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To cite this version:

Takahiro Yamazaki, José Manuel Bravo-San Pedro, Lorenzo Galluzzi, Guido Kroemer, Federico Pietrocola. Autophagy in the cancer-immunity dialogue. Advanced Drug Delivery Reviews, 2021, 169, pp.40 - 50. 10.1016/j.addr.2020.12.003 . hal-03493845

HAL Id: hal-03493845

https://hal.science/hal-03493845v1

Submitted on 16 Dec 2022

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Version of Record: https://www.sciencedirect.com/science/article/pii/S0169409X2030274X
Manuscript_3a192b1eb8326f6ff2a959c25e2007e8

Autophagy in the cancer-immunity dialogue

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Running title: Modeling the role of autophagy in tumor immunology

Keywords: antigen presentation; ATG5; beclin 1; cytotoxic T lymphocytes; dendritic cells; CGAS/STING signaling; mitophagy; T_{REG} cells.

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1. Abstract

Autophagy is quintessential for the maintenance of cellular homeostasis in all eukaryotic cells, explaining why both normal and malignant cells benefit from proficient autophagic responses. Moreover, autophagy is intimately involved in the immunological control of malignant transformation, tumor progression and response to therapy. However, the net effect of autophagy activation or inhibition on the natural growth or therapeutic response of tumors evolving in immunocompetent hosts exhibits a considerable degree of context dependency. Here, we discuss the complex cross-talk between autophagy and immuno-oncology as delineated by genetic and pharmacological approaches in mouse models of cancer.

2. Introduction

The capacity of eukaryotic cells to fulfill housekeeping duties (such as the turnover of superfluous organelles and long-lived proteins), as well as the ability to react to fluctuations in the intracellular and extracellular rheostat by reinstating the homeostatic *status quo*, is strictly dependent on macroautophagy (referred to as autophagy from here onward) [1-4]. Autophagy is an evolutionarily conserved process during which disposable or toxic cellular components are sequentially engulfed in membranous structures (so-called 'autophagosomes') and delivered to the acidic lysosomal environment for cargo degradation and recycling [5, 6]. While autophagy proceeds at a baseline level in virtually all eukaryotic cells, perturbations in cellular homeostasis produced by endogenous and exogenous metabolic, oxidative or chemical cues raise the flux of material through the autophagic pathway well beyond the physiological threshold [7-9].

There is broad consensus around the notion that autophagy actively participates to the metabolic adaptation to energetic stress, driven by the leading observation that a prominent surge in the autophagic tone occurs (both at the cellular and organismal level) in physiological scenarios of nutrient scarcity [10-12]. Accordingly, the autophagic apparatus (through the essential mediation of metabolite-specific sensors) [13] is poised to respond to decreased levels of energetically meaningful molecules by mounting a reaction that is commensurate to the magnitude of the inducing stimulus, ultimately leading to the mobilization of energetic resources (including sugars, amino acids, nucleotides and fatty acids) from intracellular stores [14]. Consistent with a paramount function in the regulation of cellular fitness, autophagy is generally regarded as a pro-survival mechanism, although its direct involvement in instances of cellular demise has also been reported [15, 16]. Similarly, the induction of autophagy is considered a *conditio sine qua non* for the translation of caloric restriction into healthspan and lifespan extension in a variety of model organisms [17-19]. Conversely, the genetic or pharmacological

inhibition of the autophagic cascade precipitates the aged phenotype [20-22], while promoting the occurrence of numerous age-associated pathologies including cancer [23-25].

In its canonical configuration [26, 27], the autophagic cascade involves the coordinated recruitment of multiple autophagy related proteins (ATGs) at a cellular location devoted to the formation of new autophagosomes [28, 29]. Overall, the process can be subdivided into four distinct stages (initiation, nucleation, elongation/closure, maturation/fusion), each of which is tightly regulated by a specific set of ATGs and accessory proteins [5]. In particular, the autophagic reaction is normally subjected to the repressive control of the mechanistic target of rapamycin (MTOR) complex 1 (mTORC1), which keeps autophagy initiation at bay through the inhibitory phosphorylation of unc-51-like autophagy-activating kinase 1 (ULK1) and autophagy-related 13 (ATG13) [2, 5]. The autophagy-suppressive function of mTORC1 is counteracted by 5' AMP-activated protein kinase (AMPK), which responds to dwindling ATP levels by igniting autophagy via convergent mechanisms that encompass not only the inhibition of mTORC1, but also the direct activation of ULK1, phosphatidylinositol 3-kinase catalytic subunit type 3 (PIK3C3, also known as Vps34) and beclin 1 (BECN1) [14, 30-32]. Autophagosome elongation is exquisitely defined by two ATG7-dependent ubiquitin-like conjugation systems [33], which catalyze the formation of the ATG12-ATG5-ATG16L1 complex as well as the conjugation of phosphatidylethanolamine moieties to microtubule associated protein 1 light chain 3 beta (MAP1LC3B; best known as LC3B) or one of its homologues [34]. The conjugation of LC3B to the autophagosome is instrumental for the sequestration of autophagic substrates [35], largely reflecting the interaction of LC3 interacting region (LIR)-containing adapter proteins including the ubiquitin-binding protein sequestosome 1 (SQSTM1; best known as p62) and LC3B [36, 37]. Importantly, the choice of the autophagosomal cargo can occur in a rather non-selective manner or be highly selective, generally depending on the autophagy-inducing stimulus [35]. Thus, while energetic stress often elicits the untargeted delivery of bulk portions of the cytoplasm for degradation, selective autophagy has been

extensively reported in response to the accumulation of permeabilized mitochondria (mitophagy), endoplasmic reticulum (ER) stress (reticulophagy), protein aggregates (aggrephagy) or invading pathogens (xenophagy) [38-41]. Of note, most ATG proteins also exert autophagy-independent functions, being involved in the regulation of essential cellular processes including cell division, non-canonical protein secretion, vesicular trafficking and inflammation [42-45].

Owing to the essential function of autophagy as a quality control mechanism in support of cellular homeostasis, pharmacological or genetic interventions that impair autophagic flux compromise the genomic stability of healthy cells and therefore precipitate malignant transformation [23, 46-51]. However, a large body of evidence supports the notion that autophagy has a Janus-faced impact on cancer biology, acting as a tumor-suppressive or tumor-promoting process depending on cancer type, stage, driver mutation(s) and other variables [23, 46-51]. In particular, established tumors obtain significant benefits from the homeostatic functions of autophagy, not only from a metabolic standpoint (autophagy supports the metabolic fitness of malignant cells facing the nutritional limitations that often characterize the tumor microenvironment, TME) [52-54] but also from a therapeutic perspective (autophagy is involved in several instance of chemo- and radioresistance) [49, 55, 56]. Adding a further layer of complexity, an in-depth understanding of the impact of autophagy on cancer biology cannot prescind from (1) the non-cell autonomous effects of the process [57, 58], and (2) the key functions of autophagy in other cells of the TME [46, 57, 59]. In fact, autophagy occurs (at a different pace) in all cellular components of the TME, hence directly intervening in the crosstalk between stromal, immune and neoplastic cells. Consistent with this notion, the modulation of autophagic responses has a robust impact on the metabolic and cellular composition of TME, in turn supporting or restraining tumor growth [46, 54, 57, 59]. Thus, autophagy regulates multiple aspects of innate and adaptive immune responses to cancer [60, 61], including (but not limited to): (1) the ability of malignant cells to emit adjuvant-like immunostimulatory signals in the course of immunogenic cell death (ICD) [62-65]; (2)

the capacity of malignant cells to establish an inflammatory microenvironment [66, 67]; (3) the ability of dendritic cells (DCs) to present tumor antigens to $CD8^+$ cytotoxic T lymphocytes (CTLs) and $CD4^+$ helper T cells [68-72]; and (4) the development, survival and effector functions of various immune cells including $CD8^+$ CTLs as well as natural killer (NK) cells [73-77].

