Death sentence: The tale of a fallen endoplasmic reticulum

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Death sentence: the tale of a fallen Endoplasmic Reticulum

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Summary

Endoplasmic Reticulum (ER) stress signaling is an adaptive mechanism triggered when protein folding demand overcomes the folding capacity of this compartment, thereby leading to the accumulation of improperly folded proteins. This stress signaling pathway is named the Unfolded Protein Response (UPR) and aims at restoring ER homeostasis. However, if this fails, mechanisms orienting cells towards death processes are initiated. Herein, we summarize the most recent findings connecting ER stress and the UPR with identified death mechanisms including apoptosis, necrosis, pyroptosis, ferroptosis, and autophagy. We highlight new avenues that could be investigated and controlled through actionable mechanisms in physiology and pathology.

Keywords: Apoptosis, Autophagy, Cell death, Endoplasmic reticulum, Ferroptosis, Pyroptosis, Unfolded Protein Response

General introduction

The endoplasmic reticulum (ER) is the gateway to the secretory pathway and one of the most abundant membrane-delimited organelles in the cell. It plays an essential role in the maintenance of lipid, calcium and protein homeostasis and is physically and functionally connected to many other cellular compartments such as the Golgi apparatus, the endo-lysosomal system, and mitochondria [1]. Thus, ER homeostasis is an essential factor for global cellular function. ER homeostasis can be challenged by an imbalance between the protein folding load and the ER protein folding capacity. Such a situation is called ER stress and is dealt with by the cell through the activation of an adaptive mechanism named the Unfolded Protein Response[1] which primarily aims at restoring ER homeostasis. If this succeeds, then the UPR is turned off and the normal cellular functions are resumed. In contrast, if stress cannot be alleviated, the UPR triggers the cell to death [1].

1- Current knowledge: the dogma

1.1. ER stress signaling pathways – generalities

When the ER is stressed, for example by the accumulation of improperly folded proteins, the UPR is triggered. The UPR is mediated by three transmembrane ER stress sensors called Protein kinase RNA-like ER Kinase (PERK), Activating Transcription Factor 6 (ATF6) and Inositol-Requiring Enzyme 1 α (IRE1α referred to as IRE1) [1]. Upon accumulation of misfolded proteins in the ER, PERK gets activated through a homo-oligomerization process leading to PERK trans-autophosphorylation and phosphorylation of its main substrate, the translation initiation factor eIF2alpha (eIF2α). This leads to translation attenuation concomitant with the synthesis of ATF4, a transcription factor controlling the expression of both pro-survival and pro-death genes such as CHOP. ATF6 is a type II transmembrane ER-resident protein, which upon ER stress is exported to the Golgi complex where it is cleaved by S1P and S2P proteases. The released cytosolic fragment, ATF6f, is a transcription factor that regulates the expression of genes involved in the control of ER protein folding, quality control and degradation [1]. The third sensor is IRE1, a type I ER-resident transmembrane protein that bears both kinase and endoribonuclease (RNase) activities in its cytoplasmic domain. Upon ER stress IRE1 is activated through mechanisms similar to PERK. IRE1 oligomerization leads to its trans-autophosphorylation through the kinase domain resulting in a conformational change and activation of its RNase domain. The IRE1 RNase domain contributes to i) the non-conventional splicing of XBP1 mRNA together with the tRNA ligase RtcB in mammalian cells [1] and ii) the cleavage of RNA (including mRNA, miRNA, rRNA) through a mechanism called Regulated IRE1-dependent decay of RNA (RIDD) [1]. The balance between *XBP1* mRNA splicing and RIDD could be controlled (at least in part) by the oligomeric status of IRE1. The *XBP1*s (spliced) mRNA lacks a 26 nucleotide intron that leads to a shift in its reading frame. The resultant transcript is translated into the XBP1s protein, a potent transcription factor contributing actively to pro-survival functions (including restoring ER homeostasis). RIDD functions are less clear with both pro-survival and pro-death roles reported.

1.2. Pro-apoptotic ER stress signaling

Unresolved ER stress conditions trigger a UPR considered “terminal” since it induces cell death (**Figure 1**). In brief, the direct activation of the UPR sensors, and in particular IRE1, has been linked to cell death processes through uncontrolled RIDD activity and the non-selective degradation of RNA. In particular, RIDD may target mRNA encoding proteins which promote survival, though RIDD may also be involved in adaptive mechanisms (see below, [2]).

Furthermore, multiple studies have demonstrated that, at least in certain cell types, this terminal UPR induces the expression of the transmembrane Death Receptor (DR) TRAIL-R2, sometimes accompanied by the up-regulation of TRAIL-R1 and their cognate ligand TRAIL, as reviewed in [3, 4]. This phenomenon has been mainly attributed to the activation of the PERK branch of the UPR and ensuing expression of CHOP. These TRAIL-Rs are not only up-regulated and exposed at the plasma membrane upon irreparable ER stress (and might thus induce apoptosis from this location), but also accumulate in the ER/Golgi compartments. Endomembrane-located TRAIL-Rs can also induce the activation of initiator caspases, though through a TRAIL-independent mechanism which has only recently been unraveled for TRAIL-R2 (see part 2.1). In addition to the direct activation of effector caspases by caspase-8, the mitochondrial apoptotic pathway can be engaged upon unresolvable ER stress, in a DR-, caspase-8-, and Bid-dependent manner and thereby contribute to effector caspase activation and the induction of cell death. Activation of the mitochondrial pathway independently of TRAIL-Rs has also been reported upon ER stress. Indeed, the PERK-dependent upregulation of CHOP modulates the expression of several members of the B-cell lymphoma 2 (BCL-2) family of proteins. This event plays a central role in the engagement of the mitochondrial apoptosis pathway [5].

The BCL-2 family is a large class of both pro- and anti-death proteins which are known to regulate the integrity of the outer mitochondrial membrane. Among these, the pro-apoptotic BH3-only proteins contain a short alpha helix known as the BCL-2 homology 3 (BH3) domain necessary for cell death. The BH3-only proteins BID, BIM, NOXA, and PUMA are activated during the terminal UPR [6] and, once activated, antagonize mitochondrial-protective proteins such as BCL-2 and BCL-XL or directly activate the multidomain proapoptotic BAX and BAK proteins to permeabilize the outer mitochondrial membrane, a process termed MOMP (mitochondrial outer membrane permeabilization) which triggers the caspase-9-dependent activation of effector caspases (e.g. caspase-3) and thus apoptosis. Although the BCL-2 family primarily localize to the mitochondrial membrane, several members are also found at the ER where they modulate mitochondrial apoptosis. An example is the multidomain BCL-2 family member BOK [7]. At the ER, BOK is both constitutively active and continuously degraded by the proteasome through the ER-associated degradation (ERAD) pathway. Upon ER stress, BOK induces apoptosis by translocating to the mitochondria where it directly triggers MOMP independently of BAX and BAK [8, 9]. Recent studies suggest a role for BOK in modulating the UPR in response to ER stress. Indeed, work done in erythrocytes derived from *Bok*$^{-/-}$ mice showed decreased ATF4 and CHOP expression compared to WT mice, although the molecular mechanism involved was not investigated [10]. BAX and BAK respond to ER stress by assembling into higher-order oligomers at the ER membrane [11] and regulate membrane permeabilization leading to the release of ER luminal chaperones, including Binding immunoglobulin Protein (BiP), Grp94, calreticulin and Protein Disulfide-isomerase (PDI), into the cytosol [12]. ER permeabilization and the subsequent release of ER resident proteins represents a new and exciting phenomenon upon ER stress and its association with cell death and the underlying mechanisms warrant further investigation.

