and cell death after acute kidney
1304 injury ⁷⁰⁰, another study reported that the neutralization of TNF but not FASL prevented tubular apoptosis
1305 and renal atrophy upon ischemia/reperfusion injury ⁷⁰⁵.

1306 TRAIL blockade reportedly protected mice against renal damage after full-thickness scald burn, burn of
1307 all layers of the skin including epidermis and dermis ⁷⁰⁸, while TNF inhibition limited nephrotoxicity, in
1308 mice treated with cisplatin ⁷⁰⁹, and acute tubulointerstitial nephritis, in cancer patients administered with
1309 immune checkpoint inhibitors ⁷¹⁰. TNF neutralization also reduced tubulointerstitial fibrosis and renal
1310 injury in a mouse model of unilateral urethral obstruction ^{711, 712}. Contesting these findings, *Tnf*^{-/-} mice
1311 showed increased fibrosis at later stages of ureteral obstruction ⁷¹³. This apparent discrepancy may reflect
1312 the distinct contribution of TNF-R1 and TNF-R2 signaling to different stages of renal fibrosis driven by
1313 urethral obstruction ⁷¹⁴. Conversely, experiments with *lpr/lpr* mice subjected to unilateral urethral
1314 ligation demonstrated a limited impact of FAS signaling to pathology ⁷¹⁵. The involvement of CASP8 in
1315 acute kidney injury is debated. While *Casp8* and *Casp3* protected kidneys against damage induced by
1316 renal ischemia, increasing the survival of these mice ^{703, 716}, such a nephroprotective effect was not
1317 observed after treatment with the broad-spectrum caspase inhibitor Z-VAD-FMK ⁷¹⁷, potentially due to
1318 caspase inhibition promoting necroptosis after DR stimulation. In line with this notion, chemical
1319 inhibitors of receptor-interacting serine/threonine kinase 1 (RIPK1) as well as deletion of *Ripk3* exerted
1320 robust nephroprotection in mouse models of ischemia/reperfusion ^{717, 718}. However, combined deletion
1321 of *Casp8* and *Ripk3* did not extend the beneficial effects of the genetic loss of *Ripk3* and was associated
1322 with a more pronounced demise of tubular epithelial cells by intrinsic apoptosis ⁷¹⁹.

1323 DR activation has also been associated with chronic kidney disorders, but evidence involving CASP8-
1324 mediated apoptotic death is lacking. The conditional deletion of *Tnf* from macrophages ⁷²⁰, as well as the
1325 administration of TNF inhibitors ^{720, 721, 722, 723}, were reported to mediate beneficial effects in murine
1326 models of diabetic nephropathy. Conversely, the impact of TRAIL on this renal condition remains
1327 unclear ^{724, 725, 726}, like that of TNF on polycystic kidney disease ^{727, 728}. As for glomerular inflammation,
1328 *gld/gld* mice (lacking FAS ligand), as well as wild-type mice treated with TNF blockers, displayed

1329 reduced tissue damage during crescentic glomerulonephritis^{729, 730, 731, 732}. Indeed, balanced TNF-R1 and
1330 TNF-R2 signaling appeared to be critical for mice to resist experimentally induced glomerulonephritis
1331^{733, 734, 735, 736, 737, 738}. This may explain apparently discrepant findings obtained with TNF-targeting
1332 measures.

1333 **Hepatic disorders.** TNF-deficient mice, as well as rodents treated with TNF inhibitors, presented with
1334 attenuated liver injury and apoptosis upon experimental ischemia/reperfusion, resulting in improved
1335 survival^{739, 740, 741}. Of note, this beneficial effect could not always be recapitulated in *lpr/lpr* and *gld/gld*
1336 mice, lacking FAS or FAS ligand, respectively⁷⁴¹. Similarly, FAS inhibition, FASL neutralization, as
1337 well as administration of low-dose TNF (as a pre-conditioning maneuver) have been shown to protect
1338 the liver against ischemia/reperfusion injury by reducing hepatic cell apoptosis and/or inflammation^{742,}
1339^{743, 744}. Protection of the liver from ischemia/reperfusion has also been observed in mice deficient for
1340 TRAIL⁷⁴⁵, as well as upon the conditional knockdown of CASP8 or CASP3, the combined deletion of
1341 *Casp8* and *Ripk3*, and the transgenic expression of a BID mutant that cannot be cleaved by CASP8^{283,}
1342^{746, 747}.

1343 *Lpr/lpr* mice lacking FAS⁷⁴⁸, *Tnfsf10*^{-/-} mice (which lack TRAIL)²⁸⁶, as well as animals exposed to
1344 TRAIL blockers⁷⁴⁹, were protected against acetaminophen-induced liver damage, in line with the notion
1345 that FAS signaling and TRAIL receptor exacerbate acetaminophen hepatotoxicity⁷⁵⁰. Along similar
1346 lines, the hepatocyte-specific deletion of the gene encoding c-FLIP enhances liver injury and fibrosis
1347 induced by treatment with CCl₄ or thioacetamide⁷⁵¹. Moreover, a large body of evidence demonstrates
1348 that the abrogation of extrinsic apoptosis protects mice against fulminant hepatitis and hemorrhage in the
1349 liver induced by FASL and TNF. This has been achieved with strategies including (but not limited to)
1350 FADD blockade^{752, 753}, *Casp8*^{595, 754, 755} or *Fadd*⁷⁵⁶ ablation, and *Casp8* silencing⁷⁵⁷. Accordingly,
1351 hepatocyte-specific deletion of *Cflar* augmented liver damage in mouse model of acute hepatic injury

1352 ⁷⁵⁸. Consistent with the notion that engagement of the intrinsic apoptotic pathway is critical for DR
1353 induced cell killing in the liver, *Bid*^{-/-} mice resist fatal hepatitis and hepatocytes apoptosis induced by
1354 FAS or TNF ^{278, 282, 759, 760}, a protection enhanced by concomitant loss of BIM or CASP8 ²⁸². Conditional
1355 deletion of the genes encoding BAX, BAK1 or PUMA, as well as overexpression of BCL2, can also
1356 protect hepatocytes from FAS-induced killing ^{761, 762, 763, 764}. The impact of loss of BAD on TNF-induced
1357 hepatitis is controversial ^{765, 766}. Mice deficient for CASP3 or treated with CASP3 or CASP8 inhibitors
1358 have also been shown to be less sensitive to FAS-induced hepatocyte apoptosis ^{767, 768}. Of note, some
1359 degree of functional compensation between caspases and alternative mechanisms of caspase activation
1360 have emerged from studies in hepatocytes responding to FAS agonists ⁷⁶⁹. Finally, FAS and TNF-R1
1361 signaling, as well as FADD activation, are involved in liver regeneration following partial hepatectomy
1362 ^{770, 771, 772, 773, 774}. In this context, liver-specific deletion of *Casp8* resulted in dysregulated hepatocyte
1363 proliferation upon partial hepatectomy coupled to the initiation of an inflammatory response ⁷⁷⁵. It has
1364 been suggested that CASP8 modulates liver regeneration by balancing NF-κB activation and necroptosis
1365 rather than by inducing apoptosis ⁷⁷⁶.

1366 *Gld/gld* mice (lacking FAS ligand) chronically fed with ethanol displayed reduced liver injury, steatosis
1367 and inflammation as compared to wild-type mice, but exhibited signs of incipient fibrosis ⁷⁷⁷. Some
1368 degree of protection against alcohol-induced liver damage has also been documented in mice deficient
1369 for the apoptosis-inducing TRAIL receptor mTRAIL-R ⁷⁷⁸ or TNF-R1 (but not TNF-R2) ⁷⁷⁹, as well as
1370 in mice receiving a TRAIL-neutralizing antibody ⁷⁸⁰. Accordingly, the hepatocyte-specific ablation of
1371 *Casp8* limited hepatic steatosis in murine models of ethanol administration, although it failed to prevent
1372 apoptotic RCD ⁷⁸¹. Conversely, apoptosis driven in hepatocytes by chronic ethanol exposure could be
1373 abolished by systemic inhibition of CASP3 with Ac-DEVD-FMK ⁷⁸².

1374 The liver-restricted overexpression of FAS induces hepatic steatosis and insulin resistance in mice
1375 subjected to a high-fat diet (HFD)⁷⁸³. In the same experimental setting, hepato-protection was observed
1376 with the hepatocyte-specific ablation of *Fas* or germline deletion of *Bid*⁷⁸³. Moreover, *Tnf* deletion⁷⁸⁴,
1377 ⁷⁸⁵, whole-body deletion of *Tnfrsf1a* (encoding TNF-R1) alone or in combination with the gene encoding
1378 TNF-R2^{786, 787} as well as inhibition of TNF^{788, 789, 790} or TNF-R1⁷⁹¹ significantly reduced hepatic
1379 steatosis, fibrosis, damage, and metabolic alterations in several diet-induced or genetic models of non-
1380 alcoholic fatty liver disease (NAFLD). In apparent contrast with these findings, the hepatocyte-specific
1381 deletion of *Tnfrsf1a* failed to protect mice from diet-driven NASH⁷⁹². Moreover, *Tnfrsf1a* deletion
1382 accelerated progression of steatosis to steatohepatitis in mice on HFD⁷⁹³. Taken together, these findings
1383 underscore the pleiotropic and context-dependent effects of TNF/TNF-R signaling in NAFLD. The
1384 impact of TRAIL on NAFLD is also debated. Indeed, contrasting evidence from experiments with mice
1385 deficient for TRAIL or treated with recombinant TRAIL suggests either a detrimental or a beneficial role
1386 to TRAIL in NAFLD induced by HFD^{794, 795, 796}.

1387 The absence of mTRAIL-R promoted hepatic inflammation and fibrosis in a genetic mouse model of
1388 cholestasis⁷⁹⁷. Similarly, *lpr/lpr* mice lacking FAS^{798, 799, 800} as well as TNF-deficient^{801, 802} and TRAIL-
1389 deficient^{803, 804} mice displayed reduced hepatocyte apoptosis and fibrogenesis after experimental
1390 cholestasis induced by bile duct ligation. In line with these results, expression of a phosphorylated FADD
1391 mimicking mutant resulted in attenuated HFD-induced hepatomegaly and steatosis⁸⁰⁵. Experiments
1392 based on the hepatocyte-specific deletion of *Cflar* (encoding c-FLIP) or transgenic overexpression of c-
1393 FLIP revealed a role for this modulator of CASP8 activation as a suppressor of hepatic steatosis and
1394 inflammation induced by HFD⁸⁰⁶. Moreover, the hepatocyte-specific deletion of *Cflar* in mice resulted
1395 in enhanced cholestatic liver injury and inflammatory responses upon bile duct ligation⁸⁰⁷. Moreover,
1396 the hepatocyte-specific deletion of *Casp8* protected mice against liver injury in models of cholestatic
1397 hepatitis caused by the administration of 3,5-diethoxycarbonyl-1,4-dihydrocollidine⁸⁰⁸, as well as in

1398 models of steatosis caused by the feeding of a methionine- and choline-deficient diet ⁸⁰⁹. A similar
1399 hepato-protection against obstructive cholestasis has been documented in mice with hepatocyte-specific
1400 *Casp8* deletion ⁸¹⁰. Furthermore, liver parenchymal cell-specific ablation of the gene encoding FADD
1401 prevented RIPK1-dependent but not TNF-R1-, FAS-, and TRAIL-R-independent hepatocyte apoptosis,
1402 chronic liver inflammation and hepato-carcinogenesis in mice with liver-specific deficiency in Inhibitor
1403 Of Nuclear Factor Kappa B Kinase Regulatory Subunit Gamma (IKBKG, best known as NEMO or
1404 IKKgamma) ^{811, 812}. Finally, decreased BID cleavage has been associated with attenuated liver injury in
1405 mouse models of chronic cholestasis ⁸¹³.

1406 **Hematologic malignancies and solid cancers.**

1407 Human patients with autoimmune lymphoproliferative syndrome (ALPS) caused by defects in FAS are
1408 known to show abnormally increased predisposition to lymphoma development ⁸¹⁴. Accordingly, FAS-
1409 deficient *lpr/lpr* mice develop plasmacytoma-like disease in advanced age ⁸¹⁵. TRAIL also seems to exert
1410 a tumor suppressive function in lymphomagenesis. The ablation of the gene encoding mTRAIL-R
1411 accelerated the development of lymphoma in *Eμ-Myc* transgenic mice ⁸¹⁶. Moreover, deficiency in
1412 TRAIL (but not in mTRAIL-R) promoted the development of lymphoma and other tumors in mice with
1413 haploinsufficiency for *Trp53* ^{817, 818}. Interestingly, mice engineered to express exclusively either
1414 membrane-bound or secreted FasL showed an increased incidence of spontaneous tumor formation when
1415 expressing only soluble FasL which was unable to induce FAS-mediated apoptosis but could exert
1416 inflammatory effects ⁸¹⁹.

1417 The role of FAS and TRAIL-R in the development of colorectal cancer is controversial. For instance, the
1418 loss of FAS was reported to enhance APC mutation induced but not inflammation induced intestinal
1419 tumorigenesis ^{820, 821, 822}. Along similar lines, while the ablation of *Tnfrsf10b* (leading to lack of mTRAIL-
1420 R) in mice did not impact tumorigenesis induced by *Apc* mutations ⁸¹⁸, the administration of TRAIL

1421 suppressed tumorigenesis in a mouse model of colitis-associated colon cancer ⁸²³. Despite some
1422 contention in this respect ^{824, 825, 826, 827}, TNF seems to contribute to the development of colorectal cancer,
1423 although whether such effects depend on the apoptotic function of TNF needs further demonstration. The
1424 administration of TNF blockers ^{828, 829, 830, 831, 832} or ablation of *Tnf* ⁸³³ or *Tnfrsf1a* ^{833, 834} limited tumor
1425 development, as shown in animal models of colorectal cancer induced by colitis, chemicals, or a mutation
1426 in *Apc*. Finally, loss of the dependence receptor DCC netrin 1 receptor (*Dcc*) accelerated cancer
1427 progression in a mouse model of *Apc* mutation driven colorectal oncogenesis ⁸³⁵. A tumor suppressor
1428 role in colorectal cancer is also described for the dependence neurotrophic tyrosine kinase, receptor, type
1429 3 (*Ntrk3*, best known as *TrkC*) ⁸³⁶. Of note, the association between gain of dependence receptors ligands
1430 (e.g., *NTN1*) with tumor progression ⁸³⁷, may make their targeting a promising anti-cancer approach ⁸³⁸
1431 (<https://clinicaltrials.gov>).

1432 With regard to other tumor types, both TNF-R1 and FAS displayed a pro-oncogenic role in hepatic and
1433 ovarian oncogenesis. Thus, conditional deletion of *Fas* in hepatocytes delayed chemically-induced
1434 hepato-carcinogenesis, while *Fas* ablation suppressed the development of ovarian tumors in phosphatase
1435 and tensin homolog (*PTEN*)-deficient/Kirsten rat sarcoma viral oncogene (*KRAS*) mutated mice ⁸³⁹.
1436 Likewise, TNF neutralization limited the onset of hepatic cancer driven by experimentally induced
1437 cholestatic hepatitis ⁸⁴⁰. Consistent with these findings, *Casp8*^{-/-} mice are protected against the
1438 development of inflammation-driven liver cancer ⁷⁵⁴. Hyperactivation of *CASP8* in the context of *RIPK1*
1439 and TNF receptor-associated factor 2 (*TRAF2*) deficiency has been implicated in the development of
1440 hepatocellular carcinoma ⁸⁴¹ although such effects may be independent of apoptosis induction ^{842, 843}. In
1441 contrast, recent studies show a tumor-suppressive function of *CASP8* in the liver and certain other tissues
1442 ^{844, 845, 846, 847}. In particular, there is evidence of a role of *CASP8* in early tumorigenesis (but not tumor
1443 progression) exerted by modulating the DNA damage response ⁸⁴⁴ or the level of chromosomal instability
1444 (*CIN*) ⁸⁴⁵.