Here, we discuss the multifaceted interactions between autophagy and various aspects of the oncogenic process as they have emerged from a variety of murine models of autophagic incompetence.

3. Autophagy in oncogenesis: an immune perspective

Our current knowledge about the role of autophagy in malignant transformation mostly derives from genetic mouse models of autophagic incompetence [78]. As the whole-body knockout of various ATG-coding genes is lethal, either during embryonic development or soon after birth [79, 80], these experimental systems normally impose partial autophagic incompetence (*e.g.*, *Becn1*$^{+/-}$ mice) [81]. Alternatively, the Cre–*lox* recombination system has been harnessed to delete a gene of interest (flanked by *loxP* sequences) upon (1) expression of the Cre recombinase in a specific tissue, (2) viral delivery of the Cre recombinase to specific organs (*e.g.*, the lungs) of adult mice, or (3) chemical activation of a Cre variant expressed systemically or in selected tissues [82-85]. Additional insights into the impact of autophagy on early oncogenesis came from the development of genetically engineered mouse models (GEMMs) of various cancer types combined with the aforementioned methods to inactivate autophagic genes [46, 48, 86]. Indeed, unlike cancer cell-based or patient-derived xenografts, GEMMs allow for the study of tumor dynamics in the tissue of origin in the context of an intact immune system [87, 88], although (at least in some cases) they exhibit limited mutational burden and hence do not necessarily mimic their human counterparts [89-91]. In some instances, this issue can be circumvented with carcinogen-driven models, such as endogenous mammary tumors driven in mice by medroxyprogesterone acetate (MPA) and 7,12-dimethylbenz[a]anthracene (DMBA) [92]. However, similar models have only been combined with autophagy defects sporadically [93].

Pioneering work from Beth Levine's group originally reported that *Becn1*$^{+/-}$ mice spontaneously develop various malignancies (including lymphomas, lung and hepatic carcinomas) [81, 94], demonstrating for the first time that autophagy mediates strong oncopreventive effects in normal tissues. Consistent with these findings, *Becn1*$^{+/-}$ mice are more susceptible to parity- and WNT1-driven mammary carcinogenesis than their littermates [95], and deletion of *Ambra1* (coding for a BECN1

interactor) places mice at increased risk for a variety of tumors [96]. Consistent with these findings, the genetic inhibition of autophagy via a doxycycline-inducible expression of a short-hairpin (shRNA) targeting ATG5 [51, 97] as well as the liver-specific mosaic deletion of *Atg5* [84] and the knockout of *Atg5* or *Atg7* in the lung or pancreas [98-100] exacerbates spontaneous or transgene-driven oncogenesis.

While some of these studies were specifically designed to interrogate how autophagy defects in healthy parenchymal cells (*e.g.*, hepatocytes) impact early oncogenesis, it is conceivable that the results obtained upon whole-body autophagy inhibition may involve (at least to some degree) defects in the pre-malignant microenvironment [101]. In support of this notion, chronic inflammation has been associated with an increased risk for malignant transformation in multiple tissues including colorectal and mammary epithelia, and autophagy robustly inhibits inflammatory responses [101-104]. Thus, ablation of essential components of the autophagic machinery coupled to the pathologically meaningful accumulation of SQSTM1 [105, 106] favors the overgeneration of reactive oxygen species (ROS) [107] and consequent production of pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin 6 (IL6) [101, 108-110]. Moreover, autophagy is directly involved in the degradation of inflammasomes [66, 111], which are supramolecular platforms for the maturation and secretion of pro-inflammatory IL-1β and IL-18, as well as one of the main endogenous activators thereof, *i.e.*, mitochondrial (mt) DNA spilling into the cytosol [112-115].

Autophagy defects can also perturb the ability of DCs and $CD8^+$ CTLs to ensure the immunological elimination of newly formed malignant cells [116, 117]. On the one hand, autophagic responses in dying cancer cells appear to be important for DCs to engage in cross-presentation to $CD8^+$ CTLs upon the uptake of apoptotic bodies, which is a key step in anticancer immunity [68, 118-120]. On the other hand, DCs require ATG5 functions to present antigens on MHC Class II molecules [71, 121, 122],

although cross-presentation seems to be unaffected by the loss of *Atg5* in DCs [69, 123]. Moreover, the proficient autophagic disposal of mitochondria driven by the loss of signal transducer and activator of transcription 3 (STAT3) [124] in intestinal epithelial cells supports cancer immunosurveillance [125] by favoring iron-dependent lysosomal permeabilization [126] coupled to accrued antigen presentation on MHC Class I molecules and DC cross-dressing (the direct transfer of pre-formed MHC Class I antigen-loaded complexes from cancer cells to DCs) [127-129].

$CD8^+$ CTLs also rely on autophagy, not only for physiological development and execution of effector functions upon encountering their cognate antigen [130, 131], but also for long-term survival upon acquisition of a memory phenotype [132, 133]. That said, the deletion of *Atg5* or another essential ATG-coding gene in $CD11c^+$ DCs or $CD8^+$ CTLs has not yet been experimentally linked to increased spontaneous or transgene-driven oncogenesis. Conversely, mice with a CD4-specific deletion of *Pik3c3* spontaneously develop duodenal adenomas with age [134], most likely as a consequence of accrued inflammation downstream of the depletion of immunosuppressive $CD4^+CD25^+FOXP3^+$ regulatory T (T_{REG}) cells [135-137], which are more reliant on autophagy for survival than their effector counterparts [138]. Conversely, preneoplastic pulmonary lesions driven in mice by $KRAS^{G12D}$ are prone to transition to lung carcinomas upon deletion of Atg5 from the lung epithelium, which is accompanied by accrued recruitment of T_{REG} cells and local immunosuppression [98]. These apparently contrasting findings highlight the importance of both cellular and microenvironmental context in the net effects of autophagy defects on malignant transformation.