1.3. Discrepancies in the literature

Some of the earliest reports of the role of ER stress in cell death implicated caspase-12 as a crucial molecular player [13, 14]. However, more recent reports suggest that neither caspase-12 nor caspase-4, which was previously associated to ER stress-induced cell death [15], are required for ER stress-induced cell death which is mediated through other caspases

[16]. Another conflict within the field is that IRE1 was reported to cleave miRNA which supress caspase-2 expression thereby promoting cell death [17]. Caspase-2 is proposed to be able to cleave pro-apoptotic BCL-2 family member BID, however, a more recent paper found that caspase-2 is neither upregulated nor activated upon ER stress [18]. These finding could point to a diversity of ER stress outputs in different cellular contexts.

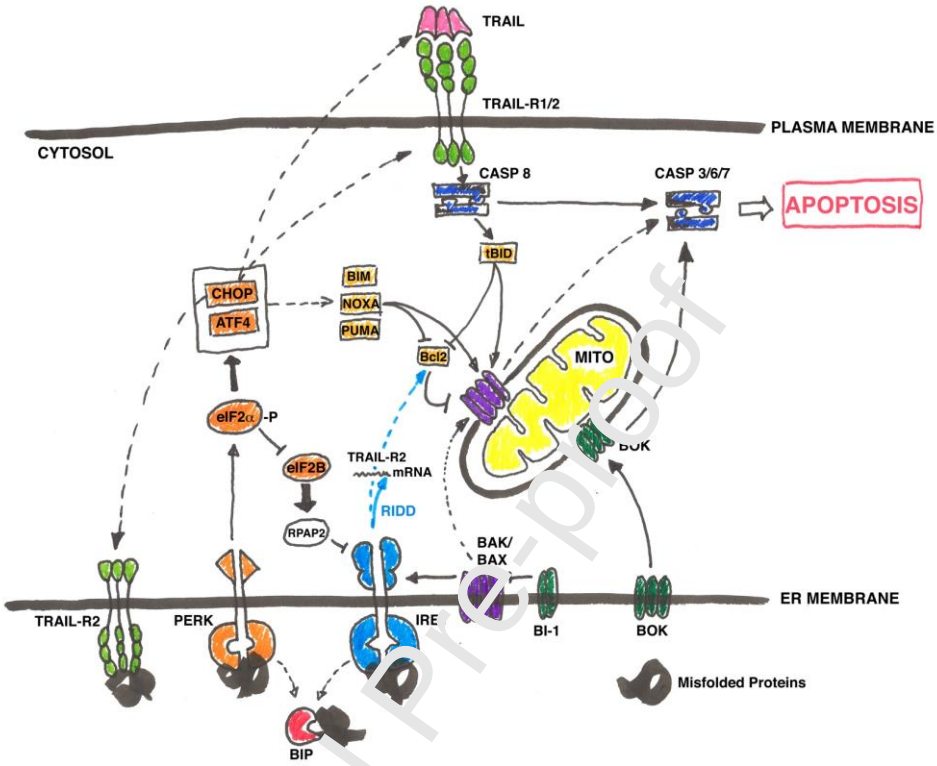

Figure 1. Cross-talks between apoptotic signaling and ER stress response. *Abbreviations: ATF4: Activating Transcription Factor 4; BAK: Bcl-2 Antagonist Killer; BAX: Bcl-2 Associated X protein; BCL-2: B-cell lymphoma 2; BIM: Bcl-2 Interacting Mediator of cell death; BiP: Binding immunoglobulin Protein; BOK: Bcl-2-related Ovarian Killer; CASP: Caspase; CHOP: C/EBP Homologous Protein; ER: Endoplasmic Reticulum; eIF2: eukaryotic translation Initiation Factor 2; IRE1: Inositol Requiring Enzyme 1; MITO: Mitochondria; PERK: Protein Kinase R-ER-like Kinase; PUMA: P53-Upregulated Modulator Of Apoptosis; RIDD: Regulated IRE1 Dependent Decay of RNA; RPAP2: RNA Polymerase II Associated Protein 2; tBID: truncated BH3 Interacting Domain Death Agonist; TRAIL: Tumor Necrosis Factor Related Apoptosis Inducing Ligand; TRAIL-R1/2: TRAIL-Receptor 1/2.*

2- Recent discoveries

2.1. New players/mechanisms in apoptotic ER signaling (Figure 1)

DRs are transmembrane proteins lacking any intrinsic catalytic activity and require ligand-induced oligomerization and conformational change to recruit adaptors, i.e. FADD in the case of TRAIL-R1/2, igniting various signaling pathways. Unliganded TRAIL-R2 exhibits an auto-inhibitory conformation, mediated by the extracellular Pre-ligand Assembly Domain, which is alleviated by TRAIL binding [19]. Thus, how the ER/Golgi-accumulated TRAIL-R2 might initiate cell death was quite enigmatic. A recent study has suggested that endomembrane TRAIL-R2 acts as a misfolded-protein sensor, providing a potential explanation for intracellular TRAIL-independent initiation of apoptosis [20]. Additional

downstream molecular levels of regulation, as described for ligand-induced DR signaling, are likely to be key in determining whether this unconventional DR activation might result in death or non-cytotoxic outcomes, e.g. cytokine production, and might thus be worth identifying. Interestingly, major players of the apoptotic pathway can modulate the nature and dynamics of protein signaling complexes associated with UPR sensors, as mainly reported for the UPRosome, a signaling platform assembled around IRE1 [21]. For instance, BAX and BAK have been suggested to interact with IRE1 and promote its activation [22]. Moreover, BI-1 was found to attenuate IRE1 signaling in various cellular models and *in vivo* [23]. Furthermore, in haemopoietic cancer cell lines, IRE1 was shown to be cleaved in a caspase-dependent manner, resulting in the accumulation of an IRE1 ER-Luminal Domain and Transmembrane segment which, at least in an overexpression system, limits BAX recruitment to the mitochondria and thus blunts apoptosis induction [24]. The role of the UPRosome in survival/death signaling may be further regulated by post-translational modification (PTM). For example, a recent study proposed that the phosphatase RPAP2, supposedly acting downstream of PERK, could, by dephosphorylating IRE1, limit its RIDD activity, thereby promoting TRAIL-R2 expression [25].

2.2 Alternative cell death induction by ER stress

2.1.1 ER stress-induced autophagic cell death (**Figure 2**) - Autophagy-dependant cell death is a form of cell death which requires autophagic machinery in order to be executed [26]. While autophagy, a regulated process of degrading and recycling cellular components, is often considered as an adaptive mechanism during ER stress, it is required for death in some instances. Generally, the switch between autophagy machinery promoting life or death is contingent on the duration of stress, or on the fitness of other cell death modalities. For instance, a death-inducing complex consisting of core autophagy protein ATG5, FADD, and caspase-8 is formed under ER stress in caspase-9-null cells, which are apoptosome-deficient [27]. It is not clear to what extent the canonical autophagy pathway plays a role in cell death in this context. The UPR promotes expression of autophagy machinery via XBP1s, ATF4, and ATF6, and more recent reports suggest roles for IRE1 in repressing [28] or activating [29, 30] autophagy depending on the cellular context; and that PERK can act independently of ATF4 in autophagy induction [28]. Very recently ATF4-induced reticulophagy was described [31] where autophagy digests the ER itself, leading to ER stress and cell death [32]. These data add further complexity to the relationship between ER stress, autophagy, and cell death, and point to a heavily context dependent role for the UPR in autophagic cell death.