1445 Consistent with a pro-tumorigenic effect of TNF, the ablation of *Tnf* or *Tnfrsf1a* or the blockade of TNF
1446 in mice conferred some protection against chemically-induced skin cancer development^{848, 849, 850, 851, 852,}
1447⁸⁵³. In contrast, the impact of genetic and pharmacological inhibition of TNF in UVB-induced skin cancer
1448 is debated^{854, 855}. Of note, the comparison between TNF-R1- vs. TNF-R2-deficient mice revealed a
1449 primary role of TNF-R1 in chemically induced skin oncogenesis⁸⁵⁰. Furthermore, TNF-R1 deficiency
1450 suppressed the development of skin cancer induced by NF-κB inhibition⁸⁵⁶. A similar role for TNF-R1
1451 in supporting tumorigenesis was described in murine models of N-methyl-N-nitrosourea/testosterone-
1452 induced prostate cancer⁸⁵⁷ and methylcholanthrene (MCA)-induced fibrosarcoma⁸⁵⁸. As opposed to
1453 TNF-R1, TNF-R2 shows tumor-suppressive functions in mouse models of tumorigenesis, such as the
1454 development of fibrosarcoma triggered by MCA⁸⁵⁸ and of breast cancer induced by transgenic
1455 expression of wingless-type MMTV integration site family, member 1 (*Wnt1*)⁸⁵⁹. Moreover, the absence
1456 of TNF impaired tumor growth in HER2-driven mammary tumorigenesis in mice⁸⁶⁰ and TNF
1457 neutralization suppressed chemically-induced oral⁸⁶¹ and urethane-induced pulmonary⁸⁶²
1458 tumorigenesis. Conversely, TNF overexpression in the airway epithelium enhanced mutant KRAS-
1459 driven lung cancer development⁸⁶³.

1460 Pre-clinical evidence indicates some tumor type-specificity for the role of TRAIL and its receptor(s) in
1461 tumorigenesis. Transgenic expression of TRAIL in the skin delayed chemically induced carcinogenesis
1462⁸⁶⁴. This effect was recapitulated in mice lacking TRADD⁸⁶⁵ but, curiously, not in mTRAIL-R-deficient
1463 mice⁸⁶⁶, with the latter actually showing enhanced lymph node metastasis. In support of an anti-tumor
1464 function for the TRAIL/TRAIL-R system, TRAIL-deficient mice as well as mice treated with TRAIL
1465 blockers displayed increased susceptibility to MCA-induced fibrosarcoma^{867, 868}. In a recent study the
1466 combined treatment with recombinant TRAIL and inhibition of cyclin-dependent kinase 9 (CDK9) was
1467 effective in a wide range of cancers⁸⁶⁹. Yet in contrast to this and in support of a tumor-supportive role

1468 of endogenous TRAIL, deficiency in mTRAIL-R limited tumor growth and improved survival in a mouse
1469 model of mutant KRAS-driven lung and pancreatic tumorigenesis⁸⁷⁰. Moreover, malignant cell-specific
1470 ablation of genes encoding mTRAIL-R or FADD reduced lung cancer growth and tumor-protective
1471 inflammation⁸⁷¹, while systemic ablation of *Tnfsf10* (leading to lack of TRAIL) had no impact on HER-
1472 2 driven breast oncogenesis⁸¹⁷. Interestingly, KRAS mutations have been shown to promote the switch
1473 of FAS and TRAIL receptors from a predominantly death-inducing into a metastasis promoting function
1474⁸⁷². Since TRAIL as well as FASL can trigger either apoptosis, necroptosis, inflammatory or pro-invasive
1475 signaling, cancer-specific preferences for one or the other of these signaling outputs likely accounts for
1476 the pleiotropic effects observed in various cancer models.

1477 **Autoimmune and inflammatory diseases.** The interpretation of results on the impact of extrinsic
1478 apoptosis in the etiology of autoimmune and inflammatory disease should consider the fact that DR
1479 engagement can also result in the initiation of an inflammatory response not related to RCD (*see* **Box 6**
1480 and **Box 7**), meaning that DR deregulation may lead to inflammatory diseases independently of the
1481 induction of extrinsic apoptosis. The notion that defects in DR signaling can cause autoimmune disease
1482 is supported by the observation that *lpr/lpr* as well as *gld/gld* mutant mice, deficient for FAS or FAS
1483 ligand, respectively, as well as humans with defects in FAS develop systemic lupus erythematosus
1484 (SLE)-like autoimmune disease accompanied by lymphadenopathy, splenomegaly and hepatomegaly⁸⁷³,
1485⁸⁷⁴. A critical role for loss of caspase-CASP8 mediated apoptosis in this disease was demonstrated by the
1486 observation that similar autoimmune disease is seen in mice lacking CASP8 and also RIPK3 or MLKL
1487 (to prevent necroptosis)^{51, 52, 875}. However, the roles of DRs in autoimmune disease are complex.
1488 TRAIL/TRAIL-R signaling was reported to protect mice and rats against autoimmune encephalomyelitis
1489^{876, 877, 878, 879, 880, 881}, autoimmune arthritis^{882, 883, 884, 885, 886} and type I diabetes^{689, 882, 887, 888, 889, 890}. Perhaps
1490 surprisingly, the presence of FAS and TNF-R1 is associated with the development of certain autoimmune
1491 conditions. Indeed, both *lpr/lpr* lacking FAS and *gld/gld* mice lacking FAS ligand, as well as TNF-R1-

1492 deficient mice, were reported to be protected against experimental encephalomyelitis ^{891, 892, 893, 894}.

1493 Similar results were obtained in mice with *Tnf* deletion in monocytes and macrophages but not in mice

1494 lacking TNF in microglial cells ⁸⁹⁵. Protection against experimentally induced autoimmune conditions

1495 were also found in mice subjected to neutralization of TNF or TNF-R1 inhibition ^{896, 897, 898, 899, 900, 901, 902,}

1496 ⁹⁰³. FAS-independent mechanisms also appear to support the pathogenesis of experimental autoimmune

1497 encephalomyelitis ^{891, 904}, with some studies pointing to a protective role for FAS-induced RCD amongst

1498 lymphocytes in this disease model ⁹⁰⁵. Moreover, FAS engagement was reported to differentially

1499 contribute to the initiation vs. the recovery from autoimmune encephalomyelitis ^{906, 907}. In particular,

1500 FASL expression in astrocytes appears to promote recovery from experimental autoimmune

1501 encephalomyelitis, as shown by persisting demyelination and paralysis of mice with an astrocyte

1502 restricted deletion of the *Fasl* gene ⁹⁰⁶. Finally, at least in some studies, *Tnf* deletion or TNF neutralization

1503 failed to attenuate the severity of autoimmune encephalomyelitis once the disease was established ^{908, 909}.

1504 Mice with defects in FASL or TNF signaling are protected against arthritis induced by immunization

1505 with xenogeneic type II collagen in complete Freund's adjuvant ^{910, 911, 912, 913}. Similar protection was

1506 observed in mice transplanted with mesenchymal stem cells engineered to express TNF inhibitors ⁹¹⁴. In

1507 keeping with this evidence, the myeloid cell specific deletion of *Fas* or the administration of antibodies

1508 that target both TNF and chemokine (C-X-C motif) ligand 10 (CXCL10) resulted in accelerated disease

1509 resolution in a model of rheumatoid arthritis induced by K/BxN serum transfer ^{915, 916}. Genetic loss of

1510 *Fas* or pharmacological inhibition of FAS conferred protection against autoimmune diabetes in certain

1511 animal models, including NOD mice ^{917, 918, 919, 920, 921, 922}. However, whether the impact of FAS on the

1512 pathogenesis of autoimmune diabetes depends on its role in the death of pancreatic β -cell ⁹¹⁷ or its role

1513 in inflammation (*e.g.*, in the context of insulinitis) remains a matter of debate ⁹²⁰. Conversely, other studies

1514 found no role for FAS in diabetes ^{923, 924, 925}. TNF neutralization is effective only in a limited sub-group

1515 of patients with inflammatory bowel disease ^{926, 927}. This is in line with the finding that deletion of the

1516 gene encoding TNF-R1 exacerbated colitis in interleukin 10 (IL10)-deficient mice⁹²⁸. Similar protection
1517 was ascribed to TRAIL/TRAIL-R signaling in a dextran sodium sulfate-induced model of colitis model
1518^{929, 930}. Finally, it has been suggested that FASL and TNF signaling contribute to the pathogenesis of
1519 acute pancreatitis^{931, 932}. A similar detrimental role has been proposed for TNF in autoimmune neuritis
1520^{933, 934, 935}, although there is also some contention⁹³⁶, as well as in spondylarthritis⁹³⁷ and psoriasis⁹³⁸.
1521 Conversely, mTRAIL-R appears to mediate beneficial effects in autoimmune thyroiditis^{939, 940, 941, 942, 943}
1522 At least in part, these findings reflect the pleiotropic effects of whole-body/systemic inhibition of DRs
1523 signaling, which concomitantly impacts both the target (*i.e.*, parenchymal) and the perpetrator (*i.e.*,
1524 immune cells) of damage.

1525 Some experimental evidence links CASP8 activation to autoimmune and inflammatory disorders. In a
1526 recent study using a chemically-induced model of intestinal inflammation, the selective absence of
1527 CASP8 in intestinal epithelial cells decreased their survival, also resulting in gut barrier dysfunction and
1528 chronic inflammation⁹⁴⁴. Of note, in these settings, inflammation can occur via a mechanism independent
1529 of the induction of necroptosis (which is inhibited by CASP8) and involving the activation of RIPK1 and
1530 the RNA Sensor RIG-I pathway^{945, 946}. Along similar lines, chronic proliferative dermatitis in mice
1531 deficient for components of the linear ubiquitin chain assembly complex (LUBAC) was associated with
1532 an increased keratinocyte apoptosis mediated by the engagement of TN-FR1 and the activation of the
1533 RIPK1- and/or FADD-CASP8 cascade^{947, 948, 949, 950, 951}. Importantly in this mouse model of an
1534 inflammatory disease the relevant contributions of cell death versus inflammatory signalling from TNF-
1535 R1 were genetically dissected demonstrating that excess apoptosis/necroptosis drove different elements
1536 of the inflammatory response depending upon the affected tissue. Concerning autoimmunity, in a mouse
1537 model of autoimmune encephalomyelitis, the oligodendrocyte-specific deletion of *Fadd* reduced
1538 demyelination and this was accompanied by limited immune cell infiltration in the spinal cord⁹⁵².
1539 Likewise, experimental autoimmune encephalomyelitis could be prevented by transgenic expression of

1540 FADD-DN (dominant negative form of FADD) in T cells ⁹⁵³ but it must be noted that this kills antigen
1541 receptor activated T cells ⁹⁵⁴. Therefore, this protective effect is due to the removal of the T cells that
1542 would cause tissue destruction. Activation of CASP8 was identified in the microglia of patients with
1543 multiple sclerosis ⁹⁵⁵. Moreover, transgenic expression of FADD-DN or *Casp8* ablation in pancreatic β
1544 cells protected mice from autoimmune diabetes ⁹⁵⁶. This indicates that the killing of these cells is
1545 mediated by death receptor induced apoptosis. BID appears to be dispensable for the development of
1546 diabetes in NOD mice ⁹⁵⁷.

1547 There are also contrasting observations on the impact of DR-induced apoptosis on the development and
1548 resolution of autoimmune rheumatoid arthritis. The absence of c-FLIP (due to *Cflar* deletion) resulted in
1549 increased disease severity but limited disease resolution in mice experiencing arthritis upon
1550 intraperitoneal injection of serum from mice expressing both the T cell receptor transgene KRN and the
1551 MHC class II molecule A(g7) (K/BxN mice) ⁹⁵⁸. In the same model, deletion of *Casp8* in all myeloid
1552 cells enhanced disease resolution, while deletion of *Casp8* selectively in dendritic cells accelerated
1553 disease onset ⁹⁵⁹. Further experiments are required to unveil the reasons for such cell type specificity for
1554 the role of CASP8 to help more clearly understand the role of extrinsic apoptosis in this and other
1555 autoimmune disorders.

1556 **Infectious diseases.** Extrinsic apoptosis is reported to act as an anti-infective mechanism. FAS deficient
1557 *lpr/lpr*, FAS ligand deficient *gld/gld* and *Bid*^{-/-} mice exhibit delayed clearance of *Citrobacter rodentium*
1558 and increased intestinal pathology ⁹⁶⁰. Confirming the importance of DR-induced apoptosis, this
1559 pathogen was shown to inhibit extrinsic apoptosis of infected enterocytes by expressing specific
1560 virulence proteins, such as N-acetylglucosamine transferase NleB1, which prevents FADD-mediated
1561 recruitment and activation of CASP8 ⁹⁶⁰ Li, 2013, 23955153 Li, 2013, 23955153 Li, 2013, 23955153 Li, 2013, 23955153. Along
1562 similar lines, *Fas*^{-/-} mice had shorter lifespan than wild-type mice after challenge with *Listeria*

1563 *monocytogenes*, succumbing to neurolisteriosis. This was proposed to be promoted by an impaired loss
1564 of monocytes due to upregulated expression of c-FLIP by the bacterial protein InlB ⁹⁶¹. In support of this
1565 result, conditional deletion of *Cflar* in myeloid cells improved *Listeria monocytogenes* clearance and
1566 animal survival ⁹⁶². FAS signaling also conferred protection from infection with (i) human herpes simplex
1567 virus 2 (HSV-2), as demonstrated by a decrease in the loss of monocyte and immune cell recruitment at
1568 the infection site in *Fas*^{-/-} and *Fasl*^{-/-} mice ⁹⁶³, and (ii) *Citrobacter rodentium* or lymphocytic
1569 choriomeningitis virus, as demonstrated by an increased neutrophil fraction in mice with conditional
1570 deletion of *Fas* in the myeloid compartment ⁹⁶⁴.

1571 Supporting an anti-infection role of CASP8, mice lacking RIPK1 kinase activity failed to control
1572 systemic *Yersinia* infection, rapidly dying because of excess apoptosis driven by a kinase independent
1573 function of RIPK1 ^{965, 966}. In line with this finding, *Ripk3*^{-/-}*Casp8*^{-/-} but not *Ripk3*^{-/-} mice died from
1574 *Toxoplasma gondii* infection due to acute toxoplasmosis, an observation supporting the anti-infection
1575 role of CASP8-mediated apoptosis ⁹⁶⁷. Moreover, hepatocyte-specific deficiency for CASP8 facilitated
1576 liver infection of mice by *Listeria monocytogenes*, resulting in inflammation and development of necrotic
1577 lesions in the liver ⁷⁷⁵. These results also suggest an interconnection of multiple RCD pathways in
1578 controlling infection. Accordingly, the deletion of Z-DNA binding protein 1 (*Zbp1*), an essential
1579 cytoplasmic sensor of Influenza A virus (IAV) Z-RNA required for the activation of mixed lineage kinase
1580 domain like pseudokinase (MLKL)-dependent necroptosis, RIPK1/FADD-dependent apoptosis and
1581 NLRP3 inflammasome-dependent pyroptosis, as well as co-deletion of the genes encoding MLKL and
1582 FADD, caused a defect in the control of Influenza A virus (IAV) infection, with these mutant mice
1583 succumbing to lethal respiratory failure. These findings support an essential role of apoptosis, necroptosis
1584 and pyroptosis in IAV clearance ^{968, 969 Oltean, 2021, 33976111, Nogusa, 2016, 27321907, Zhang, 2020, 32200799 Oltean, 2021,}
1585 ^{33976111, Nogusa, 2016, 27321907, Zhang, 2020, 32200799 Oltean, 2021, 33976111, Nogusa, 2016, 27321907, Zhang, 2020, 32200799 Oltean, 2021,}
1586 ^{33976111, Nogusa, 2016, 27321907, Zhang, 2020, 32200799}. Similarly, combined activation of apoptosis and other RCD

1587 pathways contribute to the response of mice to *Burkholderia thailandensis* infection ⁹⁷⁰. Finally,
1588 pharmacological or tissue specific genetic deletion of cIAP1 and cIAP2 results in better control of
1589 hepatitis B virus and liver stage malaria parasites due to increased TNF induced death of infected cells
1590 (Ebert, 2015 25902529; Ebert 2015, 25902530; Ebert 2020, 32234472).

1591 Experimental evidence also suggests a detrimental role of extrinsic apoptosis during certain infections.
1592 Mice deficient for both TNF-R1 and TNF-R2 displayed decreased sensitivity to lipopolysaccharide,
1593 suggesting a critical role for TNF in tissue injury during gram-negative bacterial infection ⁹⁷¹. Along
1594 similar lines, TNF-R1-deficient mice were more resistant than wild-type mice to the cytopathic effects
1595 of TNF during Sindbis virus infection, as evidenced by reduced mortality and delayed paralysis ⁹⁷².
1596 Moreover, ablation of *Ripk1* protected mice from acute liver injury after infection with *Listeria*
1597 *monocytogenes* ⁹⁷³, while knockout of *Fas* or *FasL* reduced the effect of toxin A-induced enteritis in mice
1598 infected with *Clostridium difficile*, which has been attributed to a reduction in enterocyte loss ⁹⁷⁴.
1599 Additionally, the infectious spleen and kidney necrosis virus (ISKNV) induced tissue damage in
1600 zebrafish by activation of DR-induced apoptosis by a viral protein encoding a TRADD interactor ⁹⁷⁵. Of
1601 note, in this study, the absence of CASP8 protected zebrafish from ISKNV infection. Finally,
1602 *Ripk3^{-/-}Casp8^{-/-}* mice exhibited high levels of protection from LPS-induced septic shock ⁹⁷⁶ or a lethal
1603 cytokine shock and tissue damage driven by TNF and IFN- γ , mirroring that of SARS-CoV-2 ⁹⁷⁷. This
1604 evidence suggests that the combination of several types of RCD can also mediate infection-associated
1605 pathogenesis, as demonstrated for infection with *Salmonella* ⁵⁰.