Lending further support to this notion, autophagy defects have been shown to limit, rather than to accelerate, malignant transformation in some settings. Specifically, the shRNA-mediated depletion of ATG7, ATG13 or ULK1 restrains gliomagenesis driven by *KRAS* [139]. Along similar lines, conditional deletion of RB1 inducible coiled-coil 1 (Rb1cc1) in mammary epithelial cells suppresses

the initiation of mammary carcinomas driven by the polyomavirus middle T antigen (PyMT) [140], which not only develop with delayed kinetics, but also exhibit robust type I interferon (IFN) signaling and C-X-C motif chemokine ligand 10 (CXCL10)-dependent CTL recruitment (presumably indicating an improved immunological control) [140, 141]. In line with this hypothesis, intestinal dysbiosis promoted by the conditional loss of *Atg7* in *Apc*$^{+/-}$ intestinal epithelial cells prevents the formation of pre-cancerous lesions by a CTL-dependent mechanism [142].

Taken together, these observations delineate a complex network of early oncosuppression that involves not only the autophagy-dependent preservation of homeostasis in parenchymal cells, but also the autophagy-regulated activation of immunosurveillance (**Figure 1A**). Depending on the specific molecular and cellular links underlying such regulation, autophagy defects can thus promote or suppress malignant transformation.

4. Autophagy and tumor progression

Disruption of autophagy in malignant cells drastically compromises tumor progression in a variety of GEMMs, virtually irrespective of driver mutation(s) [48]. Specifically, a convergent pattern of inhibited progression upon autophagy disruption in malignant cells has been reported in the context of $KRAS^{G12D}$- or $BRAF^{V600E}$- driven lung cancer [98, 99], $KRAS^{G12D}$-driven pancreatic ductal carcinoma (PDAC) [100, 143], castrate-naïve and castrate-resistant prostate cancer driven by phosphatase and tensin homolog (*Pten*) loss [144] and melanoma promoted by simultaneous $BRAF^{V600E}$ activation and *Pten* loss in melanocytes [145]. Of note, at least in some of these models, the impact of autophagic defects on disease progression appears to be under epistatic control by the oncosuppressor tumor protein p53 (TP53, best known as p53), as the bi-allelic loss of *Trp53* (the mouse p53-coding gene) supports tumor growth and metastatic dissemination regardless of autophagic status [98, 100]. Taken together, these data lend further ground to the function of autophagy as a key process for the preservation of cancer cell fitness in the context of microenvironmental stress [54, 146].

The realization that autophagy-proficient transgene-driven tumors progress faster than their autophagy-deficient counterparts in immunocompetent mice spurred considerable interest in the possibility that autophagy would mediate immunosuppressive effects supporting disease progression. However, GEMMs of oncogenesis are poorly visible to the adaptive immune system as a consequence of a reduced antigenic burden, and thus are not particularly appropriate for studying the cancer-immune system interaction [89-91]. Indeed, autophagic defects have ultimately been associated with both immunostimulatory and immunosuppressive TME configurations, largely depending on the specific tumor model [23]. For instance, the conditional deletion of *Atg7* $KRAS^{G12D}$-driven lung cancers (which culminates in the aberrant accumulation of mitochondria and development of benign oncocytomas) correlated with abundant tumor infiltration by CTLs and macrophages [86, 147]. In this setting,

superior immunosurveillance was attributed to an inflammatory response caused by *Atg7* deletion that was so robust as to ultimately cause the death of the animals [86]. Along similar lines, the pancreata-restricted, inducible expression of a dominant-negative (DN) variant of autophagy related 4B cysteine peptidase (ATG4B) limited the progression of PDACs driven by $KRAS^{G12D}$ and heterozygous *Trp53* loss, commensurate with the local recruitment of macrophages with antitumor activity [148].

Autophagic defects in malignant cells exert immunomodulatory functions not only by favoring local inflammation (as discussed above), but also by influencing the antigenicity and adjuvanticity of cancer cells, i.e., their capacity to be recognized by immune effectors and activate them, respectively [149]. For instance, proficient autophagic responses in PDAC cells have been linked to reduced antigenicity as a consequence of MHC Class I degradation [150]. In this setting, selectivity was ensured by the LC3-binding partner NBR1 autophagy cargo receptor (NBR1) [151], and expression of DN ATG4B in PDAC cells was sufficient to restore normal MHC Class I exposure [150]. Along similar lines, autophagy limits anticancer immune responses against highly antigenic hepatocellular carcinomas by suppressing type I IFN secretion downstream of stimulator of interferon response cGAMP interactor 1 (STING1, best known as STING), correlating with scarce tumor infiltration by immune cells and inhibited T cell effector functions [152]. Moreover, autophagy has a direct influence on the composition of the so-called “immunopeptidome”, the ensemble of peptides presented on MHC molecules at the cell surface [153, 154]. Finally, autophagy in the neoplastic cell compartment supports the adjuvanticity of cancer cells by favoring the ICD-associated release of ATP [155, 156], hence driving the recruitment and activation of DCs or their precursors to the tumor bed [157, 158].

While unraveling the role of autophagy in cancer cells to tumor progression remains a challenging task, there is growing interest in understanding the contribution of autophagic responses in host cells (notably immune cells). In this context, several studies suggest that inhibition of autophagy in the host

impairs cancer progression. For instance, the deletion of host *Atg7* in the context of established KRAS-driven lung tumors hinders disease progression presumably by creating a disadvantageous metabolic environment for hyperproliferating malignant cells [159]. Similarly, the whole-body deletion of *Atg7* limits the outgrowth of arginine auxotrophs tumor allografts, an effect that was mirrored by reduced circulating levels of arginine, due to the enhanced release of arginase 1 (ARG1) from autophagy-deficient hepatocytes [52]. Of note, ARG1 production by immunosuppressive myeloid cells infiltrating the TME is a strong inhibitor of T-cell responses [160, 161], underscoring the key notion that intercellular communication and metabolic competition between neoplastic and immune cells are critical elements in the control of tumor progression [162-164].

Mice lacking the LC3B homolog GABA type A receptor-associated protein (GABARAP) not only are protected (at least to some degree) from DMBA-driven mammary carcinogenesis but also offer a suboptimal growth environment to B16F10 melanoma xenografts [93], correlating with improved CTL and macrophage responsiveness to challenge ex vivo [93]. Similarly, the conditional whole-body deletion of *Atg5* limits the number of circulating and tumor-infiltrating CTLs, but endows them with superior effector functions against several syngeneic cancers, at least in part upon the derepression of glucose metabolism [133]. These findings appear to argue with previous observations obtained with the deletion of *Atg7* in both $CD4^+$ and $CD8^+$ T cells [132], potentially pointing to a role for autophagy in other cellular compartments for the establishment of T cell memory [130, 165-168]. Irrespective of this possibility, autophagy appears to be critical for tumor-infiltrating CTLs for preserving stemness despite the functional impairment caused by limited nutrient uptake [169], ultimately underlying the ability of T cells to persist in the TME, recover effector functions and mediate tumor clearance. Moreover, the targeted deletion of *Atg5* or *Atg7* has been associated with profound functional alterations in T_{REG} cells (resulting in limited immunosuppression and superior anticancer immunity by CTLs) [138] as well as $CD4^+$ cells in general (resulting in the acquisition of a robust T_H9 tumor-suppressive phenotype upon

stabilization of the transcription factor PU.1) [170, 171]. M2-like tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), two myeloid cell populations with robust immunosuppressive activity, also rely on autophagy for their functions [172, 173]. Thus, deletion of *Atg5* from lysozyme 2 (LYZ2)-expressing cells is sufficient to limit the proliferation of xenografted B16F10 melanomas, an effect that was attributed to the limited lysosomal degradation of MHC Class II molecules and consequent boost in antigen presentation to $CD4^+$ T cells [173].