2.1.2 ER stress-induced necroptosis (**Figure 2**) - Necroptosis, or regulated necrosis, is a form of cell death induced by diverse stimuli and involves signaling molecule RIPK3, and its effector MLKL, which forms pores in the plasma membrane [26]. Necroptosis is thought to be engaged as a back-up when apoptosis is compromised, and switches between these modes of cell death upon TNF-signaling are dependent on the PTM of TNFR1-associated complex components, in particular regulation of RIPK1 which activates RIPK3 [33]. Mouse fibroblast L929sA cells die via necroptosis upon treatment with TNF, and chemical ER stressors. Suppression of RIPK1, RIPK3, or MLKL in these cells is sufficient to switch the mode of ER stress-induced cell death from necroptosis to apoptosis; and JNK signalling enhances both cell death modalities. Though L929sA cells could be considered atypical in their response to ER stress, this study indicates that the UPR may induce

necroptosis in particular circumstances through a hitherto undescribed mechanism [34]. Indeed, necroptotic machinery can interact with ER stress sensors (section 2.3) and chemical chaperones which reduce ER stress can prevent necroptosis [35, 36], but little or no mechanistic link has been reported between the UPR sensors and execution of necroptosis. For example, CHOP induction by small molecule LGH00168 was reported to induce necroptosis in the human lung cancer cell line A549, but via Reactive Oxygen Species (ROS) production and not via CHOP-driven expression of necroptosis machinery [37]. One confounding study initially reported two PERK inhibitors as preventing RIPK1-mediated necroptosis however, it was subsequently found that these compounds also inhibited RIPK1, and that PERK was not involved in the necroptotic phenotype [38]. This lack of precise molecular links could suggest that the effect of ER stress on necroptosis may in fact be independent of the UPR, and come as a result of other physiological effects of ER stress.

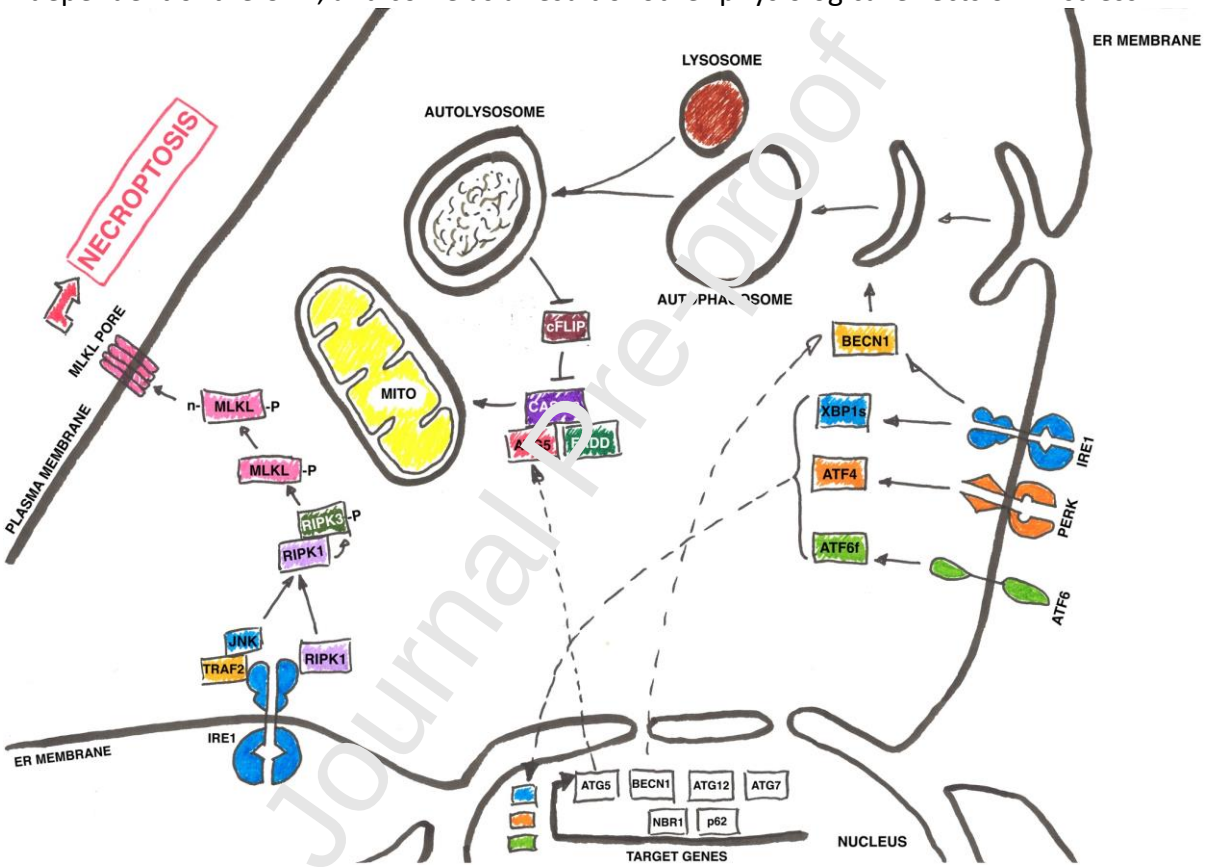

Figure 2. Cross-talks between autophagy, necroptosis signaling and ER stress response. *Abbreviations: ATF: Activating Transcription Factor; ATG: Autophagy Related; BECN1: beclin 1; CASP: Caspase; cFLIP: cellular FLICE-like Inhibitory Protein; ER: Endoplasmic Reticulum; FADD: FAS Associated Via Death Domain; IRE1: Inositol-Requiring Enzyme 1; JNK: c-Jun N-terminal Kinase; MITO: Mitochondria; MLKL: Mixed Lineage Kinase Domain-Like Pseudokinase; NBR1: NBR1 Autophagy Cargo Receptor; p62: Autophagy Receptor P62; PERK: Protein Kinase R-ER-like Kinase; RIPK: Receptor Interacting Serine/Threonine Kinase; TRAF2: TNF Receptor Associated Factor 2; XBP1s: Spliced Xbox-binding Protein 1.*

2.1.3 ER stress and pyroptosis **(Figure 3)** - Pyroptosis is a form of inflammatory Regulated Cell Death (RCD), mainly described in myeloid cells, which plays a major role in the response to pathogens. Additional roles are now reported in ischemic, neurodegenerative, and inflammatory diseases as well as various cancers [39]. Pyroptosis is

a mode of lytic cell death, resulting from the formation of pores and plasma membrane rupture and is induced by the activation of inflammasome sensors (e.g. NLRP3). This activation is often preceded by an up-regulation (the priming step), of the inflammasome sensor, adaptor, and caspases, downstream of receptors such as Toll-Like Receptors (TLRs). Of note, TLRs can also induce IRE1 activation and XBP1 splicing, which is required for some inflammatory responses [40]. Inflammasome sensors are Pattern Recognition Receptors responding to various Pathogen-Associated Molecular Patterns (PAMPs), Danger-Associated Molecular Patterns (DAMPs) and disruption of cellular homeostasis (e.g. ion fluctuations) [41]. Activation of these sensors leads to the assembly of molecular platforms called inflammasomes which activate caspases-1/4/5. These caspases can cleave gasdermin D, releasing an N-terminal domain able to form pores in the plasma membrane. A recent study has highlighted that the final plasma membrane rupture driving lytic cell death, which includes pyroptosis, is not, as long thought, the result of an osmotic event but an active process involving the protein Nerve Injury-induced protein 1 (NINJ1)[42]. In addition, caspase-1 also cleaves pro-IL-1β and pro-IL-18 into their mature inflammatory forms, which upon release also contribute to the immune-stimulatory role of pyroptosis. ER stress and ER stress response are linked with pyroptosis signaling at multiple steps. First, various ER stressors trigger the activation of NLRP3 inflammasome in a K^+ efflux- and ROS-dependent manner, and thus activate caspase-1 and the release of IL-1β in human macrophages [43]. As tested for tunicamycin, this activation depends on Voltage Dependent Anion Channel 1 (VDAC1), a mitochondrial porin, highlighting the importance of mitochondria in NLRP3 activation. However, NLRP3 activation in this context depends neither on the three UPR sensors nor on transcription. Second, two concomitant studies highlighted that activation of the UPR in pancreatic β-cells induces an up-regulation of TXNIP, through IRE1's RIDD and JNK-activating activity and via PERK-mediated up-regulation of ATF5 and Carbohydrate response element binding protein (ChREBP). Consequently, TXNIP promotes NLRP3 assembly, IL-1β and IL-18 production as well as cell death [44, 45], indicating a potential interest in targeting this pathway in the context of diabetes. This UPR-TXNIP pathway of inflammasome activation is also reported in trophoblasts cells upon hypoxia [46], circulating immune cells in type II diabetes patients [47], and hepatocytes upon ER stress and liver injury [48]. Third, NLRP3, caspase-1 and -11 can be induced upon ER stress in a CHOP-dependent manner in hepatocytes, thus highlighting a role of the UPR in "priming" the NLRP3 inflammasome [48, 49]. Saturated Fatty Acid-induced ER stress can also trigger the expression of NLRP3 in an IRE1-dependent, and supposedly RIDD-independent manner, in myeloid cells [50]. This type of priming effect has also been reported for NLRP1, downstream of IRE1, PERK and ATF4 upon ER stress in various human cell lines [51]. Translocation of ER-associated NLRP3 to mitochondria was first thought to be important for inflammasome activation [52], even though more recent data indicates that NLRP3 might actually assemble on a dispersed Trans Golgi network [53]. Furthermore, IRE1-dependent TXNIP activation upon macrophages infection by *Brucella abortus* was reported to promote mitochondrial ROS accumulation, NLRP3 activation and a caspase-2/BID axis promoting mitochondrial permeabilization and thus amplification of inflammasome activation [54]. More recently, oxidised mitochondrial DNA, which can be produced as a result of TLR-induced mitochondrial DNA replication, was demonstrated to activate the NLRP3 inflammasome [55]. Taken together, these observations imply that disruption of mitochondrial structure and/or function upon ER stress might also contribute to induction or amplification of pyroptosis.