1606 **Other diseases.** TNF is reported to impair myogenesis in a mouse model of skeletal muscle regeneration
1607 after hindlimb immobilization (hindlimb suspension) ⁹⁷⁸. Moreover, silencing of TRAIL improved
1608 muscle regeneration in mice with acute skeletal muscle injury due to local injection of BaCl₂ ⁹⁷⁹. An
1609 inhibitory role in myogenesis was also ascribed to FADD, at least in response to freezing-induced muscle

1610 injury⁹⁸⁰. In apparent contrast with this result, combined deletion of the genes encoding TNF-R1 and
1611 TNF-R2 limited skeletal muscle regeneration after cardiotoxin-induced injury^{981, 982}, suggesting the
1612 relevance of a balance between TNF-R1 and TNF-R2 signaling in this model. TRAIL neutralization
1613 increased muscular strength in a mouse model of Duchenne muscular dystrophy⁹⁸³, while other studies
1614 associated TRAIL and FASL to myositis^{984, 985}.

1615 Activation of DRs has also been implicated in the pathogenesis of acute lung injury. *Fas* silencing as
1616 well as TNF neutralization protected mice from lung injury induced by ischemia-reperfusion^{986, 987}.
1617 Similarly, deletion of *Tnfrsf1a* (encoding TNF-R1) or pharmacological inhibition of TNF-R1 or CASP8
1618 attenuated pulmonary edema formation and improved alveolar epithelial function in a murine model of
1619 acute lung injury induced by acid inhalation^{988, 989}. A similar protective effect was provided by
1620 pharmacological inhibition or genetic deletion of FASL or TNF in a lipopolysaccharide-induced mouse
1621 model of acute lung injury^{990, 991, 992, 993, 994, 995, 996}. However, in one study FAS signaling was shown to
1622 contribute to the resolution of acute lung injury by promoting the depletion of macrophages⁹⁹⁷. Using
1623 distinct mouse models of acute lung damage following sepsis, it was shown that the abrogation of FAS
1624 and TNF-R1 signaling, including the silencing of *Fadd*, decreased pulmonary apoptosis and ameliorated
1625 pathology, and in some cases this led to a survival benefit for the animals (e.g.,^{998, 999, 1000, 1001, 1002, 1003,}
1626¹⁰⁰⁴). Hyperoxia-induced lung injury and bleomycin-induced pulmonary fibrosis, a model for cancer
1627 therapy-induced lung injury, are also impacted by the DR pathway. FAS and TNF deficiency exacerbated
1628 hyperoxia-induced lung injury and/or inflammation in newborn mice^{1005, 1006}. In contrast, TNF inhibition
1629 conferred protection against hyperoxia-induced lung damage in a murine model^{1007, 1008, 1009}. Moreover,
1630 the absence of TNF-R1 (but not the absence of TNF-R2) improved survival in mice subjected to
1631 excessive oxygen supply, although without decreasing inflammation¹⁰¹⁰. In support of these results,
1632 specific ablation of *Fas* in murine fibroblasts or T cells exacerbated pulmonary fibrosis induced by
1633 bleomycin^{1011, 1012}. However, the level of bleomycin-induced pulmonary fibrosis was diminished in FAS

1634 deficient *lpr/lpr* or FAS ligand deficient *gld/gld* mice¹⁰¹³ and remained unchanged in mice treated with
1635 FAS neutralizing agents¹⁰¹⁴. Likewise, contrasting findings support or refute a role for TNF^{1015, 1016, 1017}
1636 and TRAIL^{1018, 1019} in both the onset and resolution of pulmonary fibrosis after administration of
1637 bleomycin. TNF neutralization has been reported to attenuate and enhance interstitial pulmonary fibrosis
1638 induced by nitrogen mustard¹⁰²⁰ or rituximab¹⁰²¹. Finally, FASL, TNF and/or TRAIL have been
1639 implicated in infectious or non-infectious lung disorders, including (but not limited to) infection with
1640 respiratory syncytial virus (RSV)^{1022, 1023, 1024, 1025, 1026, 1027, 1028}, adenovirus type 1 respiratory disease¹⁰²⁹,
1641 ¹⁰³⁰, allergic reaction and asthma^{1031, 1032, 1033, 1034, 1035, 1036, 1037, 1038, 1039, 1040, 1041, 1042} and idiopathic
1642 pneumonia syndrome¹⁰⁴³, as well as to chronic lung diseases (e.g., chronic obstructive pulmonary
1643 disease)^{863, 1044, 1045}.

1644 The studies discussed above illustrate that DR-induced apoptosis is at the heart of many disorders either
1645 promoting recovery or exacerbating disease. The active involvement in disease severity and progression
1646 makes this pathway a potentially tractable target for therapeutic interventions in a wide range of diseases,
1647 typically those with an inflammatory component. However, this effect may be linked to the role of DR
1648 signaling in other RCD pathways and in inflammation. Moreover, there is little consensus on the roles
1649 of FASL, TNF and/or TRAIL, highlighting a high complexity of the systems which needs further
1650 investigation.

1651 **Concluding remarks**

1652 Abundant preclinical evidence demonstrates that the intrinsic and the extrinsic pathways of apoptosis not
1653 only contribute to adult tissue homeostasis and, in the case of the intrinsic pathway, to embryonic
1654 development – the implication of CASP8 in normal development is mainly linked to its role as
1655 necroptosis inhibitor (*see Box 6 and Box 7*) - but also contribute to the pathogenesis of multiple diseases,
1656 including various cardiovascular, hepatic, neurological and renal disorders as well as multiple infectious,

1657 autoimmune, inflammatory and oncological conditions. However, despite great potential as targets for
1658 therapeutic interventions and a considerable research effort dedicated to developing effective approaches,
1659 the success of intrinsic or extrinsic apoptosis-targeting agents in clinical settings is so far limited to BH3
1660 mimetic drugs, SMAC mimetics, caspase inhibitors as well as activators or inhibitors of DR signaling,
1661 with only one compound, the BCL-2 inhibitor venetoclax (BH3 mimetic drug), approved for routine
1662 treatment of patients with CLL or AML.

1663 Rather than mitigating the enthusiasm about the clinical potential of modulators of apoptosis, this
1664 challenge suggests the need for a substantial change in the experimental design and re-interpretation of
1665 results, at different levels (**Figure 1**). One major issue is that studies evaluating the impact of apoptotic
1666 cell death on disease have not always addressed the connections between the core components of the
1667 intrinsic and extrinsic apoptotic machinery or their potential interaction and functional overlap with other
1668 RCD pathways. Also, the potential activation of alternative RCD modalities as a mechanism to
1669 compensate for the inhibition of apoptotic RCD has not always been explored and thus it has not been
1670 tried to prevent or overcome these alternative forms of RCD to achieve superior outcomes. The
1671 importance of independent replication of findings that suggest success from targeting a pathway in the
1672 treatment of a disease cannot be emphasized enough. Only then can the costly process of clinical
1673 translation be approached with confidence and with an increased chance of success. For example, the
1674 findings that overexpression of BCL2 or its pro-survival relatives can promote tumorigenesis and can
1675 render malignant cells resistant to diverse anti-cancer therapeutics had been reproduced hundreds of
1676 times before BH3 mimetic drug development was started. This is not yet the case for many of the other
1677 studies discussed here, as best demonstrated by the fact that for certain experiments diametrically
1678 opposing results were reported by different groups. These questions must be resolved before considering
1679 drug development programs.

1680 Moreover, certain regulators of apoptosis and signaling cascades have been reported to exert a variety of
1681 functions beyond cell death control, including (but not limited to) inflammation (*e.g.*, multiple activated
1682 caspases and IAPs), cell differentiation (*e.g.*, pro-and anti-apoptotic BCL2 proteins), cell proliferation
1683 and survival (*e.g.*, DR engagement). The relevance of these functions is often dependent on cell/tissue
1684 type (as it is related to variable expression levels and activation status of other regulators of RCD) and
1685 the intensity and duration of the initiating stimulus (as they can direct to a distinct biological outcome,
1686 as exemplified by DR ligation). Of note, some of these cell death unrelated functions of *bona fide* cell
1687 death regulators are highly controversial and much more work must be done to verify or discard these
1688 notions. On the one hand, this pleiotropy may result in a variable (even including an antagonistic
1689 protective *vs.* promoting) impact of apoptosis on distinct human diseases, also explaining the
1690 considerable degree of context-dependency (*e.g.*, effect of stromal and immune cells) observed for its
1691 experimental modulation. On the other, the pathogenic effect of core components of the apoptotic
1692 machinery is often mediated by such apoptosis-unrelated functions including inflammation, which may
1693 point to unexplored targets for the development of new therapeutic agents or approaches.

1694 In our opinion, investigating the molecular cascade of apoptotic cell death in the context of the functional
1695 inter-connection between apoptotic and non-apoptotic pathways, for instance by interrupting some of the
1696 molecular connections between different RCD signaling cascades, may instigate new advances,
1697 ultimately leading to clinical use of specific apoptosis-modulatory agents for the treatment of many
1698 diseases.

1699

1700 **Author's contributions.** L.G. and I.V. conceived the review. I.V., L.G. and F.P. wrote the first version of the manuscript
1701 with constructive input from all authors. E.G., C.G and G.M. prepared display items under the supervision of L.G. and I.V.

1702 L.G., I.V. and F.P. addressed requests from the Reviewers and Editors of *Cell Death and Differentiation*. All authors approved
1703 the final version of the article and figures.

1704 **Funding and acknowledgments:** I.V. is and has been supported by the Associazione Italiana per la Ricerca sul Cancro
1705 (AIRC, IG 2017 #20417 and IG 2022 #27685) and a startup grant from the Italian Institute for Genomic Medicine (Candiolo,
1706 Turin, Italy) and Compagnia di San Paolo (Torino, Italy). M.P., G.M., S.M., G.C. are supported by the Ministro dell'Università
1707 (Italy) progetto Heal Italia PE6. L.G. (as a PI unless otherwise indicated) is or has been supported by two Breakthrough Level
1708 2 grants from the US DoD BCRP (#BC180476P1; #BC210945), by a Transformative Breast Cancer Consortium Grant from
1709 the US DoD BCRP (#W81XWH2120034, PI: Formenti), by a U54 grant from NIH/NCI (#CA274291, PI: Deasy, Formenti,
1710 Weichselbaum), by a STARR Cancer Consortium grant (#I16-0064), by the 2019 Laura Ziskin Prize in Translational Research
1711 (#ZP-6177, PI: Formenti) from the Stand Up to Cancer (SU2C), by a Mantle Cell Lymphoma Research Initiative (MCL-RI,
1712 PI: Chen-Kiang) grant from the Leukemia and Lymphoma Society (LLS), by a Rapid Response Grant from the Functional
1713 Genomics Initiative (New York, US), by startup funds from the Dept. of Radiation Oncology at Weill Cornell Medicine (New
1714 York, US), by industrial collaborations with Lytix Biopharma (Oslo, Norway), Promontory (New York, US) and Onxeo
1715 (Paris, France), as well as by donations from Promontory (New York, US), the Luke Heller TECPR2 Foundation (Boston,
1716 US), Sotio a.s. (Prague, Czech Republic), Lytix Biopharma (Oslo, Norway), Onxeo (Paris, France), Ricerchiamo (Brescia,
1717 Italy), and Noxopharm (Chatswood, Australia). G.K. is supported by the Ligue contre le Cancer (équipe labellisée); Agence
1718 National de la Recherche (ANR) – Projets blancs; AMMICa US23/CNRS UMS3655; Association pour la recherche sur le
1719 cancer (ARC); Cancéropôle Ile-de-France; European Research Council Advanced Investigator Grand “ICD-Cancer”,
1720 Fondation pour la Recherche Médicale (FRM); a donation by Elior; Equipex Onco-Pheno-Screen; European Joint Programme
1721 on Rare Diseases (EJPRD); European Research Council (ICD-Cancer), European Union Horizon 2020 Projects Oncobiome
1722 and Crimson; Fondation Carrefour; Institut National du Cancer (INCa); Institut Universitaire de France; LabEx Immuno-
1723 Oncology (ANR-18-IDEX-0001); a Cancer Research ASPIRE Award from the Mark Foundation; the RHU Immunolife;
1724 Seerave Foundation; SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); and SIRIC
1725 Cancer Research and Personalized Medicine (CARPEM). This study contributes to the IdEx Université de Paris ANR-18-
1726 IDEX-0001.

1727 **Ethics delaration: conflicts of interest. See above.**

1728

1729 **Data Availability.** No data are included in the article

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5908 **Legends to Figures**

5909 **Figure 1. Principal causes of the therapeutic failure of intrinsic or extrinsic apoptosis inhibitors.**

5910 The clinical development and success of agents inhibiting apoptosis is limited by multiple contributory
5911 causes, including potential non-apoptotic, accessory or even protective roles of the targeted proteins
5912 (exemplified by the involvement of certain BCL2 family members, caspases and death receptors in
5913 processes as diverse as inflammation, cell differentiation, cell proliferation and cell survival), the high
5914 interconnectivity between RCD pathway (potentially leading to the activation of compensatory RCD
5915 variants in response to the inhibition of a specific RCD type), the low specificity and selectivity of the
5916 inhibitors developed so far (exemplified by the broad-spectrum caspase inhibitors) and the difficulty to
5917 precisely determine and quantify cell death *in vivo*. RCD, regulated cell death.

5918 **Figure 2. Molecular machinery of the intrinsic apoptosis.** Intrinsic apoptosis can be activated by a

5919 range of extracellular or intracellular stimuli, including, but not limited to, DNA damage, endoplasmic
5920 reticulum (ER) or oxidative stress, growth factor withdrawal or microtubular alterations. The critical step
5921 of the intrinsic apoptosis is the activation of the pro-apoptotic effectors of the BCL2 family, BAX, BAK
5922 and possibly BOK, which drives the outer membrane permeabilization (MOMP) and commits cells to
5923 death. MOMP results in the release from the mitochondrial intermembrane space into the cytosol of
5924 proapoptotic proteins, including CYCS and SMAC. CYCS assembles with APAF1, dATP and pro-
5925 CASP9 into the apoptosome, leading to the activation of CASP9, which in turn promotes the activation
5926 of the executioner caspases CASP3 and CASP7. The activation of the executioner caspases is facilitated
5927 by SMAC, which sequesters and/or degrades members of IAP family that inhibit apoptosis.

5928 **Figure 3. Impact of intrinsic apoptosis players on neurological disorders.** Intrinsic apoptosis is

5929 directly or indirectly involved in the pathogenesis of multiple neurological disorders, including
5930 neurodegenerative diseases, such as AD and PD, in brain damage caused by traumatic injury or

5931 neurotoxicity as well as in neuromuscular and retinal disorders. Pro- and anti-apoptotic members of the
5932 BCL2 family are depicted, respectively, in blue and green, while caspases are illustrated in pale violet.

5933 **Figure 4. Molecular machinery of the extrinsic apoptosis pathway.** Extrinsic apoptosis is initiated by
5934 the binding of FASL to FAS or TRAIL to TRAIL-R1 or TRAIL-R2, which promotes the assembly, on
5935 the cytoplasmic tail of these death receptors, of a platform known as the DISC. Extrinsic apoptosis is
5936 also triggered by the binding of TNF to TNF-R1, which promotes the assembly of the Complex II. The
5937 DISC comprises FADD, c-FLIPs and pro-CASP8. Complex II is a platform consisting of FADD and
5938 pro-CASP8 in association with either TRADD (complex IIa) or
5939 RIPK1 (complex IIb). The assembly of these complexes promotes the activation of CASP8, which
5940 mediates CASP3 and CASP7 activation either directly, by catalyzing the proteolytic activation of CASP3
5941 and CASP7 (in type I cells) or indirectly, via the proteolytic activation of the BH3-only protein BID and
5942 the outer membrane permeabilization (MOMP) (in type II cells). Extrinsic apoptosis can also be induced
5943 by dependence receptors like DCC, NTRK3, PTCH1, or UNC5A-D, which are activated by decreased
5944 concentration of the related ligand, as illustrated in the figure. However, the role of this pathway in
5945 normal physiology and disease is not yet established.