Of note, non-autophagic functions of the autophagy machinery may also modulate the immune response to developing tumors [42]. As an example, recruitment of the LC3-conjugation machinery to phagosomal membranes, following the engagement of Toll-like receptors (TLRs), Fc receptors or the pro-apoptotic receptor T cell immunoglobulin and mucin domain containing 4 (TIMD4) by dying cancer cells - a process commonly known as LC3-associated phagocytosis (LAP) [44], limits inflammatory responses in phagocytic cells [174]. Consistent with this notion, whole-body RUN domain and cysteine-rich domain containing, Beclin 1-interacting protein (*Rubcn*) deletion and consequent LAP inactivation favors type I IFN secretion by phagocytic cells including tumor-associated macrophages [175], ultimately promoting the control of B16F10 melanoma xenografts in the context of improved T-cell immunosurveillance [174].

Altogether, these observations suggest that autophagic responses in specific cellular compartments influence tumor progression by a variety of mechanisms beyond the preservation of metabolic fitness in malignant cells (**Figure 1B**).

5. Autophagy in cancer therapy: immunological aspects

It is now established that malignant lesions emerge, progress and respond to therapy in the context of a complex interaction with the host immune system [176-178]. Thus, most (if not all) conventional antineoplastic regimens with clinical activity, including cytotoxic chemotherapeutics [179], radiation therapy (RT) [180, 181] and targeted anticancer agents [182] operate by promoting (or at least not overtly counteracting) tumor-specific immunity. Moreover, over the past decade a variety of pharmacological and cellular approaches based on the (re)activation of anticancer immune responses has shown efficacy in the clinical setting, culminating with the regulatory approval of various immunotherapeutic agents for use in patients with cancer including so-called immune checkpoint inhibitors (ICIs) [183-186]. Such major conceptual and clinical revolutions called for the attentive re-evaluation of a large amount of preclinical literature on the therapeutic advantage offered by a variety of interventions (including pharmacological modulators of autophagy) [187] as documented in human cancer cells lines growing in immunodeficient mice.

Data from GEMMs of cancer lent additional support to the notion that tumor-specific immune responses are influenced by autophagic defects in both malignant and immune cells, suggesting that the pharmacological modulation of autophagy for anticancer purposes should be precisely tailored to the oncological setting and potentially even to specific features of the target lesion(s) [49, 188, 189]. Adding a further layer of complexity, currently available pharmacological inhibitors of autophagy including PI3K inhibitors (such as the experimental agents wortmannin and 3-methyladenine) [187, 190] as well as lysosomotropic drugs (like the FDA approved drugs chloroquine and hydroxychloroquine) [191, 192] suffer from various limitations, including poor specificity for the autophagic pathway [187, 193, 194] and (at least some) potential of promoting the emergence of secondary tumors [51].

Notwithstanding these considerations, both pharmacological and genetic approaches targeting the autophagic machinery have been successfully harnessed, at least in preclinical tumor models, to boost anticancer immune responses driven by antineoplastic treatments, thus offering a robust therapeutic benefit. For instance, the ability of selected chemotherapeutics including anthracyclines and oxaliplatin to drive ICD is intimately linked to ICD-associated ATP secretion, which in turn relies on proficient autophagic responses to therapy in malignant cells [156]. In line with this notion, mouse colorectal carcinoma CT26 cells succumbing to the prototypic anthracycline mitoxantrone (MTX) *in vitro* lose their capacity to provide immunological protection to syngeneic BALB/c mice against a subsequent challenge with living cells of the same type [156]. Similarly, CT26 colorectal tumors growing in BALB/c mice lose their sensitivity to MTX when genetically manipulated for ATG5 or ATG7 depletion [156]. Moreover, the sensitivity of CT26 colorectal tumors and mouse MCA205 fibrosarcomas growing in immunocompetent, syngeneic hosts to MTX or oxaliplatin can be boosted by nutritional (*e.g.*, starvation) as well as pharmacological (*e.g.*, caloric restriction mimicry with metformin, spermidine, hydroxycitrate or small molecule inhibitors of E1A binding protein p300, EP300) interventions that boost autophagy, correlating with increased ATP secretion, limited accumulation of T_{REG} cells in the TME and activation of a tumor-targeting T cell response that can be actioned with ICIs [195-197]. Similar results have been obtained in syngeneic models of: (1) mammary carcinomas responding to poorly immunogenic chemotherapeutics such as cisplatin [198] and RT [199, 200] plus fasting cycles, (2) melanoma, leukemia and lung cancer treated with caloric restriction mimetics (CRMs) only [196, 201, 202], as well as (3) brain, breast, liver and color cancer subjected to fasting cycles [203] or a fasting-mimicking diet (FMD), alone or in combination with chemo- or hormonotherapy [204-207]. In specific settings, the beneficial effects of systemic autophagy activators could be abrogated by ATG5 depletion in cancer cells [195]. Moreover, autophagy defects have been linked to an increased resistance of triple negative breast cancer (TNBC) cells to lysis by ICI-activated

CTLs through a mechanism involving tenascin C (TNC) overexpression [208], and ATG5-depleted CT26 cells are more radiosensitive than their control counterparts when they are implanted in immunocompetent (but not immunodeficient) hosts [209]. Most often, however, the relative contribution of autophagy activation in malignant *versus* non-malignant cells to superior therapeutic outcomes remains to be determined. Indeed, exposure of antigen-specific $CD8^+$ T cells to the CRM hydroxycitrate *in vitro* provides them with stem properties, favoring their persistence (and antitumor function) upon adoptive transferred to tumor-bearing hosts [169].

Lending further support to the notion that the beneficial effects of autophagy activators may not invariably stem from an increased autophagic flux in cancer cells, autophagy-deficient PDAC cells as well as PDAC cells exposed to chloroquine engage in superior antigen presentation on MHC Class I molecules, resulting in increased sensitivity to ICIs in vivo [150]. Similarly, various lysosomotropic agents have been successfully combined with therapeutic agents that engage anticancer immunity including recombinant IL2 [210, 211], peptide-based vaccination [212, 213] and RT [115] in immunocompetent syngeneic tumor models. In this latter setting, not only systemic chloroquine synergized with RT in the control of single mammary carcinoma TSA lesion established in syngeneic BALB/c, but *Atg5* or *Atg7* deletion in cancer cells enabled superior secretion of type I IFN by irradiated cells, culminating (at least in the context of ICI-based immunotherapy) with improved anticancer immunity with local and systemic outreach [115, 214]. Mechanistically, such an effect mapped to the inability of autophagy-deficient TSA cells to degrade mitochondria permeabilized by RT, resulting in the cytosolic accumulation of mtDNA and consequent activation of cyclic GMP-AMP synthase (CGAS) signaling [115, 215-217]. Similar results have been obtained in syngeneic melanoma models upon the genetic or pharmacological inhibition of Vps34 [218, 219]. Finally, proficient autophagic responses driven by hypoxia have been associated with an increased resistance of human and mouse tumor cells to lysis by NK cells, at least in part reflecting the autophagic degradation of granzyme B

(GZMB), which mediated NK cell cytotoxicity [220, 221] and gap junction protein alpha 1 (GJA1), which is involved in the formation of target cell:NK cell synapses [222].