2.1.4 ER stress and ferroptosis (**Figure 3**) - Ferroptosis is a regulated oxidative and non-apoptotic type of cell death described less than a decade ago [56]. It is implicated in an increasing number of pathologies, for example ischemic diseases, neurodegenerative disorders and type II diabetes. It has more recently gained attention amongst cancer researchers as it might constitute an actionable alternative route to eliminate tumor cells [57, 58]. Morphologically, ferroptosis is associated with mitochondrial ultrastructural changes. At the molecular level, ferroptosis is characterised by a defect in glutathione-dependent antioxidant cellular response and involves an iron- and ROS-dependent serial peroxidation of PolyUnsaturated Fatty Acids (PUFAs)-containing phospholipids, leading to cell membrane disruption. Identified molecular players of ferroptosis thus include proteins required for cystine transport (System Xc^- composed of SLC7A11/xCT and SLC2A3), its conversion to glutathione (e.g. Glutamate-Cysteine Ligase GCL) and glutathione metabolism (e.g. glutathione reductase GR), iron transport or metabolism (e.g. transferrin and its receptor TFRC), PUFA synthesis and peroxidation (e.g. Acyl-CoA synthase long-chain family member 4 ACSL4, Lipoxygenase LOX) or reversion by peroxidase (Glutathione Peroxidase 4, GPX4). Hence, typical ferroptotic agents/inhibitors impact on these various steps. This also includes IFNγ secreted by CD8+ T cells as part of an anti-tumor response, which induces a down-regulation of the System Xc- subunits, thereby promoting tumour cell ferroptosis [59]. Several lines of evidence highlight the existence of molecular links between ferroptosis and the ER stress response signaling. First of all, several ferroptotic agents can induce activation of the UPR and expression of UPR-regulated genes. For example, erastin and sulfasalazine (which target the Xc- system, and might trigger the ER stress response through cysteine depletion) induce the activation of an eIF2α/ATF4 pathway [60], though this activation does not contribute to cell demise. Sorafenib, which in addition to targeting Raf and tyrosine kinases inhibits the Xc- system, can also trigger the IRE1 and PERK branches of the UPR [61]. In this case, PERK protects cells from sorafenib-induced death. More recently, xCT was shown to be an ATF4-inducible gene and ATF4 limits sorafenib and erastin-induced ferroptosis and ROS accumulation in glioma cell lines [62]. An important link between ferroptosis and the UPR is the NRF2 transcription factor. PERK up-regulates NRF2 through ATF4 [63] and directly phosphorylates it [64], thus promoting its stabilization and the ensuing transcription of multiple genes including several controllers of redox homeostasis and both positive and negative regulators of ferroptosis (e.g. xCT, GCL, GPX4, GR, TFRC). Hence, NRF2 has been shown to both promote and limit ferroptosis [65]. Of note, mitochondria, being involved for example in iron uptake and heme biosynthesis, also plays an important role in controlling ferroptosis [66]; and molecular machinery at the ER-mitochondria interface are also likely to cross-talk to control ferroptosis, as described for apoptosis [67]. More recently, lysosomal lipid peroxidation and cathepsin B were also shown to contribute to ferroptosis [68]. Hence, further definition of the precise molecular bases of the cross-talk between ferroptosis signaling and ER stress response and inter-organelles signaling in specific pathophysiological contexts will be necessary to meaningfully target them.

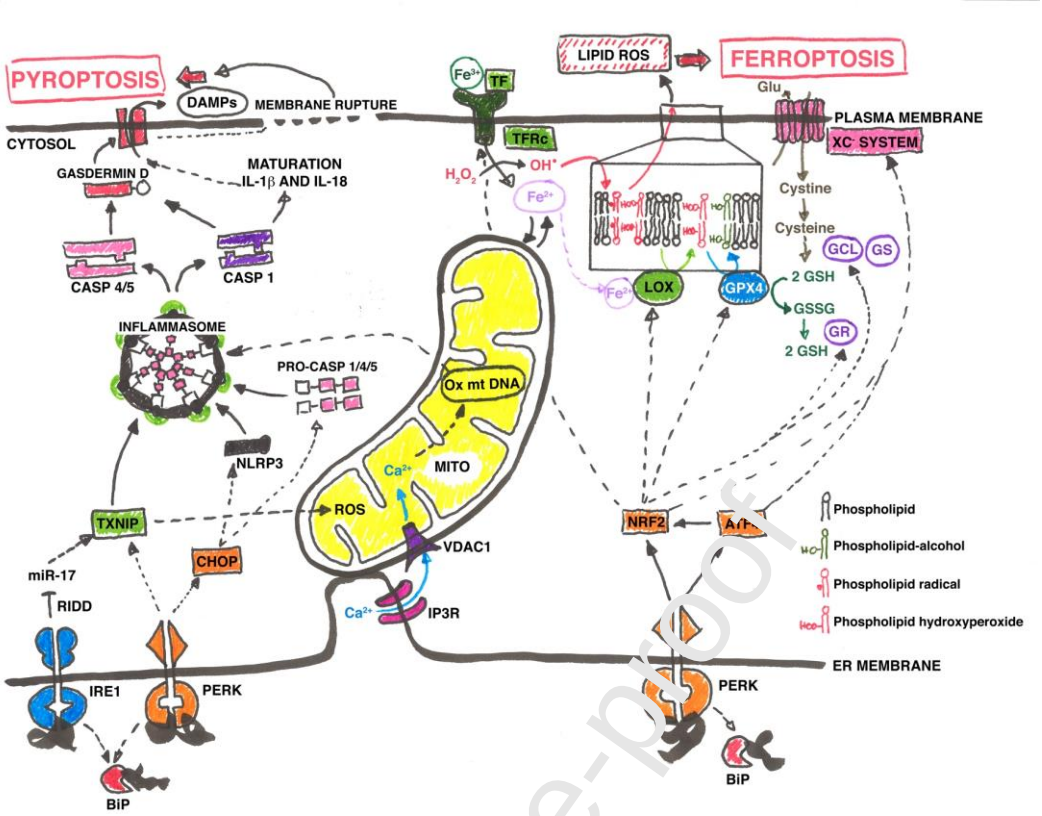

Figure 3. Cross-talks between pyroptosis, ferroptosis signaling and the Unfolded Protein Response. *Abbreviations: ATF4: Activating Transcription Factor 4; BiP: Binding immunoglobulin Protein; CASP: Caspase; CHOP: C/EBP Homologous Protein ; DAMPs: Danger Associated Molecular Patterns; ER: Endoplasmic Reticulum; GCL: Glutamate-Cysteine Ligase; GPX4: Glutathione Peroxidase 4 GR: Glutathione Reductase; GS: Glutathione Synthetase; GSH: reduced glutathione; GSSG: oxidized glutathione; IL: Interleukin; IP3R: Inositol Triphosphate Receptor; IRE1: Inositol Requiring Enzyme 1; LOX: Lipoxygenases; MITO: Mitochondria; NLRP3: NOD-like receptor family, pyrin domain containing 3; NRF2: ; Nuclear factor erythroid-2-Related Factor 2; Ox mt DNA: Oxidized mitochondrial DNA; PERK: Protein Kinase R-ER-like Kinase; PL: Phospholipid; RIDD: Regulated IRE1 Dependent Decay of RNA; ROS: Reactive Oxygen Species; TF: Transferrin; TFRC: Transferrin Receptor; TXNIP: Thioredoxin Interacting Protein; VDAC1: Voltage-Dependent Anion-selective Channel 1.*