5946 **Figure 5. Impact of extrinsic apoptosis players on neurological disorders.** Death receptor-induced
5947 apoptosis is directly or indirectly involved in the pathogenesis of multiple neurological disorders,
5948 including neurodegenerative diseases, such as AD and PD, in brain damage due to traumatic injury or
5949 neurotoxicity as well as in neuromuscular and retinal disorders.

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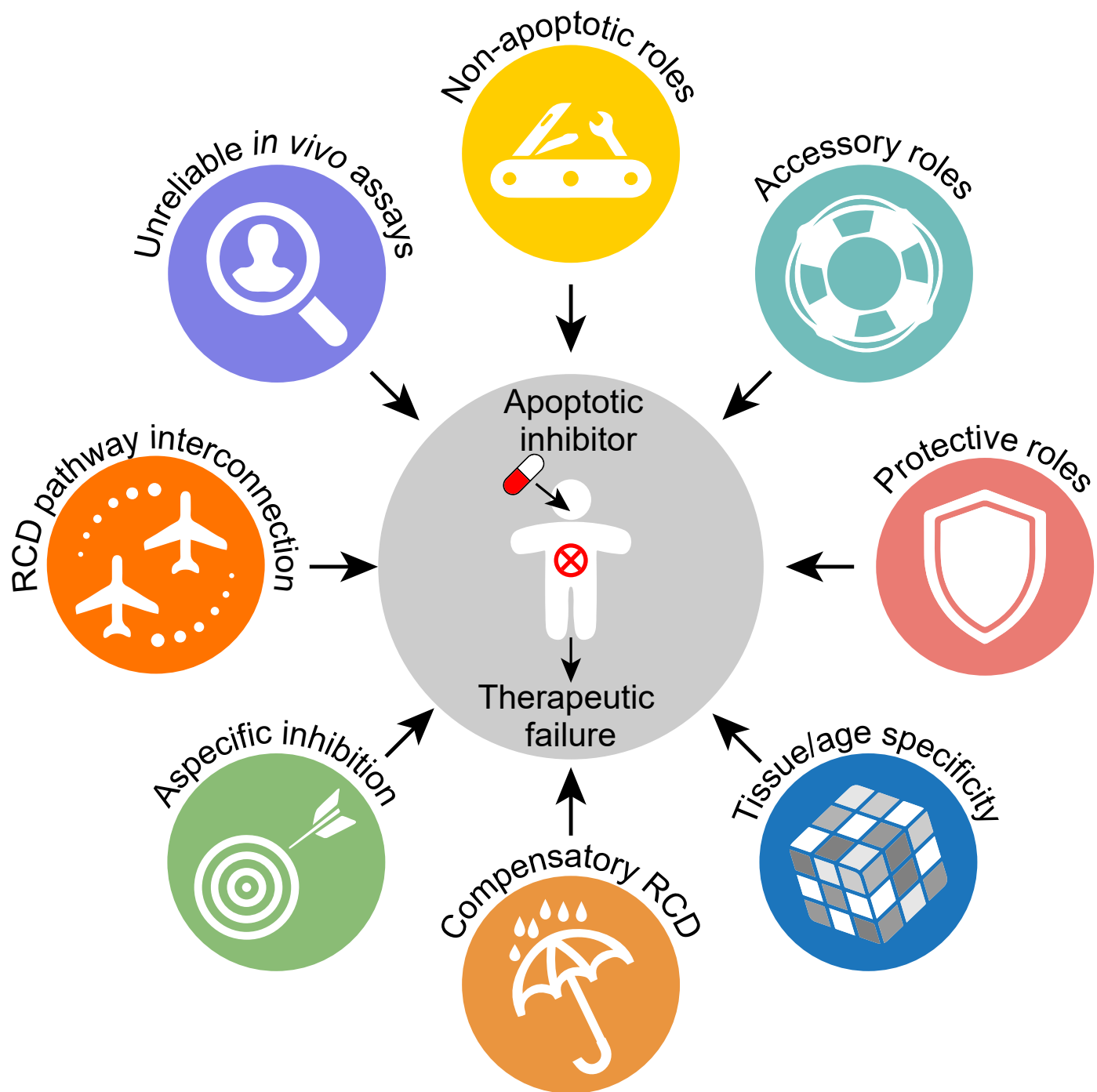


Figure 1

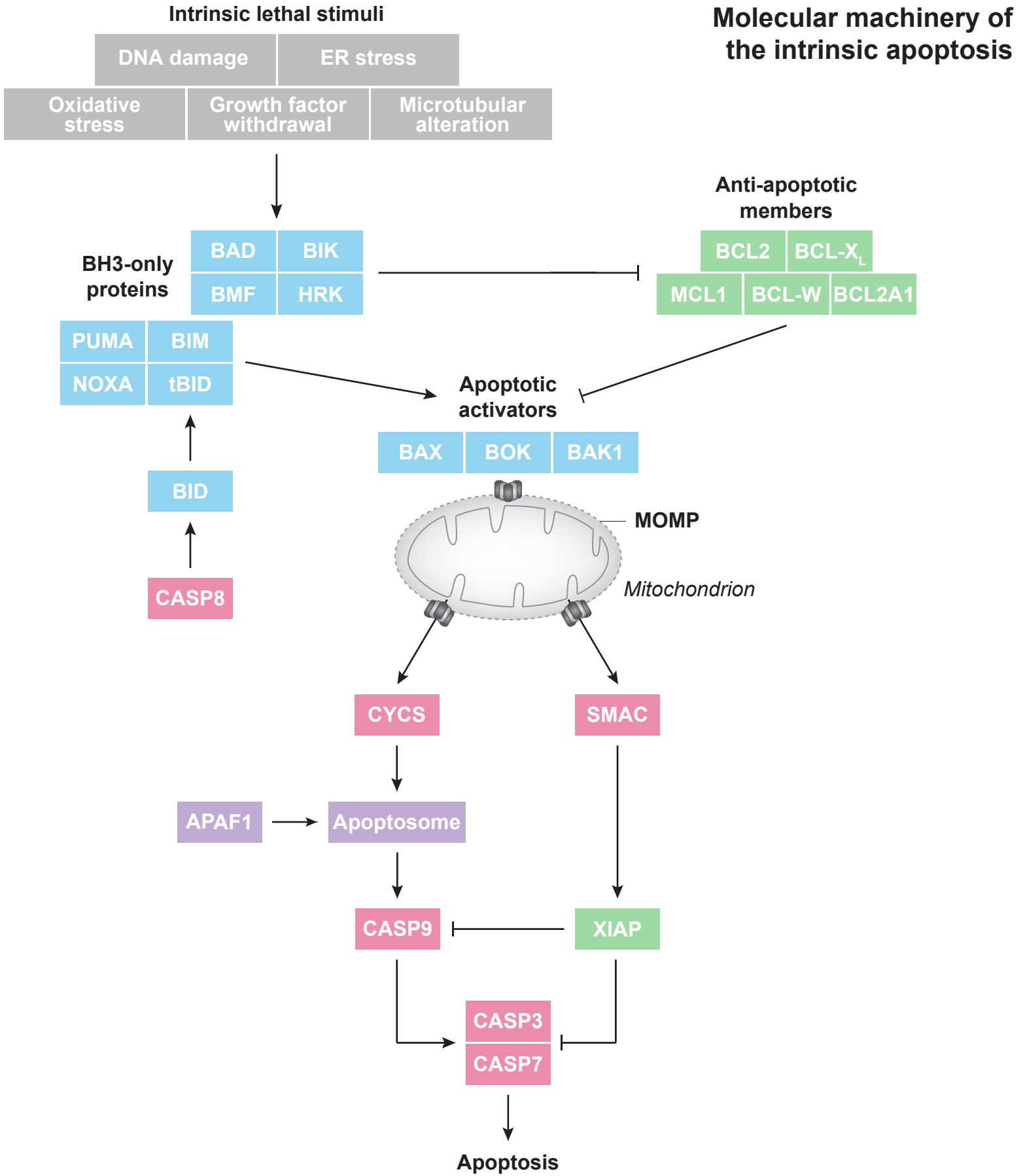
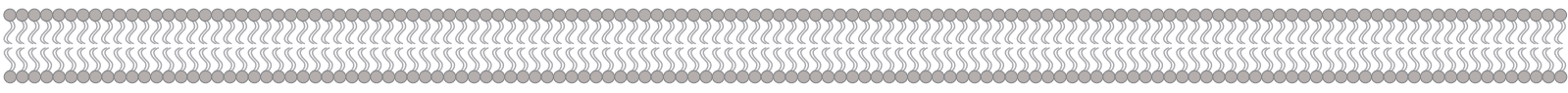
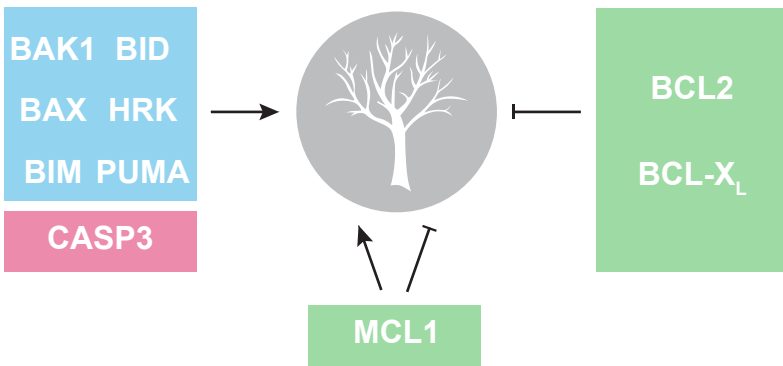
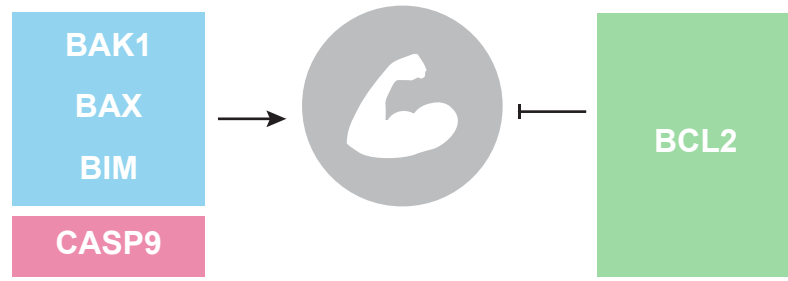