Taken together, these observations suggest that autophagy is intimately involved in the regulation of therapy-driven anticancer immune responses, although the net effect of autophagy activators and inhibitors appears to exhibit a high degree of context dependency (**Figure 2**).

6. Concluding remarks

With the caveats discuss above, mouse models have been highly instrumental to elucidate the impact of autophagy in the immunological control of malignant transformation, tumor progression and response to (immuno)therapy. With the advent of the single-cell biology era, future efforts should be dedicated to studying the effects of autophagy on the cancer-immunity dialogue from a multidimensional perspective, rigorously evaluating: (1) the cell-specific outcomes of autophagy activation/inhibition; (2) the continuous interactions between cellular components of the TME, which can be directly or indirectly affected by the modulation of autophagy; and (3) the effects of pharmacological or genetic alterations of autophagy in non-transformed tissues, both *in cis* and *in trans* (**Figure 3**). In this context, the field would undoubtedly benefit from the implementation of pharmacological (rather than genetic) tools to modulate autophagy in a cell-type specific fashion. Proteolysis targeting chimeras (PROTAC) approaches [223, 224], through which cell specificity may be achieved via differential expression of E3 ligases in different components of the TME [225, 226], represent promising tools towards this objective. Ultimately, dissecting the precise impact of autophagy in specific compartments of the TME on the activation of anticancer immunity will be central to the design of clinically useful autophagy modulators.

Acknowledgements. FP is supported by a Karolinska Institute Starting Grant and by Starting Grant from the Swedish Research Council (2019_02050_3). JMB-SP is supported by the Ramon y Cajal Program (RYC-2018-025099-I). GK is supported by the Ligue contre le Cancer (équipe labellisée); Agence National de la Recherche (ANR) – Projets blancs; ANR under the frame of E-Rare-2, the ERA-Net for Research on Rare Diseases; Association pour la recherche sur le cancer (ARC); Cancéropôle Ile-de-France; Chancelerie des universités de Paris (Legs Poix), Fondation pour la Recherche Médicale (FRM); a donation by Elior; European Research Area Network on Cardiovascular Diseases (ERA-CVD, MINOTAUR); Gustave Roussy Odyssea, the European Union Horizon 2020 Project Oncobiome; Fondation Carrefour; High-end Foreign

Expert Program in China (GDW20171100085 and GDW20181100051), Institut National du Cancer (INCa); Inserm (HTE); Institut Universitaire de France; LeDucq Foundation; the LabEx Immuno-Oncology; the RHU Torino Lumière; the Seerave Foundation; the SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); and the SIRIC Cancer Research and Personalized Medicine (CARPEM). The LG lab is supported by a Breakthrough Level 2 grant from the US Department of Defense (DoD), Breast Cancer Research Program (BRCP) (#BC180476P1), by the 2019 Laura Ziskin Prize in Translational Research (#ZP-6177, PI: Formenti) from the Stand Up to Cancer (SU2C), by a Mantle Cell Lymphoma Research Initiative (MCL-RI, PI: Chen-Kiang) grant from the Leukemia and Lymphoma Society (LLS), by a startup grant from the Dept. of Radiation Oncology at Weill Cornell Medicine (New York, US), by a Rapid Response Grant from the Functional Genomics Initiative (New York, US), by industrial collaborations with Lytix (Oslo, Norway) and Phosplatin (New York, US), and by donations from Phosplatin (New York, US), the Luke Heller TECPR2 Foundation (Boston, US) and Sotio a.s. (Prague, Czech Republic).

Author Contributions. GK and LG conceived the article. FP and TY wrote the first version of the manuscript under supervision by LG and with constructive input from GK. JMBSP prepared display items under supervision from LG and FP. TY, GK and LG addressed reviewers' concerns and editorial requests. All authors approve the final version of the article.

Competing Interests: GK reports research funding from Bayer Healthcare, Daiichi Sankyo, Glaxo Smyth Kline, Eleor, Institut Mérieux, Kaleido, Lytix Pharma, PharmaMar, Sotio, Vasculox/Tioma, consulting/advisory honoraria from The Longevity Labs, as well as a co-founder role in everImmune, Samsara therapeutics and Therafast Bio. LG reports research funding from Lytix, and Phosplatin, consulting/advisory honoraria from Boehringer Ingelheim, AstraZeneca, OmniSEQ, The Longevity Labs, Inzen, and the Luke Heller TECPR2 Foundation. All other authors have no conflicts of interest to declare.

Legends to Display Items

Figure 1. **Autophagy in malignant transformation and cancer progression, an immune perspective. A.** Genetic defects of the autophagic machinery in healthy cells favor malignant transformation via a variety of mechanisms, including an increased likelihood for oxidative DNA damage and consequent mutagenesis, the establishment of a chronic inflammation as well as the inhibition of cancer immunosurveillance by dendritic cells (DCs) and $CD8^+$ cytotoxic T lymphocytes (CTLs). **B.** Conversely, autophagic responses in transformed cells strongly support disease progression, not only as they provide a superior metabolic adaptability to growing neoplasms, but also as they favor the establishment of an immunosuppressive tumor microenvironment (TME), reduce cancer antigenicity, limit the release of ATP in the context of immunogenic cell death (ICD). Of note, autophagy in the host also appears to favor tumor progression, at least in part by preserving an advantageous metabolic microenvironment to developing neoplasms and by preventing optimal CTL and macrophage functions. CQ, chloroquine; HCQ, hydroxychloroquine; mtDNA, mitochondrial DNA; ROS, reactive oxygen species.

Figure 2. **Context-dependent impact of autophagy on the sensitivity of cancer cells to treatment.** In multiple oncological settings, proficient autophagic responses in malignant cells are instrumental for optimal anticancer immune responses driven by treatment, as demonstrated by the detrimental effects of pharmacological or genetic autophagy inhibitors as well as by beneficial effects of autophagy activators. In many of these circumstances, autophagy supports anticancer immunity by favoring the immunogenic cell death (ICD)-driven liberation of ATP in the tumor microenvironment, which is required for the recruitment and activation of dendritic cell (DC) precursors. Along similar lines autophagy in immune effector cells including cytotoxic T lymphocytes (CTLs) is generally supportive of anticancer immunity. However, various settings in which autophagy counteracts therapy-driven

anticancer immune responses have also been identified, (at least in some scenarios) reflecting the ability of autophagy to limit antigen presentation, inhibit type I interferon (IFN) secretion by malignant cells or protect them from cytotoxic immune effectors. CRM, caloric restriction mimetic; ICI, immune checkpoint inhibitor; mtDNA, mitochondrial DNA.