2.3. Cross-talks between different cell death types and involvement in the ER stress

As mentioned above (2.1.1), the switching between different modalities of cell death can depend on the fitness of different pathways to execute cell death [27], and some reports suggest a role for ER stress in modulating the fitness of particular cell death machinery. For instance, knockout of the zinc transporter SLC39A7 induces ER stress and disrupts the trafficking of cell death receptors CD95 and TNF-R1 [69]. The reduced surface expression of TNF-R1 led to reduced necroptosis in this context. ER stress-induced autophagy can cause the downregulation of c-FLIP but upregulation of TRAIL-R2, thus linking ER stress-induced autophagy with apoptotic machinery and tipping the scales towards cell death [70]. As mentioned in section 2.1.2, ER stress-induced necroptosis in L929sA cells relies to some extent on JNK signaling [34] which may be activated by stress sensor IRE1 during ER stress. Under ER stress conditions IRE1 is reported to interact with RIPK1, and this interaction promotes caspase-8 cleavage and subsequent cleavage of caspase-3, independently of death

receptor signaling [71]. In β-cells IL-1β induces ER stress and leads to ER calcium release and uptake by mitochondria, altering mitochondrial membrane potential. Intriguingly, these effects were dependent on JNK signaling [72], suggesting further involvement of IRE1.
ER stress may also act as an avenue through which insults which trigger one cell death modality can diversify and potentiate cell death by activating other pathways. For instance, ferroptotic agents have been found to induce ER stress and lead to upregulation of PUMA via CHOP transcriptional activity and to sensitize cells to TRAIL-induced cell death [73]. In this way ER stress links ferroptosis to apoptosis which together synergistically drive cell death in this context. It remains to be seen to what extent additional cross-talk between regulated cell death pathways described in contexts like infection [74], such as NLRP3 activation and pyroptosis driven by MLKL, gasdermins cleavage by apoptotic caspases, or even molecular complexes driving PANoptosis (which can result in pyroptosis, necroptosis or apoptosis), might also be relevant to ER-stress driven pathologies. The studies outlined in this section suggest that future crosstalk mechanisms may be heavily context dependent and rely on the abundance of the different cell death machineries. However complex, understanding these mechanisms is essential for our understanding of how ER stress contributes to many diseases, and opens the door to potential therapeutic interventions.

3- Concluding remarks/perspectives

In summary, ER stress signaling, in particular the UPR, and RCD signaling pathways are linked through mechanisms which are still being unravelled. Further defining these mechanisms for instance by identifying new actors in those interconnected pathways (e.g. new regulators of the UPR, other regulated death receptors) will be required for their appropriate pharmacological targeting in pathologies in which promoting (e.g. cancer) or restricting (e.g. degenerative diseases) UPR-dependent cell death might be meaningful. These pharmacological targets might comprise, but might not be limited to, activators/inhibitors of UPR sensors, their various specific activities and downstream effectors in addition to signaling pathway nodes of RCD (e.g. RIPK1, caspases, BCL-2 family members, cFLIP, IAPs, GPX4). These tools might thus allow us to target persister cells (cells which do not execute cell death upon sustained UPR engagement) or limit aberrant undesirable cell death downstream of the UPR.
Beyond defining the mechanisms linking the UPR to a given RCD mode, it will also be necessary to consider and further investigate the molecular plasticity between RCD pathways. For instance, the potential redundancy between cell death pathways triggered upon ER stress might be exploitable to ensure execution of cell death when desirable (i.e. preferentially promote one RCD pathway to target cells resisting to another RCD). Whether or not additional RCD forms and PANoptosis are also triggered in some ER stress conditions remains to be investigated. More generally, considering the consequences of each type of UPR-driven RCD on surrounding tissue homeostasis (e.g. inflammation, compensatory proliferation) will likely be key in appropriately designing these future therapeutic strategies.

Declaration of competing interest

EC is a founder of Cell Stress Discoveries ltd. Otherwise, the authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] A. Almanza, A. Carlesso, C. Chintha, S. Creedican, D. Doultsinos, B. Leuzzi, A. Luis, N. McCarthy, L. Montibeller, S. More, A. Papaioannou, F. Puschel, M.L. Sassano, J. Skoko, P. Agostinis, J. de Belleroche, L.A. Eriksson, S. Fulda, A.M. Gorman, S. Healy, A. Kozlov, C. Munoz-Pinedo, M. Rehm, E. Chevet, A. Samali, Endoplasmic reticulum stress signalling - from basic mechanisms to clinical applications, Febs j, 286 (2019) 241-278.

[2] M. Maurel, E. Chevet, J. Tavernier, S. Gerlo, Getting RIDD of RNA: IRE1 in cell fate regulation, Trends Biochem Sci, 39 (2014) 245-254.

[3] E. Lafont, Stress management : Death Receptor Signalling and its Cross-talks with the Unfolded Protein Response in Cancer, Cancers, 12 (2020).

[4] D. Stöhr, A. Jeltsch, M. Rehm, TRAIL receptor signaling: From the basics of canonical signal transduction toward its entanglement with ER stress and the unfolded protein response, International review of cell and molecular biology, 351 (2020) 57-99.

[5] H. Urra, E. Dufey, F. Lisbona, D. Rojas-Rivera, C. Hetz, When ER stress reaches a dead end, Biochim Biophys Acta, 1833 (2013) 3507-3517.

[6] P. Pihán, A. Carreras-Sureda, C. Hetz, BCL-2 family: integrating stress responses at the ER to control cell demise, Cell Death Differ, 24 (2017) 1478-1487.

[7] M.A. Carpio, M. Michaud, W. Zhou, J.K. Fisher, L.D. Walensky, S.G. Katz, BCL-2 family member BOK promotes apoptosis in response to endoplasmic reticulum stress, Proc Natl Acad Sci U S A, 112 (2015) 7201-7206.

[8] F. Llambi, Y.M. Wang, B. Victor, M. Yang, D.M. Schneider, S. Gingras, M.J. Parsons, J.H. Zheng, S.A. Brown, S. Pelletier, T. Moldoveanu, T. Chen, D.R. Green, BOK Is a Non-canonical BCL-2 Family Effector of Apoptosis Regulated by ER-Associated Degradation, Cell, 165 (2016) 421-433.

[9] S. Einsele-Scholz, S. Malmsheimer, K. Bertram, D. Stehle, J. Johänning, M. Manz, P.T. Daniel, B.F. Gillissen, K. Schulze-Osthoff, F. Essmann, Bok is a genuine multi-BH-domain protein that triggers apoptosis in the absence of Bax and Bak, J Cell Sci, 129 (2016) 2213-2223.

[10] S.H. Kang, O. Perales, M. Michaud, S.G. Katz, BOK promotes erythropoiesis in a mouse model of myelodysplastic syndrome, Annals of hematology, 98 (2019) 2089-2096.

[11] X. Wang, K.E. Olberding, C. White, C. Li, Bcl-2 proteins regulate ER membrane permeability to luminal proteins during ER stress-induced apoptosis, Cell Death Differ, 18 (2011) 38-47.