Figure 2

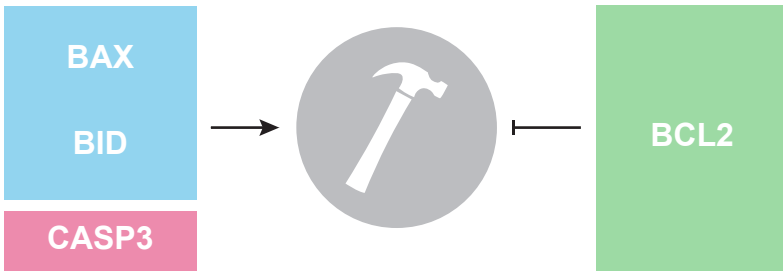
Neurodegenerative disorders



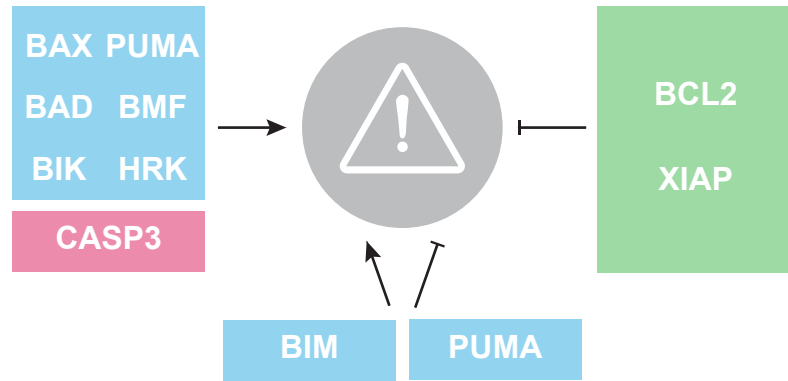
Neuromuscular disorders



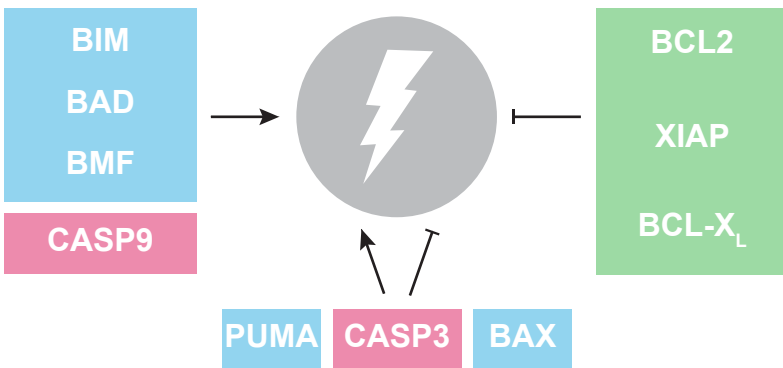
Traumatic brain injuries



Neurotoxicities



Pre/post ischemic injuries



Retinal disorders

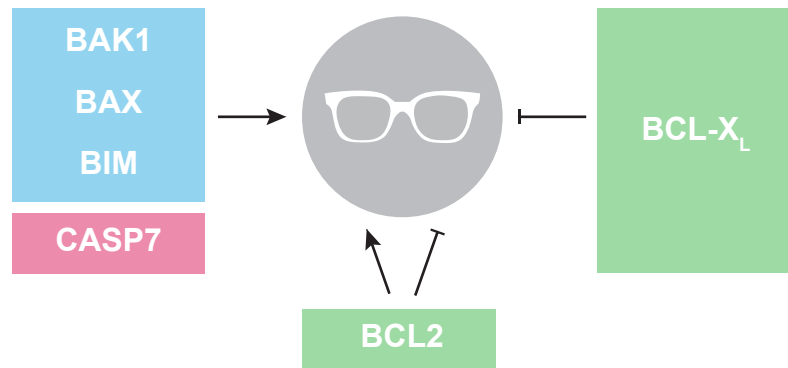


Figure 3

Molecular machinery of the extrinsic apoptosis

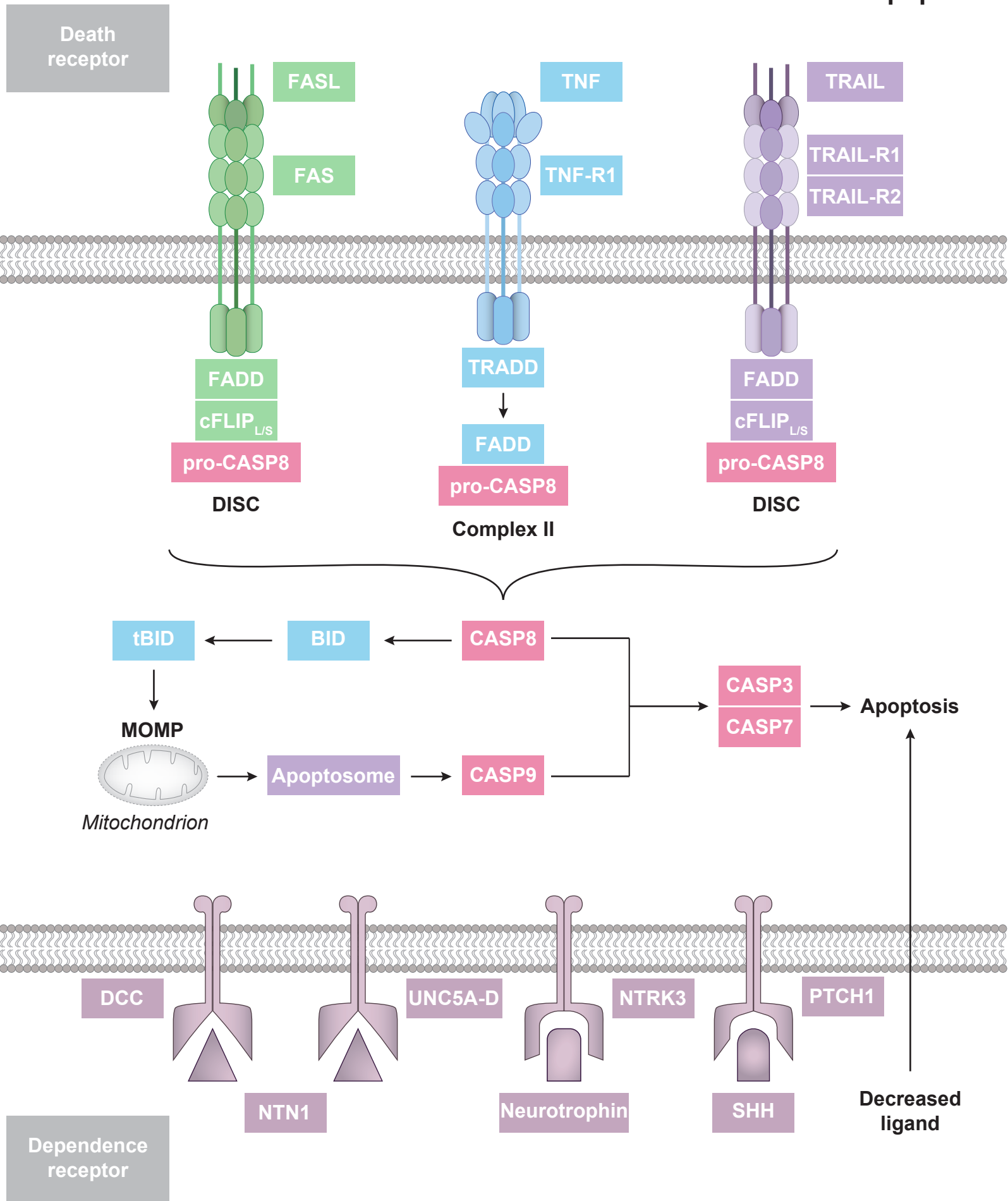
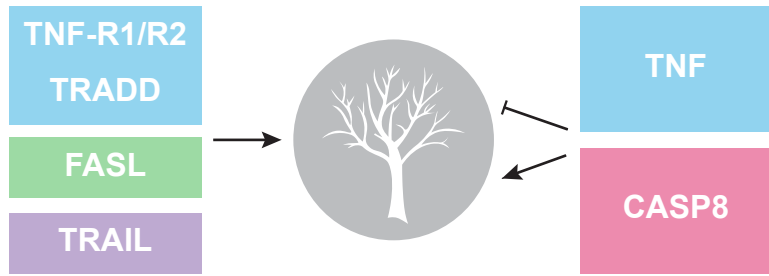
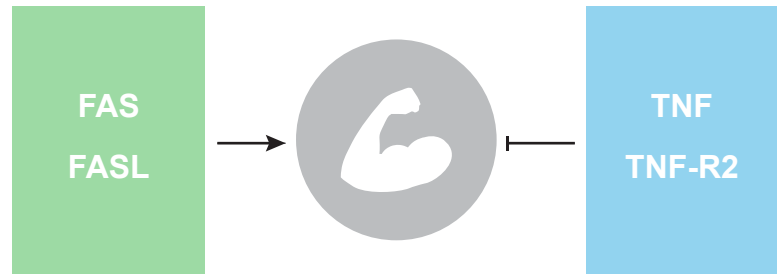


Figure 4

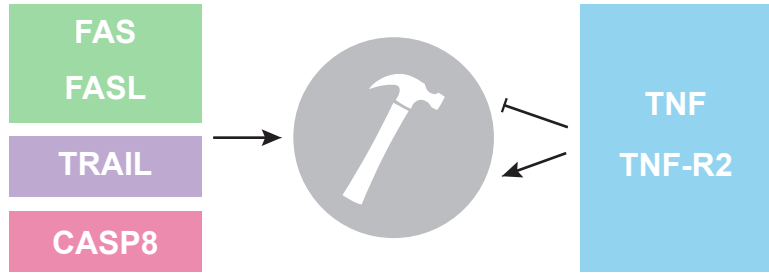
Neurodegenerative disorders



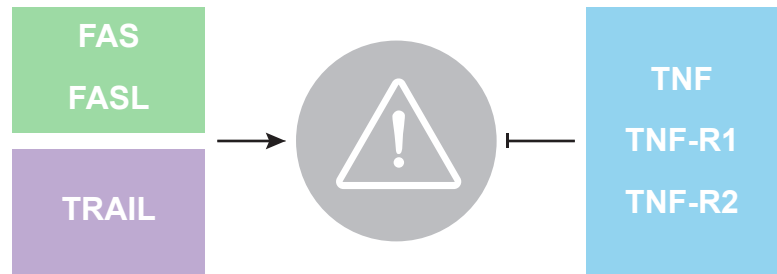
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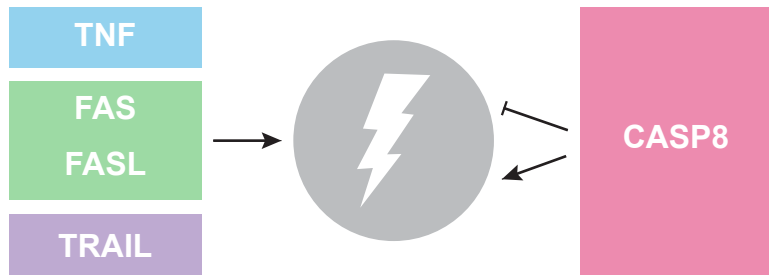
Traumatic brain injuries



Neurotoxicities



Pre/post ischemic injuries



Retinal disorders

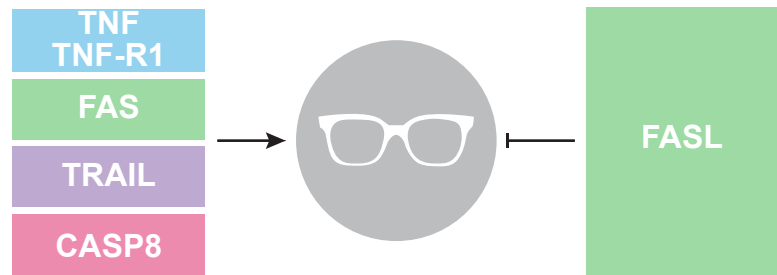


Figure 5

1 **Box 1. Principle of intrinsic apoptosis.**

2 Intrinsic apoptosis is a type of regulated cell death (RCD) initiated by perturbations of the extracellular
3 or intracellular microenvironment including (but not limited to) DNA damage, endoplasmic reticulum or
4 oxidative stress, growth factor withdrawal, microtubular alteration. The critical step is mitochondrial
5 outer membrane permeabilization (MOMP)^{1,2,3,4}. MOMP - which involves constitutive outer membrane
6 proteins, such as the voltage-dependent anion channel (VDAC), is modulated by the activity of multiple
7 pro-apoptotic and anti-apoptotic members of the BCL2, apoptosis regulator (BCL2) protein family^{5,6,7,}
8 ^{8,9}. In response to apoptotic stimuli, MOMP leads to the sequential activation of the initiator caspase 9
9 (CASP9) and then the executioner caspases CASP3 and CASP7^{10,11,12,13,14}. Two functionally distinct
10 classes of pro-apoptotic BCL2 proteins have been identified. The first class encompasses the apoptotic
11 activators BCL2 associated X, apoptosis regulator (BAX), BCL2 antagonist/killer 1 (BAK1), and BCL2
12 family apoptosis regulator (BOK)¹⁵. Once activated by apoptotic stimuli, BAX, BAK1 and BOK induce
13 MOMP by generating pores across the outer mitochondrial membrane (OMM)^{16,17,18,19,20}. These pro-
14 apoptotic factors promote the release into the cytosol of several apoptogenic factors, including
15 cytochrome c, somatic (CYCS) and diablo IAP-binding mitochondrial protein (DIABLO; also known as
16 second mitochondrial activator of caspases, SMAC)²¹. CYCS exerts apoptogenic activity by associating
17 with apoptotic peptidase activating factor 1 (APAF1) and pro-CASP9 to generate a complex known as
18 the apoptosome, leading to sequential activation of CASP9 and the executioner caspases CASP3 and
19 CASP7²². DIABLO/SMAC contributes to CASP3 and CASP7 activation by associating with and
20 inhibiting X-linked inhibitor of apoptosis (XIAP) and other members of the inhibitor of apoptosis (IAP)
21 protein family which restrain caspase activation²³.

22 The second class of pro-apoptotic BCL2 proteins (known as BH3-only proteins²⁴) include BCL2
23 associated agonist of cell death (BAD), BCL2 binding component 3 (BBC3; best known as p53-

24 upregulated modulator of apoptosis, PUMA), BCL2 interacting killer (BIK), BCL2 like 11 (BCL2L11;
25 best known as BCL2-interacting mediator of cell death, BIM), Bcl2 modifying factor (BMF), BH3
26 interacting domain death agonist (BID), BCL2 interacting protein harakiri (HRK, also known as DP5),
27 and phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1; best known as NOXA^{25,26}). Of these,
28 caspase-cleaved BID (tBID), BIM, PUMA, and NOXA have been reported to also be able to promote
29 BAX and BAK1 activation through a direct interaction with these proteins at the mitochondria^{27,28,29,30,}
30^{31,32,33}. All BH3-only proteins, including BAD, BIK, BMF and HRK activate BAX and BAK1 indirectly
31 by associating with anti-apoptotic BCL2 family members, thereby blocking the inhibitory binding of the
32 latter to BAX and BAK1^{5,9,31,33,34,35}. Some BH3-only proteins, particularly BIM, PUMA and tBID,
33 can potently bind and inhibit all anti-apoptotic BCL-2 proteins whereas others bind only some (e.g.,
34 NOXA only binds MCL1 and A1)^{31,33,36,37}. It is noteworthy that BAX and BAK1 can induce apoptosis
35 in the absence of all BH3-only proteins when the anti-apoptotic BCL2 proteins are genetically removed
36 or inhibited by BH3 mimetic drugs^{33,34}. However, BAX and BAK1 activation in the absence of BH3-
37 only proteins occurs at slower kinetics compared to that in the presence of BH3-only proteins³³. These
38 findings support the existence of both BH3-dependent and BH3-independent activation of BAX and
39 BAK1 where BH3-only proteins function as catalysts for BAX and BAK activation^{33,38}. In this context,
40 BAX and BAK are also reported to be activated by the tumor protein p53 (TP53; best known as p53) in
41 a fashion independent of BH3-only proteins^{39,40}. The anti-apoptotic members of the BCL2 family
42 encompass BCL2, apoptosis regulator (BCL2), BCL2 like 1 (BCL2L1; best known as BCL-X_L), MCL1,
43 BCL2 family apoptosis regulator (MCL1), BCL2 like 2 (BCL2L2; best known as BCL-W), and BCL2
44 related protein A1 (BCL2A1; best known as A1)^{5,6,7,8}. The anti-apoptotic activity of these BCL2
45 proteins mainly involves MOMP maintenance, although, a non-canonical, cellular redox-dependent
46 mechanism of cytoprotection has been ascribed in cancer cells at least for BCL2^{41,42,43,44}

47

49 **Box 2. Impact of pro-apoptotic BCL2 proteins on health.**

50 Deletion of BCL2-associated X protein (*Bax*), BCL2-antagonist/killer 1 (*Bak1*) or BCL2-related ovarian
51 killer (*Bok*) does not significantly affect mouse development ^{45, 46, 47}, with the exception of a mild
52 lymphocyte and neuron accumulation in *Bax*^{-/-} mice which also exhibit male infertility due to
53 seminiferous tubule malformation ^{45, 48}. Of note, a recent study has demonstrated that such defects in
54 germ cells occur in the fetal period ⁴⁹, supporting the requirement for intrinsic apoptosis in testicular
55 development ^{50, 51}. Subsequent studies confirmed the role of BAX in neurogenesis, in particular the
56 development of hippocampal and cerebellar neurons, cortical interneurons and astrocytes ^{52, 53, 54, 55, 56, 57}.
57 Accordingly, *Bax*^{-/-} mice exhibit impaired neurological functions manifesting with increased anxiety,
58 depression-like traits, compromised social and sexual behavior, and impaired spatial representation and
59 olfactory system function ^{58, 59, 60}. These mice also show accelerated medulloblastoma formation ⁶¹, which
60 is in line with the oncosuppressive activity of apoptotic (and non-apoptotic) regulated cell death (RCD)
61 ⁶².

62 Ablation of *Bok* does not compromise the relatively normal development of BAK1- or BAX-deficient
63 mice, although *Bax*^{-/-}*Bok*^{-/-} mice exhibit an increased number of mature oocytes ⁶³. In contrast, co-deletion
64 of *Bax* and *Bak1* causes perinatal death in the vast majority (more than 90%) of mice, mainly due to
65 multiple developmental abnormalities and feeding difficulties ^{46, 64}. Importantly, the developmental
66 defects of *Bax*^{-/-}*Bak1*^{-/-} mice are exacerbated by additional deletion of *Bok*, underscoring not only some
67 functional redundancy between BAX, BAK1 and BOK, but also a crucial role of pro-apoptotic BCL2
68 family members in the development of the central nervous system (CNS) and hematopoietic
69 compartment ⁶⁴. However, since some *Bax*^{-/-}*Bak1*^{-/-} and *Bax*^{-/-}*Bak1*^{-/-}*Bok*^{-/-} mice can reach adulthood ^{46,}
70 ⁶⁴, additional systems must be at play to compensate for defects in apoptosis in other organs. It is worth
71 noting that the developmental defects of *Bax*^{-/-}*Bak1*^{-/-} mice can be further aggravated by deletion of

72 autophagy related 5 (*Atg5*)⁶⁵, which is involved in autophagy as well as in non-canonical vesicular
73 pathways like LC3-associated phagocytosis^{66, 67}. However, whether autophagy-dependent cell death
74 compensates for the apoptotic defects of *Bax*^{-/-}*Bak1*^{-/-} mice remains to be formally determined^{68, 69}.

75 Further corroborating the relevance of intrinsic apoptosis for proper development, the few surviving *Bax*^{-/-}
76 *Bak1*^{-/-} mice and *Bax*^{-/-}*Bak1*^{-/-}*Bok*^{-/-} mice display phenotypes related to defective programmed cell death
77 (PCD), including webbed feet (due to the incomplete removal of interdigital webs), imperforate vagina
78 and midline fusion defects including facial cleft^{46, 64}. CNS issues exhibited by these animals include a
79 striking expansion of the tissue regions that harbor the neural stem cell pool^{46, 64} as well as impaired
80 function of the motor⁷⁰ and visual^{71, 72} systems. Although the number of apoptotic cells were reduced
81 to the limit of detection in embryos lacking BAX, BAK1 and BOK⁶⁴, anomalies in the urinary tract were
82 conspicuously absent in these animals⁶⁴. This sparked a study examining if BID, in addition to linking
83 the death receptor (DR) pathway and the intrinsic apoptotic pathway (**Box 5**), could act in a way similar
84 to BAX and BAK1. Indeed, while loss of BID alone did not lead to anomalies during embryonic and
85 fetal development, additional deletion of *Bid* in *Bax*^{-/-}*Bak1*^{-/-}*Bok*^{-/-} mice revealed a redundant
86 requirement for BID in urogenital tract development⁷³. In its previously recognized role, BID in the form
87 of tBID activates BAX and BAK1, which would not have caused additional anomalies in the absence of
88 BAX and BAK1. Therefore, these results indicate that BID can act in parallel with BAX, BAK1 and
89 BOK. Congruently, full-length BID⁷³ or tBID⁷⁴ can mediate mitochondrial permeabilization and cause
90 cytochrome c, somatic (CYCS) release. In this context it is worth considering that BID has been reported
91 to be structurally similar to the multi-BH domain BCL2 family proteins, such as BAX and BCL-X_L^{9, 75,}
92 ^{76, 77}.

93 Tissue-specific ablation of *Bax* and *Bak1*, confirmed the crucial role of these proteins in the hematopoietic
94 system, and specifically in the homeostasis and functionality of B cells⁷⁸, T cells⁷⁹, megakaryocytes⁸⁰

95 and platelets ⁸¹. Mice reconstituted with fetal liver cells from *Bax*^{-/-}*Bak1*^{-/-} mice display massive
96 lymphadenopathy and defective T cell proliferation, and the severity of these defects is even more
97 pronounced when *Bak1*^{-/-}*Bax*^{-/-}*Bok*^{-/-} fetal liver cells are used for reconstitution, an experimental setting
98 that also reveals signs of autoimmunity ^{82, 83, 84}. Similarly, mice reconstituted with a *Bak1*^{-/-}*Bax*^{-/-}
99 hematopoietic compartment develop a fatal systemic lupus erythematosus (SLE)-like autoimmune
100 disease ⁸⁵. Moreover, the inducible co-deletion of *Bax* and *Bak1* in lymphocytes of adult mice results in
101 the development of severe autoimmune glomerulonephritis ⁷⁸. Finally, conditional knockout mouse
102 models reveal a crucial contribution of BAX and BAK1 to endothelial cell homeostasis ^{86, 87}, but little
103 impact on cardiac and intestinal functions, as shown by the absence of hyperplasia ^{88, 89}. These results
104 demonstrate that the multi-BH domain pro-apoptotic BCL2 proteins play critical roles for the normal
105 development of multiple tissues but that, surprisingly, a few mice can reach weaning or even adulthood
106 when all of these effectors of apoptosis are removed ⁶⁴.