Figure 3. **Differential impact of autophagy on cancer cells and their host.** Autophagy impinges on the cancer-immunity dialogue by a variety of mechanisms that originate from neoplastic cells as well as from non-transformed components of the tumor microenvironment (TME). Ultimately, all such mechanisms influence (*i.e.*, promote or counteract) oncogenesis, tumor progression as well as (natural and therapy-driven) anticancer immune responses. Thus, numerous oncogenic and oncosuppressive functions of autophagy involve immunological pathways. DC, dendritic cell; CTL, cytotoxic T lymphocyte; ICD, immunogenic cell death; IFN, interferon.

References

[1] N. Mizushima, Autophagy: process and function, Genes Dev, 21 (2007) 2861-2873.

[2] I. Dikic, Z. Elazar, Mechanism and medical implications of mammalian autophagy, Nat Rev Mol Cell Biol, 19 (2018) 349-364.

[3] L. Murrow, J. Debnath, Autophagy as a stress-response and quality-control mechanism: implications for cell injury and human disease, Annu Rev Pathol, 8 (2013) 105-137.

[4] B. Levine, G. Kroemer, Biological Functions of Autophagy Genes: A Disease Perspective, Cell, 176 (2019) 11-42.

[5] C. He, D.J. Klionsky, Regulation mechanisms and signaling pathways of autophagy, Annu Rev Genet, 43 (2009) 67-93.

[6] R.M. Perera, R. Zoncu, The Lysosome as a Regulatory Hub, Annu Rev Cell Dev Biol, 32 (2016) 223-253.

[7] S.W. Ryter, S.M. Cloonan, A.M. Choi, Autophagy: a critical regulator of cellular metabolism and homeostasis, Mol Cells, 36 (2013) 7-16.

[8] C.F. Bento, M. Renna, G. Ghislat, C. Puri, A. Ashkenazi, M. Vicinanza, F.M. Menzies, D.C. Rubinsztein, Mammalian Autophagy: How Does It Work?, Annu Rev Biochem, 85 (2016) 685-713.

[9] V. Sica, L. Galluzzi, J.M. Bravo-San Pedro, V. Izzo, M.C. Maiuri, G. Kroemer, Organelle-Specific Initiation of Autophagy, Mol Cell, 59 (2015) 522-539.

[10] N. Mizushima, A. Yamamoto, M. Matsui, T. Yoshimori, Y. Ohsumi, In vivo analysis of autophagy in response to nutrient starvation using transgenic mice expressing a fluorescent autophagosome marker, Mol Biol Cell, 15 (2004) 1101-1111.

[11] J.D. Rabinowitz, E. White, Autophagy and metabolism, Science, 330 (2010) 1344-1348.

[12] C.M. Anderson, K.F. Macleod, Autophagy and cancer cell metabolism, Int Rev Cell Mol Biol, 347 (2019) 145-190.

[13] R. Singh, A.M. Cuervo, Autophagy in the cellular energetic balance, Cell Metab, 13 (2011) 495-504.

[14] L. Galluzzi, F. Pietrocola, B. Levine, G. Kroemer, Metabolic control of autophagy, Cell, 159 (2014) 1263-1276.

[15] 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.

[16] D. Denton, S. Kumar, Autophagy-dependent cell death, Cell Death Differ, 26 (2019) 605-616.

[17] A. Meléndez, Z. Tallóczy, M. Seaman, E.L. Eskelinen, D.H. Hall, B. Levine, Autophagy genes are essential for dauer development and life-span extension in C. elegans, Science, 301 (2003) 1387-1391.

[18] E. Morselli, M.C. Maiuri, M. Markaki, E. Megalou, A. Pasparaki, K. Palikaras, A. Criollo, L. Galluzzi, S.A. Malik, I. Vitale, M. Michaud, F. Madeo, N. Tavernarakis, G. Kroemer, Caloric restriction and resveratrol promote longevity through the Sirtuin-1-dependent induction of autophagy, Cell Death Dis, 1 (2010) e10.

[19] L. Fontana, L. Partridge, V.D. Longo, Extending healthy life span--from yeast to humans, Science, 328 (2010) 321-326.

[20] A.M. Leidal, B. Levine, J. Debnath, Autophagy and the cell biology of age-related disease, Nat Cell Biol, 20 (2018) 1338-1348.

[21] M. Hansen, D.C. Rubinsztein, D.W. Walker, Autophagy as a promoter of longevity: insights from model organisms, Nat Rev Mol Cell Biol, 19 (2018) 579-593.

[22] L.D. Cassidy, M. Narita, Dynamic modulation of autophagy: implications for aging and cancer, Mol Cell Oncol, 7 (2020) 1754723.

[23] M.D. Rybstein, J.M. Bravo-San Pedro, G. Kroemer, L. Galluzzi, The autophagic network and cancer, Nat Cell Biol, 20 (2018) 243-251.

[24] A. Nencioni, I. Caffa, S. Cortellino, V.D. Longo, Fasting and cancer: molecular mechanisms and clinical application, Nat Rev Cancer, 18 (2018) 707-719.

[25] R. Buono, V.D. Longo, Starvation, Stress Resistance, and Cancer, Trends Endocrinol Metab, 29 (2018) 271-280.

[26] P. Codogno, M. Mehrpour, T. Proikas-Cezanne, Canonical and non-canonical autophagy: variations on a common theme of self-eating?, Nat Rev Mol Cell Biol, 13 (2011) 7-12.

[27] D. Fracchiolla, S. Martens, Sorting out "non-canonical" autophagy, EMBO J, 37 (2018).

[28] Z. Xie, U. Nair, D.J. Klionsky, Atg8 controls phagophore expansion during autophagosome formation, Mol Biol Cell, 19 (2008) 3290-3298.

[29] C.A. Lamb, T. Yoshimori, S.A. Tooze, The autophagosome: origins unknown, biogenesis complex, Nat Rev Mol Cell Biol, 14 (2013) 759-774.

[30] J. Kim, M. Kundu, B. Viollet, K.L. Guan, AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1, Nat Cell Biol, 13 (2011) 132-141.

[31] R.A. Saxton, D.M. Sabatini, mTOR Signaling in Growth, Metabolism, and Disease, Cell, 168 (2017) 960-976.

[32] K. Inoki, J. Kim, K.L. Guan, AMPK and mTOR in cellular energy homeostasis and drug targets, Annu Rev Pharmacol Toxicol, 52 (2012) 381-400.

[33] I. Dikic, Proteasomal and Autophagic Degradation Systems, Annu Rev Biochem, 86 (2017) 193-224.

[34] I. Tanida, T. Ueno, E. Kominami, LC3 conjugation system in mammalian autophagy, Int J Biochem Cell Biol, 36 (2004) 2503-2518.

[35] A. Stolz, A. Ernst, I. Dikic, Cargo recognition and trafficking in selective autophagy, Nat Cell Biol, 16 (2014) 495-501.

[36] V. Rogov, V. Dötsch, T. Johansen, V. Kirkin, Interactions between autophagy receptors and ubiquitin-like proteins form the molecular basis for selective autophagy, Mol Cell, 53 (2014) 167-178.