[12] K. Kanekura, X. Ma, J.T. Murphy, L.J. Zhu, A. Diwan, F. Urano, IRE1 prevents endoplasmic reticulum membrane permeabilization and cell death under pathological conditions, Sci Signal, 8 (2015) ra62.

[13] T. Nakagawa, H. Zhu, N. Morishima, E. Li, J. Xu, B.A. Yankner, J. Yuan, Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta, Nature, 403 (2000) 98-103.

[14] N. Morishima, K. Nakanishi, K. Tsuchiya, T. Shibata, E. Seiwa, Translocation of Bim to the endoplasmic reticulum (ER) mediates ER stress signaling for activation of caspase-12 during ER stress-induced apoptosis, J Biol Chem, 279 (2004) 50375-50381.
[15] J. Hitomi, T. Katayama, Y. Eguchi, T. Kudo, M. Taniguchi, Y. Koyama, T. Manabe, S. Yamagishi, Y. Bando, K. Imaizumi, Y. Tsujimoto, M. Tohyama, Involvement of caspase-4 in endoplasmic reticulum stress-induced apoptosis and Abeta-induced cell death, J Cell Biol, 165 (2004) 347-356.
[16] E.A. Obeng, L.H. Boise, Caspase-12 and caspase-4 are not required for caspase-dependent endoplasmic reticulum stress-induced apoptosis, J Biol Chem, 280 (2005) 29578-29587.
[17] J.P. Upton, L. Wang, D. Han, E.S. Wang, N.E. Huskey, L. Lim, M. Truitt, M.T. McManus, D. Ruggero, A. Goga, F.R. Papa, S.A. Oakes, IRE1α cleaves select microRNAs during ER stress to derepress translation of proapoptotic Caspase-2, Science, 338 (2012) 818-822.
[18] J.J. Sandow, L. Dorstyn, L.A. O'Reilly, M. Tailler, S. Kumar, A. Strasser, P.G. Ekert, ER stress does not cause upregulation and activation of caspase-2 to initiate apoptosis, Cell Death Differ, 21 (2014) 475-480.
[19] L. Pan, T.M. Fu, W. Zhao, L. Zhao, W. Chen, C. Qiu, W. Liu, Z. Liu, A. Piai, Q. Fu, S. Chen, H. Wu, J.J. Chou, Higher-Order Clustering of the Transmembrane Anchor of DR5 Drives Signaling, Cell, 176 (2019) 1477-1489.e1414.
[20] M. Lam, S.A. Marsters, A. Ashkenazi, P. Walter, Misfolded proteins bind and activate death receptor 5 to induce apoptosis during unresolved endoplasmic reticulum stress, Elife, 9 (2020).
[21] H. Urra, P. Pihán, C. Hetz, The UPRosome - decoding novel biological outputs of IRE1α function, J Cell Sci, 133 (2020).
[22] C. Hetz, P. Bernasconi, J. Fisher, A.H. Lee, M.C. Bassik, B. Antonsson, G.S. Brandt, N.N. Iwakoshi, A. Schinzel, L.H. Glimcher, S.J. Korsmeyer, Proapoptotic BAX and BAK modulate the unfolded protein response by a direct interaction with IRE1alpha, Science, 312 (2006) 572-576.
[23] C. Lebeaupin, M. Blanc, D. Vallée, H. Keller, B. Bailly-Maitre, BAX inhibitor-1: between stress and survival, Febs j, 287 (2020) 1722-1736.
[24] A. Shemorry, J.M. Harnoss, O. Guttman, S.A. Marsters, L.G. Komuves, D.A. Lawrence, A. Ashkenazi, Caspase-mediated cleavage of IRE1 controls apoptotic cell commitment during endoplasmic reticulum stress, Elife, 8 (2019).
[25] T.K. Chang, D.A. Lawrence, M. Lu, J. Tan, J.M. Harnoss, S.A. Marsters, P. Liu, W. Sandoval, S.E. Martin, A. Ashkenazi, Coordination between Two Branches of the Unfolded Protein Response Determines Apoptotic Cell Fate, Mol Cell, 71 (2018) 629-636.e625.
[26] L. Galluzzi, I. Vitale, S.A. Aaronson, J.M. Abrams, D. Adam, P. Agostinis, E.S. Alnemri, L. Altucci, I. Amelio, D.W. Andrews, M. Annicchiarico-Petruzzelli, A.V. Antonov, E. Arama, E.H. Baehrecke, N.A. Barlev, N.G. Bazan, F. Bernassola, M.J.M. Bertrand, K. Bianchi, M.V. Blagosklonny, K. Blomgren, C. Borner, P. Boya, C. Brenner, M. Campanella, E. Candi, D. Carmona-Gutierrez, F. Cecconi, F.K. Chan, N.S. Chandel, E.H. Cheng, J.E. Chipuk, J.A. Cidlowski, A. Ciechanover, G.M. Cohen, M. Conrad, J.R. Cubillos-Ruiz, P.E. Czabotar, V. D'Angiolella, T.M. Dawson, V.L. Dawson, V. De Laurenzi, R. De Maria, K.M. Debatin, R.J. DeBerardinis, M. Deshmukh, N. Di Daniele, F. Di Virgilio, V.M. Dixit, S.J. Dixon, C.S. Duckett, B.D. Dynlacht, W.S. El-Deiry, J.W. Elrod, G.M. Fimia, S. Fulda, A.J. García-Sáez, A.D. Garg, C. Garrido, E. Gavathiotis, P. Golstein, E. Gottlieb, D.R. Green, L.A. Greene, H. Gronemeyer, A. Gross, G. Hajnoczky, J.M. Hardwick, I.S. Harris, M.O. Hengartner, C. Hetz, H. Ichijo, M.

Jäättelä, B. Joseph, P.J. Jost, P.P. Juin, W.J. Kaiser, M. Karin, T. Kaufmann, O. Kepp, A. Kimchi, R.N. Kitsis, D.J. Klionsky, R.A. Knight, S. Kumar, S.W. Lee, J.J. Lemasters, B. Levine, A. Linkermann, S.A. Lipton, R.A. Lockshin, C. López-Otín, S.W. Lowe, T. Luedde, E. Lugli, M. MacFarlane, F. Madeo, M. Malewicz, W. Malorni, G. Manic, J.C. Marine, S.J. Martin, J.C. Martinou, J.P. Medema, P. Mehlen, P. Meier, S. Melino, E.A. Miao, J.D. Molkentin, U.M. Moll, C. Muñoz-Pinedo, S. Nagata, G. Nuñez, A. Oberst, M. Oren, M. Overholtzer, M. Pagano, T. Panaretakis, M. Pasparakis, J.M. Penninger, D.M. Pereira, S. Pervaiz, M.E. Peter, M. Piacentini, P. Pinton, J.H.M. Prehn, H. Puthalakath, G.A. Rabinovich, M. Rehm, R. Rizzuto, C.M.P. Rodrigues, D.C. Rubinsztein, T. Rudel, K.M. Ryan, E. Sayan, L. Scorrano, F. Shao, Y. Shi, J. Silke, H.U. Simon, A. Sistigu, B.R. Stockwell, A. Strasser, G. Szabadkai, S.W.G. Tait, D. Tang, N. Tavernarakis, A. Thorburn, Y. Tsujimoto, B. Turk, T. Vanden Berghe, P. Vandenabeele, M.G. Vander Heiden, A. Villunger, H.W. Virgin, K.H. Vousden, D. Vucic, E.F. Wagner, H. Walczak, D. Wallach, Y. Wang, J.A. Wells, W. Wood, J. Yuan, Z. Zakeri, B. Zhivotovsky, L. Zitvogel, G. Melino, G. Kroemer, Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018, Cell Death Differ, 25 (2018) 486-541.

[27] S. Deegan, S. Saveljeva, S.E. Logue, K. Pakos-Zebrucka, S. Gupta, P. Vandenabeele, M.J. Bertrand, A. Samali, Deficiency in the mitochondrial apoptotic pathway reveals the toxic potential of autophagy under ER stress conditions, Autophagy, 10 (2014) 1921-1936.