107 Amongst the BH3-only proteins, BCL2 like 11 (BCL2L11, best known as BIM) appears the most critical
108 for embryonic development and tissue homeostasis, as shown by the fact that approximately 30% of
109 BIM-deficient mice die during embryogenesis ⁹⁰. Surviving BIM-deficient mice display severe defects in
110 the hematopoietic system including lymphoid hyperplasia and marked splenomegaly, and on a mixed
111 C57BL/6 x 129SV background many of these mice spontaneously develop systemic autoimmunity often
112 resulting in fatal kidney disease ⁹⁰, a condition that can be accelerated by depletion of immunosuppressive
113 CD4+CD25+FOXP3+ regulatory T (T_{REG}) cells ⁹¹. Cells from BIM-deficient mice are profoundly
114 resistant to growth factor deprivation, glucocorticoids, deregulated calcium flux and ER stress ^{90, 92}.
115 Accordingly, BIM-deficient mice also display dysregulated T cell development and homeostasis ^{93, 94, 95},
116 ^{96, 97} and hence exhibit defective cellular ^{98, 99, 100} and humoral ^{101, 102, 103} immune responses. *Bcl2l11*
117 deletion (loss of BIM) has also been shown to extend the survival of granulocytes ¹⁰⁴ and to perturb the
118 development of mammary glands ^{105, 106}, gastric epithelium ¹⁰⁷ and the retina ¹⁰⁸. Moreover, aged BIM

119 deficient mice show reduced adiposity ¹⁰⁹. Of note, systemic deletion of *Bax* or *Bak1* exacerbates the
120 hematopoietic dysregulation of BIM-deficient mice ¹¹⁰. Conditional knockout systems confirmed a key
121 role for BIM in the hematopoietic system homeostasis ^{111, 112, 113, 114}, and revealed a role for BIM in the
122 survival and differentiation of hippocampal neurons ¹¹⁵. Of note, myeloid cell-specific deletion of
123 *Bcl2l1l* induces a systemic lupus erythematosus (SLE)-like disease that resembles the pathology
124 developing in mice that lack BIM in all cells ¹¹⁶.

125 Mice lacking BH3 interacting domain death agonist (BID), phorbol-12-myristate-13-acetate-induced
126 protein 1 (PMAIP1, best known as NOXA) or BCL2 binding component 3 (BBC3, best known as
127 PUMA) display normal embryonic development ^{117, 118, 119, 120}. In these studies on BID-deficient mice,
128 substantial reduction in FAS ligand-induced apoptosis was seen in hepatocytes ^{117, 121}, pancreatic cells
129 ^{117, 122, 123} and possibly neurons ^{124, 125}. Moreover, *Bid*^{-/-} mice display a dysregulated myeloid compartment
130 resulting in an increased likelihood of leukemogenesis ¹²⁵, as well as cardiac dysfunction ¹²⁶. Conditional
131 gene deletion studies confirmed the relevance of BID in the homeostasis and functionality of hepatocytes
132 and T cells ^{127, 128, 129}.

133 PUMA contributes to normal ovarian development, as shown by the evidence that two-thirds of the germ
134 cells produced during embryonic development undergo PUMA-mediated cell death shortly after
135 formation ¹³⁰. Moreover, cells from PUMA-deficient mice are profoundly resistant to p53-induced
136 apoptosis triggered by genotoxic drugs and lymphoid cells are also resistant to glucocorticoids, phorbol
137 ester and growth factor deprivation ^{119, 120, 131, 132, 133}. Cells from NOXA-deficient mice also showed
138 resistance to DNA damage-inducing drugs, although to a lesser extent compared to cells lacking PUMA
139 ^{119, 134}. Moreover, *Pmaip1*^{-/-} mice (lacking NOXA) show limited stress-induced erythropoiesis ¹³⁵.
140 Germline deletion of the gene encoding PUMA or NOXA *also* affects humoral immune responses ^{136, 137}
141 and increases the abundance of multiple cell types in the retina ¹³⁸. Interestingly, the loss of PUMA

142 greatly impairs radiation induced thymic lymphoma development and the formation of liver cancer ¹³⁹,
143 ^{140, 141, 142} (see main text), potentially reflecting the ability of apoptotic cells to secrete mitogenic and
144 immunosuppressive molecules such as prostaglandin E2 (PGE₂) ^{143, 144}. PUMA was also shown to play
145 a role in radiation-induced intestinal damage ¹⁴⁵.

146 Co-deletion of two or more genes coding for BH3-only proteins confirmed the pronounced relevance of
147 BIM for development and underscored some degree of functional redundancy in the system. On the one
148 hand, mice lacking both PUMA and NOXA develop normally but their cells are profoundly resistant to
149 genotoxic agents, as resistant as cells lacking p53 ¹⁴⁶. Concomitant loss of PUMA but not the additional
150 loss of NOXA, BAD, BID or BIK increases the severity of hematopoietic defects imposed by the lack of
151 BIM ^{147, 148, 149, 150}. On the other hand, *Bcl2l1l^{-/-}Bbc3^{-/-}Bid^{-/-}* and *Bcl2l1l^{-/-}Bbc3^{-/-}Bid^{-/-}Pmaip1^{-/-}* mice
152 displayed perinatal embryonic lethality and increased incidence of developmental defects, including
153 webbed feet, imperforate vagina, and supernumerary neurons similar in extent to those seen in *Bax^{-/-}*
154 *Bak1^{-/-}* mice ^{33, 151}. Of note, triple deficiency of BID, BIM, and PUMA completely abrogates BAX/BAK1
155 dependent apoptosis in cerebellar granule neurons and T lymphocytes ¹⁵¹, providing in vivo evidence
156 supporting direct activation of BAX and BAK1 by the BH3-only proteins.

157 Mice lacking BCL2-associated agonist of cell death (*Bad*), BCL2 interacting killer (*Bik*), BCL2
158 modifying factor (*Bmf*) and harakiri, BCL2 interacting protein (contains only BH3 domain) (*Hrk*) are
159 viable and develop normally ^{152, 153, 154, 155}. That said, BAD-deficient mice display a prolonged platelet
160 lifespan ¹⁵⁶, while *Bmf^{+/+}* mice are characterized by mild lymphadenopathy, vaginal atresia ^{154, 157} as well
161 as minor defects in mammary gland development and oogenesis ^{106, 158}. Interestingly, female *Bmf^{+/+}* mice
162 had significantly more primordial follicles than wild-type control animals associated with an extended
163 fertile life span ¹⁵⁹, while *Bmf^{+/+}* mice developed an accelerated gamma irradiation-induced thymic
164 lymphoma ¹⁵⁴. Combined deletion of some of the above listed BH3-only protein-coding genes does not

165 cause significant embryonic lethality or developmental abnormalities. Moreover, the combined absence
166 of BIK and NOXA did not accelerate c-MYC-driven lymphoma development ¹⁶⁰, while increased
167 spontaneous tumorigenesis has been documented in *Bad*^{-/-}*Bmf*^{±/-} mice ¹⁶¹. Conversely, the absence of
168 some of these BH3-only proteins aggravates the defects caused by the loss of *Bcl2l11* (the gene encoding
169 BIM). This applies to: (1) *Bad* co-deletion with *Bcl2l11*, which enhances lymphocyte accumulation ¹⁵⁶,
170 (2) *Bik* co-deletion with *Bcl2l11*, which causes male infertility due to defective spermatogenesis ¹⁶², a
171 phenotype resembling that of BAX-deficient mice, and (3) *Bmf* co-deletion with *Bcl2l11*, which
172 considerably increases the incidence of developmental defects, vaginal atresia, lymphadenopathy,
173 autoimmune glomerulonephritis, and spontaneous development of hematological malignancies ^{157, 163},
174 ¹⁶⁴.

175

176 **Box 3. Impact of anti-apoptotic BCL2 proteins on health.**

177 While myeloid cell leukemia sequence 1 (*Mcl1*) deletion in mice induces embryonic lethality at the
178 blastocyst (embryonic E3) stage prior to implantation^{165, 166}, embryos lacking BCL2-like 1 (BCL2L1,
179 best known as BCL-X_L) die around embryonic day 13.5) with substantial cell depletion in the developing
180 central nervous system (CNS) and erythroid progenitors¹⁶⁷. Concomitant deletion of BCL2-associated
181 X protein (*Bax*) or caspase 9 (*Casp9*) considerably limited neuronal cell death genotype caused by the
182 absence of BCL-X_L^{168, 169}. Concomitant deletion of BCL2 like 11 (*Bcl2l11*, the gene encoding BIM)
183 rescues the erythroid progenitors (but not the neuronal) cells from death in BCL-X_L-deficient mice¹⁷⁰.
184 *Bcl2*^{-/-} mice are born but exhibit severe defects in their kidneys, alterations of the CNS, lymphoid cell
185 depletion as well as premature graying of their hair and they succumb to polycystic kidney disease at a
186 young age^{171, 172, 173, 174, 175, 176, 177}. These defects can all be rescued by concomitant deletion of the gene
187 encoding BIM, and, remarkably, in the case of some defects the loss of even a single allele of *Bim* is
188 sufficient¹⁷¹. Mice with deletion of B cell leukemia/lymphoma 2 related protein A1a (*Bcl2a1a*, one of
189 three isoforms of BCL2A1 in mice) or loss of all isoforms of BCL2A1 (best known as A1) show no
190 developmental defects but display minor defects in the hematopoietic compartment^{178, 179, 180, 181}. The
191 absence of BCL-W results in male infertility due to defective spermatogenesis^{182, 183, 184}.

192 As opposed to homozygous deletion, haploinsufficiency for genes encoding MCL1 or BCL-X_L did not
193 result in defects in normal development^{165, 167}. However, *Mcl1*^{+/-} mice display significant, albeit minor
194 decreases in certain hematopoietic cell types^{185, 186}, and poor hematopoietic recovery from stress, such
195 as gamma-radiation or treatment with 5-FU, which can be rescued by deletion of BCL2 binding
196 component 3 (*Bbc3*; the gene encoding PUMA)¹⁸⁶. Moreover, the loss of one *Bcl2l1* allele (encoding
197 BCL-X_L) limits male fertility due to defects in germ cell development¹⁸⁷ and shortens platelet lifespan
198¹⁸⁸. Of note, while combined haploinsufficiency for *Mcl1* and *Bcl2*, for *Mcl1* and *Bcl2a1a* or for *Bcl2l1*

199 and *Bcl2* does not markedly affect embryonic development in mice ^{189, 190, 191}, *Mcl1*^{+/-}*Bcl2l1*^{+/-} double
200 heterozygote mice display severe developmental defects and die during embryogenesis or early
201 postnatally ¹⁹⁰. Remarkably this defect that can be rescued by concomitant deletion of a single allele of
202 the gene encoding BIM. These observations suggest that embryonic development is safeguarded by a
203 delicate balance between pro- and anti-apoptotic BCL2 proteins.

204 Conditional knockout studies confirmed the importance of the different pro-survival BCL2 family
205 members in specific tissues at precise developmental stages. These studies showed that MCL1 is critical
206 for the development and/or maintenance of most (but not all) hematopoietic cell populations including
207 stem and progenitor cells ¹⁹², immature as well as mature B and T lymphocytes ^{193, 194, 195, 196} Jain, 2017,
208 28972012;¹⁹⁷, natural killer (NK) cells ¹⁹⁸, neutrophils ^{199, 200}, mast cells and basophils ²⁰¹, as well as Ig
209 secreting plasma cells ^{202, 203}. Accumulating evidence suggests that the survival of some hematopoietic
210 cell subsets is safeguarded by the combined activity of two or even more anti-apoptotic BCL2 family
211 members ²⁰⁴. Conditional deletion of *Bcl2l1* alone (leading to lack of BCL-X_L) or in combination with
212 loss of *Mcl1* demonstrated functional redundancy between BCL-X_L and MCL1 in developing
213 lymphocytes ^{205, 206} and megakaryocytes ^{188, 207, 208, 209}. Conversely, BCL2 and A1 appear to have
214 overlapping actions in the survival of B cells and neutrophils ^{189, 210, 211} but not megakaryocytes and
215 platelets ²¹². Data from hematopoietic chimeric mice confirm the role of these proteins in hematopoiesis
216 ^{104, 167, 213, 214}. BCL2 is reported to contribute to the development and homeostasis of the mouse epidermis
217 ²¹⁵. Along similar lines, MCL1 and BCL-X_L play roles in the development and homeostasis of several
218 tissues including the myocardium ^{216, 217}, the CNS ^{218, 219, 220, 221, 222, 223, 224, 225, 226}, the hepatic parenchyma
219 ^{227, 228, 229, 230, 231}, vascular endothelium ²³², thymic epithelium ²³³, as well as the intestinal ²³⁴, mammary
220 ^{235, 236}, lung ²³⁷ and renal ²³⁸ epithelium.

221 There are substantial differences in the severity of the defects caused by the conditional deletion of
222 different pro-survival BCL2 family genes and between distinct tissues. For instance, conditional deletion
223 of *Mcl1* in mouse hematopoietic stem/progenitor cells¹⁹², erythroid cells²³⁹ or T_{REG} cells²⁴⁰ is lethal. In
224 the latter case, lethality is ascribed to multiorgan autoimmunity caused by the depletion of the pool of
225 T_{REG} cells²⁴⁰. Similarly, the megakaryocyte-specific combined deletion of the genes encoding MCL1
226 and BCL-X_L provokes embryonic or perinatal lethality²⁰⁷, which can be rescued by the absence of BAK1
227⁸⁰. Similar findings have been obtained upon the ablation of *Mcl1* from the CNS or the myocardium, or
228 the specific removal of the gene encoding BCL-X_L from the respiratory epithelium, although these
229 experiments did not include rescue approaches^{217, 218, 219, 237}. The functional overlap between MCL1 and
230 BCL-X_L appears to be particularly relevant in the CNS and liver^{225, 228}. Of note, the requirement of
231 MCL1 and BCL-X_L for neurogenesis appears to fluctuate between different stages of differentiation. The
232 neurodevelopmental defects imposed by the deletion of *Mcl1* or *Bcl2l1* can be rescued by the absence of
233 BAX^{169, 225}. The detrimental effects of the hepatocyte-specific ablation of *Bcl2l1* or *Mcl1* can be rescued
234 by deletion of *Bax* and *Bak1* as well as by that of *Bcl2l1l* (encoding BIM) and/or BH3 interacting domain
235 death agonist (*Bid*)^{241, 242}. These observations demonstrate that organogenesis and adult tissue
236 homeostasis depend on the balance between both anti-apoptotic and pro-apoptotic members of the BCL2
237 family. Further substantiating this notion, deletion of the gene encoding BCL-X_L from keratinocyte
238 precursors limits skin cancer development driven by ultraviolet B (UVB) rays and chemical carcinogens
239²⁴³. Conversely, the hepatocyte-specific deletion of *Mcl1* promotes hepatic carcinogenesis²⁴⁴, as does the
240 deletion of *Mcl1* in intestinal epithelial cells²³⁴. These latter findings may appear counterintuitive, as
241 pre-malignant cells are expected to be more susceptible to succumb to environmental stress in the absence
242 of MCL1 or BCL-X_L. However, both hepatic and intestinal carcinogenesis involve a robust inflammatory
243 component that is exacerbated by tissue damage and cell death²⁴⁵. Moreover, MCL1-deficient tissues
244 show an increased cell turnover, which results in elevated level of replicative stress and genetic

245 instability, potentially promoting carcinogenesis ^{231, 234}. Also, when many cells die, progenitors get
246 mobilized and must divide extensively. This increases the risk of such cells acquiring mutations that may
247 drive neoplastic transformation, as firstly shown in a murine model of radiation induced thymic T cell
248 lymphoma development ^{139, 140}.