[37] C. Behrends, M.E. Sowa, S.P. Gygi, J.W. Harper, Network organization of the human autophagy system, Nature, 466 (2010) 68-76.

[38] J.C. Farré, S. Subramani, Mechanistic insights into selective autophagy pathways: lessons from yeast, Nat Rev Mol Cell Biol, 17 (2016) 537-552.

[39] D. Gatica, V. Lahiri, D.J. Klionsky, Cargo recognition and degradation by selective autophagy, Nat Cell Biol, 20 (2018) 233-242.

[40] L. Galluzzi, E.H. Baehrecke, A. Ballabio, P. Boya, J.M. Bravo-San Pedro, F. Cecconi, A.M. Choi, C.T. Chu, P. Codogno, M.I. Colombo, A.M. Cuervo, J. Debnath, V. Deretic, I. Dikic, E.L. Eskelinen, G.M. Fimia, S. Fulda, D.A. Gewirtz, D.R. Green, M. Hansen, J.W. Harper, M. Jäättelä, T. Johansen, G.

Juhasz, A.C. Kimmelman, C. Kraft, N.T. Ktistakis, S. Kumar, B. Levine, C. Lopez-Otin, F. Madeo, S. Martens, J. Martinez, A. Melendez, N. Mizushima, C. Münz, L.O. Murphy, J.M. Penninger, M. Piacentini, F. Reggiori, D.C. Rubinsztein, K.M. Ryan, L. Santambrogio, L. Scorrano, A.K. Simon, H.U. Simon, A. Simonsen, N. Tavernarakis, S.A. Tooze, T. Yoshimori, J. Yuan, Z. Yue, Q. Zhong, G. Kroemer, Molecular definitions of autophagy and related processes, Embo j, 36 (2017) 1811-1836.

[41] G. Zaffagnini, S. Martens, Mechanisms of Selective Autophagy, J Mol Biol, 428 (2016) 1714-1724.

[42] L. Galluzzi, D.R. Green, Autophagy-Independent Functions of the Autophagy Machinery, Cell, 177 (2019) 1682-1699.

[43] M. Ponpuak, M.A. Mandell, T. Kimura, S. Chauhan, C. Cleyrat, V. Deretic, Secretory autophagy, Curr Opin Cell Biol, 35 (2015) 106-116.

[44] B.L. Heckmann, E. Boada-Romero, L.D. Cunha, J. Magne, D.R. Green, LC3-Associated Phagocytosis and Inflammation, J Mol Biol, 429 (2017) 3561-3576.

[45] C. Amaya, C.M. Fader, M.I. Colombo, Autophagy and proteins involved in vesicular trafficking, FEBS Lett, 589 (2015) 3343-3353.

[46] N. Santana-Codina, J.D. Mancias, A.C. Kimmelman, The Role of Autophagy in Cancer, Annu Rev Cancer Biol, 1 (2017) 19-39.

[47] R. Mathew, V. Karantza-Wadsworth, E. White, Role of autophagy in cancer, Nat Rev Cancer, 7 (2007) 961-967.

[48] E. White, The role for autophagy in cancer, J Clin Invest, 125 (2015) 42-46.

[49] J.M.M. Levy, C.G. Towers, A. Thorburn, Targeting autophagy in cancer, Nat Rev Cancer, 17 (2017) 528-542.

[50] S.K. Bhutia, S. Mukhopadhyay, N. Sinha, D.N. Das, P.K. Panda, S.K. Patra, T.K. Maiti, M. Mandal, P. Dent, X.Y. Wang, S.K. Das, D. Sarkar, P.B. Fisher, Autophagy: cancer's friend or foe?, Adv Cancer Res, 118 (2013) 61-95.

[51] L.D. Cassidy, A.R.J. Young, C.N.J. Young, E.J. Soilleux, E. Fielder, B.M. Weigand, A. Lagnado, R. Brais, N.T. Ktistakis, K.A. Wiggins, K. Pyrillou, M.C.H. Clarke, D. Jurk, J.F. Passos, M. Narita, Temporal inhibition of autophagy reveals segmental reversal of ageing with increased cancer risk, Nat Commun, 11 (2020) 307.

[52] L. Poillet-Perez, X. Xie, L. Zhan, Y. Yang, D.W. Sharp, Z.S. Hu, X. Su, A. Maganti, C. Jiang, W. Lu, H. Zheng, M.W. Bosenberg, J.M. Mehnert, J.Y. Guo, E. Lattime, J.D. Rabinowitz, E. White, Autophagy maintains tumour growth through circulating arginine, Nature, 563 (2018) 569-573.

[53] N.N. Pavlova, C.B. Thompson, The Emerging Hallmarks of Cancer Metabolism, Cell Metab, 23 (2016) 27-47.

[54] A.C. Kimmelman, E. White, Autophagy and Tumor Metabolism, Cell Metab, 25 (2017) 1037-1043.

[55] W. Kim, S. Lee, D. Seo, D. Kim, K. Kim, E. Kim, J. Kang, K.M. Seong, H. Youn, B. Youn, Cellular Stress Responses in Radiotherapy, Cells, 8 (2019).

[56] A.G. Smith, K.F. Macleod, Autophagy, cancer stem cells and drug resistance, J Pathol, 247 (2019) 708-718.

[57] L. Galluzzi, T. Yamazaki, G. Kroemer, Linking cellular stress responses to systemic homeostasis, Nat Rev Mol Cell Biol, 19 (2018) 731-745.

[58] J. Thorburn, L. Staskiewicz, M.L. Goodall, L. Dimberg, A.E. Frankel, H.L. Ford, A. Thorburn, Non-cell-autonomous Effects of Autophagy Inhibition in Tumor Cells Promote Growth of Drug-resistant Cells, Mol Pharmacol, 91 (2017) 58-64.

[59] E.E. Mowers, M.N. Sharifi, K.F. Macleod, Functions of autophagy in the tumor microenvironment and cancer metastasis, Febs j, 285 (2018) 1751-1766.

[60] W. He, W. Xiong, X. Xia, Autophagy Regulation of Mammalian Immune Cells, Adv Exp Med Biol, 1209 (2019) 7-22.

[61] C. Gerada, K.M. Ryan, Autophagy, the innate immune response and cancer, Mol Oncol, 14 (2020) 1913-1929.

[62] F. Pietrocola, J.M. Bravo-San Pedro, L. Galluzzi, G. Kroemer, Autophagy in natural and therapy-driven anticancer immunosurveillance, Autophagy, 13 (2017) 2163-2170.