[28] M. Luhr, M.L. Torgersen, P. Szalai, A. Hashim, A. Brech, J. Staerk, N. Engedal, The kinase PERK and the transcription factor ATF4 play distinct and essential roles in autophagy resulting from tunicamycin-induced ER stress, J Biol Chem, 294 (2019) 8197-8217.

[29] C. Yan, J. Liu, J. Gao, Y. Sun, L. Zhang, H. Song, L. Xue, L. Zhan, G. Gao, Z. Ke, Y. Liu, J. Liu, IRE1 promotes neurodegeneration through autophagy-dependent neuron death in the Drosophila model of Parkinson's disease, Cell Death Dis, 10 (2019) 800.

[30] E. Sozen, B. Yazgan, O.E. Tok, T. Demirel, F. Ercan, J.D. Proto, N.K. Ozer, Cholesterol induced autophagy via IRE1/JNK pathway promotes autophagic cell death in heart tissue, Metabolism: clinical and experimental, 106 (2020) 154205.

[31] S. Zielke, S. Kardo, L. Zein, M. Mari, A. Covarrubias-Pinto, M.N. Kinzler, N. Meyer, A. Stolz, S. Fulda, F. Reggiori, D. Kögel, S. van Wijk, ATF4 links ER stress with reticulophagy in glioblastoma cells, Autophagy, (2020) 1-17.

[32] Y. Liao, B. Duan, Y. Zhang, X. Zhang, B. Xia, Excessive ER-phagy mediated by the autophagy receptor FAM134B results in ER stress, the unfolded protein response, and cell death in HeLa cells, J Biol Chem, 294 (2019) 20009-20023.

[33] T. Vanden Berghe, W.J. Kaiser, M.J. Bertrand, P. Vandenabeele, Molecular crosstalk between apoptosis, necroptosis, and survival signaling, Molecular & cellular oncology, 2 (2015) e975093.

[34] S. Saveljeva, S.L. Mc Laughlin, P. Vandenabeele, A. Samali, M.J. Bertrand, Endoplasmic reticulum stress induces ligand-independent TNFR1-mediated necroptosis in L929 cells, Cell Death Dis, 6 (2015) e1587.

[35] W. Wang, X. Qing, B. Wang, K. Ma, Y. Wei, Z. Shao, Tauroursodeoxycholic Acid Protects Nucleus Pulposus Cells from Compression-Induced Apoptosis and Necroptosis via Inhibiting Endoplasmic Reticulum Stress, Evidence-based complementary and alternative medicine : eCAM, 2018 (2018) 6719460.

[36] H. Fan, H.B. Tang, J. Kang, L. Shan, H. Song, K. Zhu, J. Wang, G. Ju, Y.Z. Wang, Involvement of endoplasmic reticulum stress in the necroptosis of microglia/macrophages after spinal cord injury, Neuroscience, 311 (2015) 362-373.

[37] Y.M. Ma, Y.M. Peng, Q.H. Zhu, A.H. Gao, B. Chao, Q.J. He, J. Li, Y.H. Hu, Y.B. Zhou, Novel CHOP activator LGH00168 induces necroptosis in A549 human lung cancer cells via ROS-mediated ER stress and NF-κB inhibition, Acta pharmacologica Sinica, 37 (2016) 1381-1390.
[38] D. Rojas-Rivera, T. Delvaeye, R. Roelandt, W. Nerinckx, K. Augustyns, P. Vandenabeele, M.J.M. Bertrand, When PERK inhibitors turn out to be new potent RIPK1 inhibitors: critical issues on the specificity and use of GSK2606414 and GSK2656157, Cell Death Differ, 24 (2017) 1100-1110.
[39] D.E. Place, T.D. Kanneganti, Cell death-mediated cytokine release and its therapeutic implications, J Exp Med, 216 (2019) 1474-1486.
[40] F. Martinon, X. Chen, A.H. Lee, L.H. Glimcher, TLR activation of the transcription factor XBP1 regulates innate immune responses in macrophages, Nat Immunol, 11 (2010) 411-418.
[41] Y. Xue, D. Enosi Tuipulotu, W.H. Tan, C. Kay, S.M. Man, Emerging Activators and Regulators of Inflammasomes and Pyroptosis, Trends in immunology, 40 (2019) 1035-1052.
[42] N. Kayagaki, O.S. Kornfeld, B.L. Lee, I.B. Stowe, K. O'Rourke, Q. Li, W. Sandoval, D. Yan, J. Kang, M. Xu, J. Zhang, W.P. Lee, B.S. McKenzie, G. Ulas, J. Payandeh, M. Roose-Girma, Z. Modrusan, R. Reja, M. Sagolla, J.D. Webster, V. Cho, T.D. Andrews, L.X. Morris, L.A. Miosge, C.C. Goodnow, E.M. Bertram, V.M. Dixit, NINJ1 mediates plasma membrane rupture during lytic cell death, Nature, (2021).
[43] P. Menu, A. Mayor, R. Zhou, A. Tardivel, H. Ichijo, K. Mori, J. Tschopp, ER stress activates the NLRP3 inflammasome via an UPR-independent pathway, Cell Death Dis, 3 (2012) e261.
[44] A.G. Lerner, J.P. Upton, P.V. Praveen, R. Ghosh, Y. Nakagawa, A. Igbaria, S. Shen, V. Nguyen, B.J. Backes, M. Heiman, N. Heintz, P. Greengard, S. Hui, Q. Tang, A. Trusina, S.A. Oakes, F.R. Papa, IRE1alpha induces thioredoxin-interacting protein to activate the NLRP3 inflammasome and promote programmed cell death under irremediable ER stress, Cell metabolism, 16 (2012) 250-264.
[45] C.M. Oslowski, T. Hara, B. O'Sullivan-Murphy, K. Kanekura, S. Lu, M. Hara, S. Ishigaki, L.J. Zhu, E. Hayashi, S.T. Hui, D. Greiner, R.J. Kaufman, R. Bortell, F. Urano, Thioredoxin-interacting protein mediates ER stress-induced β cell death through initiation of the inflammasome, Cell metabolism, 16 (2012) 265-273.
[46] S.B. Cheng, A. Nakashima, W.J. Huber, S. Davis, S. Banerjee, Z. Huang, S. Saito, Y. Sadovsky, S. Sharma, Pyroptosis is a critical inflammatory pathway in the placenta from early onset preeclampsia and in human trophoblasts exposed to hypoxia and endoplasmic reticulum stressors, Cell Death Dis, 10 (2019) 927.
[47] A. Szpigel, I. Hainaut, A. Carlier, N. Venteclef, A.F. Batto, E. Hajduch, C. Bernard, A. Ktorza, J.F. Gautier, P. Ferré, O. Bourron, F. Foufelle, Lipid environment induces ER stress, TXNIP expression and inflammation in immune cells of individuals with type 2 diabetes, Diabetologia, 61 (2018) 399-412.
[48] C.Y. Han, H.S. Rho, A. Kim, T.H. Kim, K. Jang, D.W. Jun, J.W. Kim, B. Kim, S.G. Kim, FXR Inhibits Endoplasmic Reticulum Stress-Induced NLRP3 Inflammasome in Hepatocytes and Ameliorates Liver Injury, Cell Rep, 24 (2018) 2985-2999.
[49] C. Lebeaupin, E. Proics, C.H. de Bieville, D. Rousseau, S. Bonnafous, S. Patouraux, G. Adam, V.J. Lavallard, C. Rovere, O. Le Thuc, M.C. Saint-Paul, R. Anty, A.S. Schneck, A. Iannelli, J. Gugenheim, A. Tran, P. Gual, B. Bailly-Maitre, ER stress induces NLRP3 inflammasome activation and hepatocyte death, Cell Death Dis, 6 (2015) e1879.
[50] M.M. Robblee, C.C. Kim, J. Porter Abate, M. Valdearcos, K.L. Sandlund, M.K. Shenoy, R. Volmer, T. Iwawaki, S.K. Koliwad, Saturated Fatty Acids Engage an IRE1α-Dependent