249

250 **Box 4. Impact of the apoptosome and apoptotic caspases on health**

251 The whole-body deletion of apoptotic peptidase activating factor 1 (*Apaf1*) or caspase 9 (*Casp9*) is
252 associated with fetal lethality around E14.5 to E16.5^{246, 247, 248}. Severe abnormalities in APAF1-deficient
253 fetuses include webbed feet, craniofacial malformations, incomplete neural tube closure and/or excessive
254 brain growth and exencephaly resulting in alteration of the central nervous system (CNS) including in
255 the visual, olfactory, and auditory systems^{246, 248, 249, 250, 251, 252}. Similar defects in the developing brain
256 result from *Casp9* deletion^{166, 248, 253}, a phenotype that was not exacerbated by *Casp2* co-deletion²⁵⁴.
257 The absence of CASP9 did not rescue neuronal defects due p53 hyperactivation in neural crest cells²⁵⁵.
258 Of note, evidence linking mutations in *APAF1*, *CASP9* and *CASP3* to neural tube defects in humans has
259 been reported^{256, 257}. Mice lacking cytochrome c, somatic (CYCS) die in midgestation²⁵⁸, while the
260 deletion of cytochrome c, testis (*Cyct*), which is specifically expressed in male gonads is associated with
261 normal development but male infertility²⁵⁹. The neuron-specific ablation of *Cyct* results in postnatal cell
262 death²⁶⁰. Confirming that the detrimental effects of *Cyct* deletion result from impaired apoptosis, mice
263 expressing a mutant CYCS that retains the ability to shuttle electrons as a component of the mitochondrial
264 respiratory chain but is unable to assemble the apoptosome exhibit perinatal lethality and developmental
265 brain defects similar to APAF1- and CASP9-deficient mice²⁶¹.
266 Importantly, the genetic background of the mouse strains appears to significantly influence the impact of
267 the absence of core components of the apoptotic machinery on embryonic development. Thus, while
268 genetic deletion of *Casp3* in 129S1/SvImJ mice results in embryonic or early postnatal lethality due to
269 the severe defects in brain development that are only partially rescued by concomitant deletion of the
270 gene encoding BCL-X_L, on a C57BL/6 background *Casp3*^{-/-} mice develop normally and survive into
271 adulthood^{262, 263, 264, 265}. A similar impact of genetic background on phenotype has also been observed

272 for *Apaf1*^{-/-} and *Casp9*^{-/-} mice^{266,267}. Although *Casp3*^{-/-} mice reach adulthood on a C57BL/6 background,
273 they exhibit defects in complex brain functions including attention and (in males) social behavior^{268,269},
274 as well as ear and vestibular dysfunction including hearing loss^{270,271,272,273,274}. Abnormalities were also
275 seen in the kidney and spleen of aged *Casp3*^{-/-} mice²⁷⁵. Survival of *Casp3*^{-/-} mice to adulthood in
276 C57BL/6 mice was ascribed to the compensatory activation of CASP7²⁷⁶. The combined ablation of
277 *Casp3* and *Casp7* causes embryonic lethality on the C57BL/6 background, although death is caused by
278 severe cardiac rather than brain defects²⁷⁷. Such phenotypic differences may originate from some degree
279 of substrate selectivity exhibited by CASP3 vs. CASP7^{278,279,280,281,282}. Moreover, a recent study
280 performed in *Casp7*^{-/-} mice indicates that CASP7 acts as a facilitator of the variants of RCD occurring in
281 the context of pore-driven lysis rather than an apoptotic executioner²⁸³.

282 Approximately 5% of APAF1-deficient mice develop normally and survive into adulthood, although
283 males are often sterile due to defective spermatogenesis²⁴⁷; their phenotype is reminiscent of the
284 phenotype of mice deficient for BAX, BAK1 and BOK (*i.e.*, *Bak1*^{-/-}*Bax*^{-/-}*Bok*^{-/-} mice)⁶⁴. Of note, rare
285 adult *Apaf1*^{-/-} male mice that retain fertility display expansion of the lateral brain ventricles coupled with
286 behavioral abnormalities and growth retardation²⁶⁷. Conversely, the rare mice expressing a CYCS
287 variant specifically deficient in apoptotic functions that survive into adulthood exhibit impaired
288 lymphocyte homeostasis²⁶¹. Whole-body deletion of diablo, IAP-binding mitochondrial protein (*Diablo*,
289 coding for a pro-apoptotic factor also known as SMAC) alone or along with HtrA serine peptidase 2
290 (*Htra2*) does not result in developmental defects in mice^{284,285}, while the *Diablo*^{-/-}*Casp3*^{-/-} genotype
291 accrues the perinatal lethality observed in *Casp3*^{-/-} mice²⁸⁶. Mice lacking the X-linked inhibitor of
292 apoptosis (XIAP, the main target of the pro-apoptotic activity of SMAC and HTRA2) are also viable and
293 develop normally, possibly due to functional compensation by other members of the inhibitor of
294 apoptosis protein (IAP) family^{287,288}, but they exhibit mild defects in late pregnancy that do not
295 compromise lactation²⁸⁷. Consistent with this SMAC-mimetic drugs that were designed to induce

296 apoptosis by antagonizing IAPs are quite well tolerated ²⁸⁹. *Xiap*^{-/-} mice also show dysregulated innate
297 immune responses ²⁹⁰, most likely linked to the modulatory role of XIAP in inflammation and necroptosis
298 ^{291, 292, 293}, or to the inability of these animals to resolve infections ²⁹⁴. Accordingly, loss-of-function
299 mutations in *XIAP* are associated with X-linked lymphoproliferative syndrome type 2 in humans ^{291, 295},
300 ^{296, 297}.

301 The myocardium-specific deletion of *Casp3* and *Casp7* impairs heart development in mice resulting in
302 myocyte hypertrophy ²⁹⁸. The role of APAF1, CASP9 and CASP3 in hematopoiesis remains debated.
303 Specific ablation of *Apaf1* or *Casp9* from the hematopoietic system using lethally irradiated wild-type
304 mice reconstituted with hematopoietic stem/progenitor cells deficient for these factors did not expand
305 the lymphoid or myeloid cell compartments ²⁹⁹. Likewise, no hematopoietic defects emerge from the
306 whole-body deletion of *Casp3* ²⁷⁷. Moreover, mice lacking *Casp9* in the hematopoietic system display a
307 proper generation and functionality of megakaryocytes and platelets ³⁰⁰. Moreover, the clearance of
308 *Casp9*^{-/-} thymocytes seems to occur in a caspase-independent fashion ³⁰¹. In the same line, although
309 apoptosis is widely believed to be crucial for epithelial cell death and shedding in the intestine, during
310 steady state, executioner CASP3 and CASP7 are dispensable for intestinal epithelial cell turnover at the
311 top of intestinal villi, intestinal tissue dynamics, microbiome, and immune cell composition, suggesting
312 high redundancy in non-challenged conditions ³⁰². Apparently at odds with these observations, *Casp3*^{-/-}
313 mice were reported to have abnormally increased numbers of splenic B cells manifesting increased
314 proliferative capacity ³⁰³, as well as a dysregulated activity in bone marrow stromal stem cells that
315 attenuated osteogenic differentiation ³⁰⁴. A similar debate revolves around the requirement for APAF1
316 and caspase activity in thymocyte selection and/or T cell responses ^{299, 305, 306, 307, 308, 309}. Mouse bone
317 marrow chimeras deficient for APAF1 or CASP9 in their hematopoietic cells displayed a defect in
318 hematopoietic stem/progenitor cells that is caused by the aberrant type 1 interferon production caused by
319 the fact that hematopoietic cells undergoing normal programmed cell death do not die in a “neat” non-

320 inflammatory manner^{310, 311}. Taken together, these findings suggest that BAX/BAK1 dependent death
321 of hematopoietic cells does not require caspases but that caspases are needed to prevent an inflammation
322 causing form of cell demolition^{312, 313, 314, 315}. However, neither the degree of functional redundancy
323 exhibited by CASP3, CASP6 and CASP7, nor the potential for APAF1-independent CASP3 activation
324 has been formally excluded in these studies, most of which involved single genetic alterations.

325

326 **Box 5. Principles of extrinsic apoptosis.**

327 Extrinsic apoptosis is a regulated cell death (RCD) process frequently triggered by immune effector cells
328 expressing TNF superfamily death ligands binding the death receptor (DRs) upon binding of a cognate
329 ligand^{316, 317, 318}. The principal DRs which will be discussed in the review are the Fas cell surface death
330 receptor (FAS; also known as CD95 or APO-1), the TNF receptor superfamily member 1A (TNFRSF1A;
331 best known as TNF-R1), the TNF receptor superfamily member 10a (TNFRSF10A; best known as
332 TRAIL-R1 or DR4) and the TNF receptor superfamily member 10b (TNFRSF10B; best known as
333 TRAIL-R2 or DR5). FAS is activated by the binding of FAS ligand (FASLG; also known as CD95L or
334 APO-1L; FASL in mice), which is primarily expressed by effector immune cells³¹⁸. TNF-R1 is activated
335 by tumor necrosis factor (TNF), a functionally pleiotropic cytokine expressed in cells in the spleen,
336 thymus and certain other adult tissues³¹⁶. Of note, while the soluble form of TNF preferentially binds to
337 TNF-R1, the membrane-anchored form mainly interacts with the TNF receptor superfamily member 1B
338 (TNFRSF1B, best known as TNF-R2), which does not have death domain and therefore is not a DR³¹⁹.
339 Finally, TRAIL-R1 and TRAIL-R2 are specifically activated by the binding of TNF superfamily member
340 10 (TNFSF10; best known as TRAIL), which is expressed by a variety of cell subtypes of the innate as
341 well as adaptive system, including monocytes, macrophages and effector T cells, as either a soluble or
342 membrane-bound version³²⁰. Of note, mice express only one TRAIL receptor (TRAIL-R2, referred in
343 this article as mTRAIL-R) which is equally homologous to human TRAIL-R1 and TRAIL-R2.

344 Upon ligand binding and trimerization and in certain instances formation of higher order complexes, the
345 engagement of DRs promotes the assembly of multi-protein complexes, such as the death-inducing
346 signaling complex (DISC) and complex II, resulting in the activation of caspase 8 (CASP8) and apoptosis
347^{321, 322, 323, 324}. The DISC, which is assembled on the cytoplasmic tail of ligated FAS, TNF-R1, TRAIL-
348 R1 or TRAIL-R2, is comprised of the molecular adaptor Fas-associated death domain protein (FADD),

349 Fas (TNFRSF6)-associated via death domain (FADD), CASP8, and (FADD-like IL-1 β -converting
350 enzyme)-inhibitory protein distinct isoforms of CASP8 and FADD like apoptosis regulator (CFLAR;
351 best known as c-FLIP), including the alternative splicing variants, the long form c-FLIP_L and the short
352 form c-FLIP_S and (in human) c-FLIP_R^{325, 326, 327, 328, 329, 330}. Of note, c-FLIPs are catalytically inactive
353 CASP8-like molecules acting as a modulator of CASP8 activation. Unlike FAS- and TRAIL-R-
354 associated DISCs, complex II is a cytosolic complex assembled secondarily upon TNF-R1 ligation, in
355 conditions of reduced pro-survival signaling and protein synthesis as for instance upon administration of
356 inhibitors of inhibitor of apoptosis proteins (IAPs) and cycloheximide³³¹. Complex II consists of FADD
357 and CASP8 in association with either TNF-R1-associated death domain protein (TRADD) (complex IIa)
358 or receptor interacting serine/threonine kinase 1 (RIPK1) (complex IIb), which is involved in the
359 modulation of apoptosis and necroptosis³³². Upon the recruitment to the DISC (complex I), CASP8 is
360 activated by a process involving CASP8 oligomerization and autoproteolysis. CASP8 then acts as the
361 executor of extrinsic apoptosis by favoring the proteolytic activation of the effector caspases CASP3 and
362 CASP7³³³. This direct pathway is sufficient for FAS ligand induced killing thymocytes and mature
363 lymphocytes (so-called type 1 cells), but the efficient killing of hepatocytes, pancreatic β cells, and most
364 cancer cells (so-called type 2 cells) requires pathway amplification through caspase-8 mediated
365 proteolytic activation of the BH3-only protein BID, leading to engagement of the intrinsic apoptotic
366 pathway^{117, 334, 335, 336, 337, 338, 339 PMID: 9501089 PMID: 9501089 PMID: 9501089 PMID: 9501089}. Of note, the absence of
367 XIAP converts type 2 cells into type 1 cells¹²³, indicating that a limited amount of caspase activity is
368 needed for cell killing.

369 Once activated, CASP8 also cleaves RIPK1 leading to the inhibition of necroptosis and the maintenance
370 of inflammatory homeostasis³⁴⁰. As a further layer of complication, the engagement of DRs by their
371 respective ligands does not necessarily culminate in the activation of the extrinsic apoptosis signaling

372 pathway. Indeed, the engagement of FAS, TRAIL-Rs and TNF-R1 can also result in the activation of
373 pro-survival pathways which is often but not always dependent on NF- κ B signaling^{320, 341}, or,
374 alternatively, in the initiation of inflammatory responses, the promotion of processes including cell
375 differentiation/activation (as is the case of lymphocytes), and the activation or inhibition of other RCD
376 variants, particularly necroptosis and pyroptosis³⁴². The induction of inflammatory chemokines and
377 cytokines downstream of the activation of FAS and TRAIL-Rs is mediated by FADD and CASP8 by a
378 mechanism that can be independent of apoptosis induction^{343, 344}.

379 Extrinsic apoptosis can be activated by another class of cell surface receptors known as dependence
380 receptor. In this case, cell death is ignited by the decrease in the availability of a specific ligand on which
381 these receptors depend, while the latter through the binding of a cognate ligand^{345, 346}. The dependence
382 receptors include (but are not limited to) the DCC netrin 1 receptor (DCC) and distinct types of unc-5
383 netrin receptors (UNC5A, UNC5B, UNC5C, and UNC5D), all of which are bound by netrin 1 (NTN1),
384 and the neurotrophic receptor tyrosine kinase 3 (NTRK3) and patched 1 (PTCH1), which are,
385 respectively, ligated by neurotrophin and sonic hedgehog (SHH). The activation of dependence receptors
386 stimulates hitherto poorly characterized signaling cascade often dependent on caspase activation, leading
387 to the induction of cell death^{347, 348}. It is noteworthy that the relevance of the dependence receptor-
388 induced apoptosis for normal physiology and disease is not established.

389 **Box 6. Impact of death receptors on health.**

390 A large body of data demonstrates that death receptor (DR) signaling is crucial for the maintenance of
391 adult tissue homeostasis but not for embryonic development as demonstrated by the normal appearance
392 of mice double knockout for caspase 8 and mixed lineage kinase domain like pseudokinase (*Casp8*^{-/-}
393 *Mkl1*^{-/-} mice) or CASP8 and receptor-interacting serine-threonine kinase 3 (*Casp8*^{-/-}*Ripk3*^{-/-} mice) (before
394 they develop lymphadenopathy and splenomegaly)^{349, 350, 351, 352, 353, 354}. Mouse strains with spontaneous
395 mutations in TNF receptor superfamily member 6 (*Fas*) - the so-called *lpr/lpr* mice – or Fas ligand (TNF
396 superfamily, member 6) (*Fasl*) - the so-called *gld/gld* mice - are viable but develop progressive
397 lymphoproliferative and systemic lupus erythematosus (SLE)-like disorders^{355, 356, 357, 358, 359}. The
398 severity of these pathologies is greatly influenced by genetic background: fairly mild on a C57BL/6
399 background but very severe on the MRL or NOD backgrounds. Mice with heterozygous *Fas* or *Fasl*
400 mutations are normal³⁵⁹. These lymphoproliferative and autoimmune disorders are not accompanied by
401 impaired thymocyte development³⁶⁰. Transgenic overexpression of BCL2³³⁵ or MCL1³⁶¹ in the
402 lymphocyte compartment of *lpr/lpr* mice or the absence of BIM³⁶² massively exacerbate
403 lymphadenopathy. This is consistent with the notion that intrinsic apoptosis and DR-induced apoptosis
404 are distinct in lymphoid cells and act additively. FAS or FASL deficiency also perturbs the homeostasis
405 or function of other mouse tissues, including (but not limited to) the liver³⁶⁰, kidney³⁶³, retina³⁶⁴,
406 pancreas³⁶⁵ and intestinal epithelium³⁶⁶, but these effects may all be a consequence of the deregulation
407 of the lymphoid system in these mice, for example causing excess production of certain cytokines and
408 chemokines.