Pathway to Activate the NLRP3 Inflammasome in Myeloid Cells, Cell Rep, 14 (2016) 2611-2623.
[51] A. D'Osualdo, V.G. Anania, K. Yu, J.R. Lill, R.J. Kaufman, S. Matsuzawa, J.C. Reed, Transcription Factor ATF4 Induces NLRP1 Inflammasome Expression during Endoplasmic Reticulum Stress, PLoS One, 10 (2015) e0130635.
[52] R. Zhou, A.S. Yazdi, P. Menu, J. Tschopp, A role for mitochondria in NLRP3 inflammasome activation, Nature, 469 (2011) 221-225.
[53] J. Chen, Z.J. Chen, PtdIns4P on dispersed trans-Golgi network mediates NLRP3 inflammasome activation, Nature, 564 (2018) 71-76.
[54] D.N. Bronner, B.H. Abuaita, X. Chen, K.A. Fitzgerald, G. Nuñez, Y. He, X.M. Yin, M.X. O'Riordan, Endoplasmic Reticulum Stress Activates the Inflammasome via NLRP3- and Caspase-2-Driven Mitochondrial Damage, Immunity, 43 (2015) 451-462.
[55] Z. Zhong, S. Liang, E. Sanchez-Lopez, F. He, S. Shalapour, X.J. Lin, J. Wong, S. Ding, E. Seki, B. Schnabl, A.L. Hevener, H.B. Greenberg, T. Kisseleva, M. Karin, New mitochondrial DNA synthesis enables NLRP3 inflammasome activation, Nature, 560 (2018) 198-203.
[56] S.J. Dixon, K.M. Lemberg, M.R. Lamprecht, R. Skouta, E.M. Zaitsev, C.E. Gleason, D.N. Patel, A.J. Bauer, A.M. Cantley, W.S. Yang, B. Morrison, 3rd, B.R. Stockwell, Ferroptosis: an iron-dependent form of nonapoptotic cell death, Cell, 149 (2012) 1060-1072.
[57] B. Hassannia, P. Vandenabeele, T. Vanden Berghe, Targeting Ferroptosis to Iron Out Cancer, Cancer Cell, 35 (2019) 830-849.
[58] C.M. Bebber, F. Müller, L. Prieto Clemente, J. Weber, S. von Karstedt, Ferroptosis in Cancer Cell Biology, Cancers, 12 (2020).
[59] W. Wang, M. Green, J.E. Choi, M. Gijón, P.D. Kennedy, J.K. Johnson, P. Liao, X. Lang, I. Kryczek, A. Sell, H. Xia, J. Zhou, G. Li, J. Li, W. Li, S. Wei, L. Vatan, H. Zhang, W. Szeliga, W. Gu, R. Liu, T.S. Lawrence, C. Lamb, Y. Tanno, M. Cieslik, E. Stone, G. Georgiou, T.A. Chan, A. Chinnaiyan, W. Zou, CD8(+) T cells regulate tumour ferroptosis during cancer immunotherapy, Nature, 569 (2019) 270-274.
[60] S.J. Dixon, D.N. Patel, M. Welsch, R. Skouta, E.D. Lee, M. Hayano, A.G. Thomas, C.E. Gleason, N.P. Tatonetti, B.S. Slusher, B.R. Stockwell, Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis, Elife, 3 (2014) e02523.
[61] M. Rahmani, E.M. Davis, T.R. Crabtree, J.R. Habibi, T.K. Nguyen, P. Dent, S. Grant, The kinase inhibitor sorafenib induces cell death through a process involving induction of endoplasmic reticulum stress, Mol Cell Biol, 27 (2007) 5499-5513.
[62] D. Chen, Z. Fan, M. Rauh, M. Buchfelder, I.Y. Eyupoglu, N. Savaskan, ATF4 promotes angiogenesis and neuronal cell death and confers ferroptosis in a xCT-dependent manner, Oncogene, 36 (2017) 5593-5608.
[63] C. Sarcinelli, H. Dragic, M. Piecyk, V. Barbet, C. Duret, A. Barthelaix, C. Ferraro-Peyret, J. Fauvre, T. Renno, C. Chaveroux, S.N. Manie, ATF4-Dependent NRF2 Transcriptional Regulation Promotes Antioxidant Protection during Endoplasmic Reticulum Stress, Cancers, 12 (2020).
[64] S.B. Cullinan, D. Zhang, M. Hannink, E. Arvisais, R.J. Kaufman, J.A. Diehl, Nrf2 is a direct PERK substrate and effector of PERK-dependent cell survival, Mol Cell Biol, 23 (2003) 7198-7209.
[65] A. Anandhan, M. Dodson, C.J. Schmidlin, P. Liu, D.D. Zhang, Breakdown of an Ironclad Defense System: The Critical Role of NRF2 in Mediating Ferroptosis, Cell chemical biology, 27 (2020) 436-447.

[66] A.M. Battaglia, R. Chirillo, I. Aversa, A. Sacco, F. Costanzo, F. Biamonte, Ferroptosis and Cancer: Mitochondria Meet the "Iron Maiden" Cell Death, Cells, 9 (2020).
[67] D. Eletto, E. Chevet, Y. Argon, C. Appenzeller-Herzog, Redox controls UPR to control redox, J Cell Sci, 127 (2014) 3649-3658.
[68] P. Nagakannan, M.I. Islam, M. Conrad, E. Eftekharpour, Cathepsin B is an executioner of ferroptosis, Biochimica et biophysica acta. Molecular cell research, (2020) 118928.
[69] A. Fauster, M. Rebsamen, K.L. Willmann, A. César-Razquin, E. Girardi, J.W. Bigenzahn, F. Schischlik, S. Scorzoni, M. Bruckner, J. Konecka, K. Hörmann, L.X. Heinz, K. Boztug, G. Superti-Furga, Systematic genetic mapping of necroptosis identifies SLC39A7 as modulator of death receptor trafficking, Cell Death Differ, 26 (2019) 1138-1155.
[70] S.H. Lee, H.J. Moon, Y.S. Lee, C.D. Kang, S.H. Kim, Potentiation of TRAIL-induced cell death by nonsteroidal anti-inflammatory drug in human hepatocellular carcinoma cells through the ER stress-dependent autophagy pathway, Oncology reports, 44 (2020) 1136-1148.
[71] Y. Estornes, M.A. Aguileta, C. Dubuisson, J. De Keyser, V. Goossens, K. Kersse, A. Samali, P. Vandenabeele, M.J. Bertrand, RIPK1 promotes death receptor-independent caspase-8-mediated apoptosis under unresolved ER stress conditions, Cell Death Dis, 5 (2014) e1555.
[72] G. Verma, H. Bhatia, M. Datta, JNK1/2 regulates ER-mitochondrial Ca2+ cross-talk during IL-1β-mediated cell death in RINm5F and human primary β-cells, Molecular biology of the cell, 24 (2013) 2058-2071.
[73] S.H. Hong, D.H. Lee, Y.S. Lee, M.J. Jo, Y.A. Jeong, W.T. Kwon, H.A. Choudry, D.L. Bartlett, Y.J. Lee, Molecular crosstalk between ferroptosis and apoptosis: emerging role of ER stress-induced p53-independent PUMA expression, Oncotarget, 8 (2017) 115164-115178.
[74] S. Bedoui, M.J. Herold, A. Strasser, Emerging connectivity of programmed cell death pathways and its physiological implications, Nat Rev Mol Cell Biol, 21 (2020) 678-695.

Authorship issues

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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Eric Chevet is a founder of Cell Stress Discoveries ltd. Otherwise, the authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Highlights

- Endoplasmic Stress signaling is functionally linked to multiple Regulated Cell Death (RCD) pathways;
- RCD modes include pyroptosis, apoptosis, necroptosis and autophagy-associated cell death;
- ER-stress-induced RCD pathways are functionally intertwined;
- Targeting RCD will likely be useful in controlling ER stress-associated diseases.