409 Conditional deletion of *Fas* and *Fasl* in specific immune cell subsets as well as transgenic expression of
410 FAS in lymphocytes confirms the crucial role of FASL-FAS signaling in the homeostasis of lymphocytes
411 and dendritic cells (DCs)^{367, 368, 369, 370, 371}. In this context, experiments in *lpr/lpr* mice deleted of BH3-

412 only protein BCL2 like 11 (*Bcl2l11*, the gene encoding BIM) demonstrate some degree of cooperation
413 between FAS and BIM in preserving the functionality of the immune system³⁶². However, abrogating
414 FAS-FASL signaling ultimately has heterogeneous organismal consequences. The lymphoproliferative
415 disorder caused by *Fas* or *Fasl* deletion confers protection from autoimmune diabetes³⁷². This may be
416 explained by the fact that the distortion of the T cell repertoire caused by the lymphadenopathy in the
417 *lpr/lpr* and *gld/gld* mice prevents the development of diabetogenic T cells. Finally, FAS appears to exert
418 tumor suppressive effects in lymphoid cells. Indeed, both *gld/gld* mice as well as *lpr/lpr* mice lacking the
419 T cell compartment have increased incidence of B cell lymphoma^{373, 374, 375}. Loss of FAS also predisposes
420 humans to B lymphoma (see below).

421 As for the other DRs, mice lacking TNF receptor superfamily member 10b (TNFRSF10B, best known
422 as TRAIL-R2 or mTRAIL-R) or its ligand TNF superfamily member 10 (*TNFSF10*, best known as
423 TRAIL) are viable, fertile, and do not spontaneously develop autoimmune diseases^{376, 377, 378, 379}.
424 Moreover, these mice exhibit normal immune system development and function^{380, 381, 382, 383}. Along
425 similar lines, the whole-body deletion of the DR ligand tumor necrosis factor (*Tnf*) does not affect mouse
426 development and fertility^{384, 385}. However, *Tnf*^{-/-} mice often show early hearing loss and, despite
427 presenting with an overtly functional immune system, these mice exhibit abnormally increased
428 susceptibility to spontaneous bacterial infection, which has been ascribed to multiple defects including
429 defective lymphoid organ architecture as well as deficient granuloma and germinal center formation^{384,}
430 ^{385, 386, 387, 388}. Impaired responses to pathogens have been documented in *Tnf*^{+/-} mice³⁸⁴ as well as in mice
431 lacking TNF receptor superfamily member 1A (TNFRSF1A, best known as TNF-R1)^{386, 389, 390}.
432 Conversely, mice overexpressing TNF in cardiomyocytes suffer from lethal dilated cardiomyopathy,
433 demonstrating that balanced TNF signaling is essential for the homeostasis of the cardiac tissue^{391, 392,}
434 ³⁹³. Of note, while the lack of TRAIL enhances the severity of lymphoproliferative and autoimmune
435 disorders in *gld/gld* mice³⁹⁴, the lack of TNF attenuates the lymphoproliferative phenotype, extending

436 the survival of *gld/gld* mice³⁹⁵. The latter is probably due to the reduction in TNF-mediated inflammation
437 attenuating lymphadenopathy caused by the absence of FAS ligand. These findings confirm the
438 pleiotropy and redundancy of DR signaling, encompassing not only apoptotic and non-apoptotic
439 regulated cell death (RCD)-related effects, but also various pro-survival and pro-inflammatory modules.
440 Multiple clinical observations support the role of FAS ligand/FAS signaling in human hematopoiesis³⁹⁶,
441³⁹⁷. Most human patients with autoimmune lymphoproliferative syndrome (ALPS) - a primary
442 immunodeficiency manifesting with lymphadenopathy, splenomegaly as well as abnormal numbers,
443 development and function of lymphocytes carry loss-of-function mutations in *FAS* or *FASLG*^{398, 399, 400,}
444^{401, 402, 403, 404}. ALPS patients also display an increased incidence of non-Hodgkin and Hodgkin lymphoma
445⁴⁰⁵. While no mutations in the genes encoding TRAIL, TRAIL-R1 and TRAIL-R2 have so far been linked
446 to human autoimmune diseases, autosomal dominant mutations in *TNFRSF1A* (leading to lack of TNF-
447 R1) have been identified in patients affected by TNF receptor-associated periodic syndrome (TRAPS),
448 characterized by severe abdominal pain, arthralgias, and myalgias^{406, 407, 408}.

449

450 **Box 7. Impact of extrinsic apoptosis complexes and caspases on health.**

451 Several signal transducers in the death receptor (DRs) pathway are essential for embryonic development
452 in mice. Thus, deletion of Fas (TNFRSF6)-associated via death domain (*Fadd*), caspase 8 (*Casp8*) or
453 CASP8 and FADD-like apoptosis regulator (*Cflar*) is embryonic lethal at mid-gestation as a consequence
454 of severe vascular as well as cardiac defects associated with spontaneous intra-abdominal hemorrhage
455 ^{409, 410, 411, 412, 413, 414}. Of note, CASP8-deficient mice also exhibit neural tube defects ⁴¹³. A similar
456 embryonic lethality has also been documented in mice expressing a mutant form of FADD deficient in
457 its death domain ⁴¹⁰. The absence of other components of DR-associated signaling complexes, such as
458 TNFRSF1A associated via death domain (TRADD) and receptor-interacting serine/threonine kinase 1
459 (RIPK1), causes different abnormalities. Thus, while *Tradd*^{-/-} mice develop normally and do not display
460 major hematopoietic defects ^{415, 416, 417}, *Ripk1*^{-/-} mice die early after birth due to severe multiorgan
461 inflammation ^{418, 419}. These findings are attributed to the pleiotropic contribution of RIPK1 and TRADD
462 to a variety of processes beyond apoptosis, most notably necroptotic regulated cell death (RCD) and
463 inflammation. This is exemplified by the observation that the embryonic lethality caused by the absence
464 of CASP8 or FADD can be rescued by the concomitant loss of MLKL or RIPK3 (see text). Mice lacking
465 baculoviral IAP repeat-containing 3 (BIRC3; best known as IAP1) and X-linked inhibitor of apoptosis
466 (XIAP) or IAP1 and BIRC2 (best known as IAP2) but not mice lacking IAP2 and XIAP display
467 embryonic lethality ⁴²⁰. These findings indicate specific functional redundancies among the inhibitor of
468 apoptosis protein family. IAP1/IAP2-deficient mice display mid-gestation lethality, which was rescued
469 to birth by the deletion of TNF receptor superfamily member 1A (*Tnfrsf1a*, encoding TNF-R1) but not
470 that of TNF receptor superfamily member 1B (*Tnfrsf1b*, best known as TNF-R2) ⁴²⁰. Loss of one allele
471 of *Ripk1* or loss of *Ripk3* prolonged embryonic survival of these mice ⁴²⁰. It is noteworthy, that, as
472 discussed above, genetic background effects might contribute to the phenotype, as mice with concomitant

473 knockout of the genes encoding IAP1 and IAP2 using mutant alleles generated in C57BL/6 embryonic
474 stem cells die in midgestation ⁴²⁰, whereas *Iap1*^{-/-} and *Xiap*^{-/-} double mutants generated using 129Sv
475 embryonic stem cells are viable ⁴²¹.

476 It was demonstrated that embryonic lethality in *Casp8*^{-/-} and *Fadd*^{-/-} mice is due to excessive necroptosis,
477 reflecting the ability of CASP8 to limit necroptosis downstream of DR activation ^{349, 350, 422, 423}.
478 Accordingly, deletion of genes encoding key components of the necroptotic machinery such as RIPK3
479 or MLKL prevents all developmental defects and embryonic lethality in FADD- or CASP8-deficient
480 embryos ^{349, 350, 351, 352, 354, 423, 424}. Of note, *Casp8*^{-/-}*Ripk3*^{-/-} and *Casp8*^{-/-}*Mkl1*^{-/-} mice develop progressive
481 lymphoproliferative disorders that resemble those caused by the absence of FAS or FASL ^{350, 351, 423}.
482 Moreover, embryonic lethality around E10.5 in mice lacking c-FLIP and the perinatal lethality of *Ripk1*^{-/-}
483 mice depend on aberrant activation of both DR-induced apoptosis and DR-induced necroptosis. Indeed,
484 the lethality of these animals can be rescued by concomitant deletion of *Fadd* and *Ripk3*, *Casp8* and
485 *Ripk3*, or *Fadd* and *Mkl1* ^{349, 350, 351, 352, 353, 354}. Of note, mice with loss of *Ripk1* that prevents its CASP8-
486 mediated cleavage die around E10.5 of embryonic development and this can be prevented by the
487 combined absence of RIPK3 and CASP8 ^{340, 425, 426}. In a heterozygous state these mutations in the gene
488 encoding RIPK1 cause severe auto-inflammation. As an additional layer of complexity, although the
489 deletion of *Tradd* rescues *Ripk1*^{-/-}*Ripk3*^{-/-} embryos from perinatal lethality, triple knockout mice die
490 postnatally ^{427, 428}. Moreover, TRADD deficiency does not prevent the embryonic lethality caused by the
491 loss of FADD ⁴²⁸. Additional studies confirm the importance of the inter-connectivity between multiple
492 regulated cell death (RCD) pathways. Mice with a mutation that prevents auto-proteolytic activation of
493 CASP8 develop normally ⁴²⁹, but akin to complete loss of *CASP8*, mutations in the CASP8 catalytic site
494 result in embryonic lethality around E10.5 due to aberrant necroptosis ^{425, 430}, while the genetic ablation
495 of *Mkl1* or *Mkl1* plus *Fadd* prevent E10.5 embryonic lethality in these mice, the compound mutant mice

496 die soon after birth, likely due to aberrant inflammation and pyroptosis^{431, 432}. These observations point
497 to the central role for CASP8 in the regulation of multiple RCD variants and inflammatory processes⁴³³.
498 The tissue-specific deletion of *Fadd* or *Casp8* in mouse endothelial cells results in an embryonic lethal
499 phenotype that resembles that of germline *Fadd* or *Casp8* deletion^{434, 435}. Conversely, the absence of
500 FADD in cardiomyocytes or cardiac progenitor cells appears to have no impact on embryonic
501 development⁴³⁴. Again, abrogation of necroptosis rescued the lethal phenotype of endothelial cell
502 specific *Fadd* or *Casp8* deletion⁴³⁴, lending additional support to inhibitory role of FADD and CASP8
503 in necroptotic RCD. FADD, CASP and CFLAR (best known as c-FLIP) have also been implicated in
504 hematopoietic system homeostasis. However, the absence of FADD in specific immune cell subsets in
505 mice via distinct experimental approaches, such as conditional gene deletion, injection of *Fadd*^{-/-}
506 embryonic stem cells into *Rag1*^{-/-} blastocysts or transgenic expression of a dominant-negative variant of
507 FADD does not drive lymphoproliferative disorders. Instead, FADD appears to be critical for the
508 proliferation and/or development of T lymphocytes^{436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446} and B cells⁴⁴⁷,
509 most likely by preventing necroptosis through activation of CASP8 which then prevents RIPK1/RIPK3
510 mediated activation of MLKL. Similar conclusions were derived from the analysis of mice with
511 lymphocyte-specific ablation of *Casp8* or *Cflar*^{448, 449, 450, 451, 452, 453}. A role for CASP8 in T cell
512 proliferation has also emerged from the realization of the anti-proliferative effects of caspase inhibitors
513⁴⁵⁴. The T cell-specific deletion of *Casp8* attenuates autoimmunity and improved the survival of mice
514 lacking the BH3-only protein BCL2 like 11 (BCL2L11, best known as BIM) by limiting T cell
515 proliferation and survival⁴⁵⁵. Apparently at odds with these findings, the conditional deletion of *Casp8*
516 in T cells has also been associated with an age-dependent, lymphoproliferative immune disorder
517 resembling the condition of patients with *CASP8* mutations⁴⁵⁶. Whether mouse genetic background or
518 other contextual variables (*e.g.*, the mouse microbiota) underlie such apparent discrepancies remains to
519 be elucidated.

520 The conditional loss of the functions of FADD or CASP8 also revealed a role for these proteins in early
521 hematopoiesis, which may relate to their ability to promote the proliferation and differentiation of
522 hematopoietic stem and progenitor cells by preventing necroptosis^{435, 457, 458}. Conditional deletion of
523 *Fadd* in myeloid cells resulted in increased myeloid and B cell populations coupled to activation of
524 inflammatory responses⁴⁵⁹. Along similar lines, the macrophage-restricted deletion of *Casp8* induced a
525 mild systemic inflammatory disease potentially linked to altered macrophage polarization^{460, 461}, while
526 the DC-specific deletion of the genes encoding c-FLIP or CASP8 elicited splenomegaly, inflammatory
527 responses and autoimmune disorders^{462, 463, 464}. These effects all seem to be unrelated to the pro-apoptotic
528 functions of FADD and CASP8 but reflect their ability to prevent necroptosis^{350, 423, 443, 459, 460, 465, 466, 467}.
529 Corroborating these findings, loss-of-function mutations in *FADD*^{468, 469, 470, 471}, *CASP8* or *CASP10*^{472,}
530^{473, 474} and *TRADD*⁴⁷⁵ have been associated with ALPS-like syndromes and certain hematological
531 diseases in humans. Of note, patients with ALPS bearing mutations in *FADD* or *CASP8* but not ALPS
532 patients with mutations in *FAS* or *FASLG* also exhibit immunodeficiency coupled with lymphocytic
533 infiltrations in multiple organs, granulomas and/or inflammatory bowel disease^{468, 472, 476, 477, 478}.

534 Tissue-specific deletion of *Fadd*, *Casp8* and *Cflar* has also revealed a role for these proteins in the
535 homeostasis of the liver, skin and intestine, although severity of the phenotype varies quite considerably,
536 ranging from mild inflammatory response to embryonic or early postnatal lethality, again likely due to
537 unleashed necroptosis. Conditional deletion of *Cflar* (resulting in lack of c-FLIP) in intestinal epithelial
538 cells, hepatocytes or keratinocytes resulted in embryonic or perinatal lethality due to aberrant activation
539 of cell death^{479, 480, 481, 482}. The inducible deletion of *Cflar* from the intestinal epithelium of adult mice
540 caused severe inflammation that was often fatal⁴⁸². These findings are in line with the crucial role of c-
541 FLIP as an inhibitor of necroptosis^{349, 483}. Along similar lines, *Fadd* deletion in epidermal keratinocytes
542 or intestinal epithelial cells causes severe chronic inflammation due to the induction of aberrant
543 necroptosis^{484, 485, 486, 487, 488, 489, 490}. Accordingly, the removal of FADD (or CASP8) in intestinal

544 epithelial cells resulted in chronic inflammatory colitis and ileitis, which was prevented by concomitant
545 deletion of *Ripk3* or *Mklk*^{430, 432, 485, 487, 490, 491}. In one of these studies, acute deletion of *Casp8* in the gut
546 of adult mice resulted in enterocyte death, leading to disruption of tissue homeostasis, sepsis and death
547⁴⁹⁰. In this context, CASP8-deficient enterocytes displayed decreased *in vivo* survival and migration
548 potential⁴⁹². Specific deletion of *Casp8* in endothelial cells results in small intestinal hemorrhage and
549 bowel inflammation, suggesting a key role of CASP8 in vascular homeostasis in the small intestine⁴⁹³.
550 Expression of a catalytically inactive variant of CASP8 resulted in embryonic lethality similar to *Casp8*
551^{-/-} mice, which was rescued by concomitant deletion of *Mkl*⁴³⁰. However, unexpectedly, catalytically
552 inactive CASP8 mutant mice also deficient for MLKL died perinatally. Loss of CASP8 catalytic activity
553 specifically in intestinal epithelial cells induced intestinal inflammation similar to absence of CASP8 in
554 the intestinal epithelium. This intestinal phenotype was aggravated by *Mkl* deletion, resulting in
555 premature death dependent on the induction of inflammatory responses and pyroptosis⁴³⁰. As an added
556 layer of complexity, deletion of tumor necrosis factor (*Tnf*) or *Tnfrsf1a* (encoding TNF-R1) attenuated
557 colitis, but not ileitis, in mice with an intestinal epithelial cell-specific deletion of *Fadd* or *Casp8*^{482, 485}.
558 A recent study indicated that this effect may also involve the aberrant activation of pyroptosis. Indeed,
559 the CASP8-dependent activation of gasdermin D (GSDMD) appears to promote ileitis in mice with
560 FADD-deficient intestinal epithelial cells⁴⁹⁴. These results are in line with the crucial involvement of
561 CASP8 and FADD in the activation of inflammation^{495, 496} and indicate that the FADD-CASP8 axis
562 regulates tissue homeostasis by balancing apoptosis, necroptosis, pyroptosis and inflammation.

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