[63] L. Galluzzi, I. Vitale, S. Warren, S. Adjemian, P. Agostinis, A.B. Martinez, T.A. Chan, G. Coukos, S. Demaria, E. Deutsch, D. Draganov, R.L. Edelson, S.C. Formenti, J. Fucikova, L. Gabriele, U.S. Gaipl, S.R. Gameiro, A.D. Garg, E. Golden, J. Han, K.J. Harrington, A. Hemminki, J.W. Hodge, D.M.S. Hossain, T. Illidge, M. Karin, H.L. Kaufman, O. Kepp, G. Kroemer, J.J. Lasarte, S. Loi, M.T. Lotze, G. Manic, T. Merghoub, A.A. Melcher, K.L. Mossman, F. Prosper, O. Rekdal, M. Rescigno, C. Riganti, A. Sistigu, M.J. Smyth, R. Spisek, J. Stagg, B.E. Strauss, D. Tang, K. Tatsuno, S.W. van Gool, P. Vandenabeele, T. Yamazaki, D. Zamarin, L. Zitvogel, A. Cesano, F.M. Marincola, Consensus guidelines for the definition, detection and interpretation of immunogenic cell death, J Immunother Cancer, 8 (2020) e000337.

[64] B. Nayagom, I. Amara, M. Habiballah, F. Amrouche, P. Beaune, I. de Waziers, Immunogenic cell death in a combined synergic gene- and immune-therapy against cancer, Oncoimmunology, 8 (2019) e1667743.

[65] D.V. Krysko, A.D. Garg, A. Kaczmarek, O. Krysko, P. Agostinis, P. Vandenabeele, Immunogenic cell death and DAMPs in cancer therapy, Nat Rev Cancer, 12 (2012) 860-875.

[66] Y. Matsuzawa-Ishimoto, S. Hwang, K. Cadwell, Autophagy and Inflammation, Annu Rev Immunol, 36 (2018) 73-101.

[67] M.E. Rodriguez-Ruiz, I. Vitale, K.J. Harrington, I. Melero, L. Galluzzi, Immunological impact of cell death signaling driven by radiation on the tumor microenvironment, Nat Immunol, 21 (2020) 120-134.

[68] Y. Li, L.X. Wang, G. Yang, F. Hao, W.J. Urba, H.M. Hu, Efficient cross-presentation depends on autophagy in tumor cells, Cancer Res, 68 (2008) 6889-6895.

[69] H.K. Lee, L.M. Mattei, B.E. Steinberg, P. Alberts, Y.H. Lee, A. Chervonsky, N. Mizushima, S. Grinstein, A. Iwasaki, In vivo requirement for Atg5 in antigen presentation by dendritic cells, Immunity, 32 (2010) 227-239.

[70] J. Martinek, T.C. Wu, D. Cadena, J. Banchereau, K. Palucka, Interplay between dendritic cells and cancer cells, Int Rev Cell Mol Biol, 348 (2019) 179-215.

[71] V.L. Crotzer, J.S. Blum, Autophagy and its role in MHC-mediated antigen presentation, J Immunol, 182 (2009) 3335-3341.

[72] F. Kotsias, I. Cebrian, A. Alloatti, Antigen processing and presentation, Int Rev Cell Mol Biol, 348 (2019) 69-121.

[73] N. Germic, Z. Frangez, S. Yousefi, H.U. Simon, Regulation of the innate immune system by autophagy: monocytes, macrophages, dendritic cells and antigen presentation, Cell Death Differ, 26 (2019) 715-727.

[74] T.E. O'Sullivan, C.D. Geary, O.E. Weizman, T.L. Geiger, M. Rapp, G.W. Dorn, 2nd, M. Overholtzer, J.C. Sun, Atg5 Is Essential for the Development and Survival of Innate Lymphocytes, Cell Rep, 15 (2016) 1910-1919.

[75] N. Germic, Z. Frangez, S. Yousefi, H.U. Simon, Regulation of the innate immune system by autophagy: neutrophils, eosinophils, mast cells, NK cells, Cell Death Differ, 26 (2019) 703-714.

[76] A.J. Clarke, A.K. Simon, Autophagy in the renewal, differentiation and homeostasis of immune cells, Nat Rev Immunol, 19 (2019) 170-183.

[77] S. Wang, P. Xia, G. Huang, P. Zhu, J. Liu, B. Ye, Y. Du, Z. Fan, FoxO1-mediated autophagy is required for NK cell development and innate immunity, Nat Commun, 7 (2016) 11023.

[78] A. Kuma, M. Komatsu, N. Mizushima, Autophagy-monitoring and autophagy-deficient mice, Autophagy, 13 (2017) 1619-1628.

[79] N. Mizushima, B. Levine, Autophagy in mammalian development and differentiation, Nat Cell Biol, 12 (2010) 823-830.

[80] A. Kuma, M. Hatano, M. Matsui, A. Yamamoto, H. Nakaya, T. Yoshimori, Y. Ohsumi, T. Tokuhisa, N. Mizushima, The role of autophagy during the early neonatal starvation period, Nature, 432 (2004) 1032-1036.

[81] X. Qu, J. Yu, G. Bhagat, N. Furuya, H. Hibshoosh, A. Troxel, J. Rosen, E.L. Eskelinen, N. Mizushima, Y. Ohsumi, G. Cattoretti, B. Levine, Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene, J Clin Invest, 112 (2003) 1809-1820.

[82] H. Kim, M. Kim, S.K. Im, S. Fang, Mouse Cre-LoxP system: general principles to determine tissue-specific roles of target genes, Lab Anim Res, 34 (2018) 147-159.

[83] H. Gu, Y.R. Zou, K. Rajewsky, Independent control of immunoglobulin switch recombination at individual switch regions evidenced through Cre-loxP-mediated gene targeting, Cell, 73 (1993) 1155-1164.

[84] A. Takamura, M. Komatsu, T. Hara, A. Sakamoto, C. Kishi, S. Waguri, Y. Eishi, O. Hino, K. Tanaka, N. Mizushima, Autophagy-deficient mice develop multiple liver tumors, Genes Dev, 25 (2011) 795-800.

[85] M. Komatsu, S. Waguri, T. Ueno, J. Iwata, S. Murata, I. Tanida, J. Ezaki, N. Mizushima, Y. Ohsumi, Y. Uchiyama, E. Kominami, K. Tanaka, T. Chiba, Impairment of starvation-induced and constitutive autophagy in Atg7-deficient mice, J Cell Biol, 169 (2005) 425-434.

[86] J.Y. Guo, G. Karsli-Uzunbas, R. Mathew, S.C. Aisner, J.J. Kamphorst, A.M. Strohecker, G. Chen, S. Price, W. Lu, X. Teng, E. Snyder, U. Santanam, R.S. Dipaola, T. Jacks, J.D. Rabinowitz, E. White, Autophagy suppresses progression of K-ras-induced lung tumors to oncocytomas and maintains lipid homeostasis, Genes Dev, 27 (2013) 1447-1461.

[87] K. Kersten, K.E. de Visser, M.H. van Miltenburg, J. Jonkers, Genetically engineered mouse models in oncology research and cancer medicine, EMBO Mol Med, 9 (2017) 137-153.

[88] J. Heyer, L.N. Kwong, S.W. Lowe, L. Chin, Non-germline genetically engineered mouse models for translational cancer research, Nat Rev Cancer, 10 (2010) 470-480.

[89] A. Buqué, L. Galluzzi, Modeling Tumor Immunology and Immunotherapy in Mice, Trends Cancer, 4 (2018) 599-601.

[90] B. Olson, Y. Li, Y. Lin, E.T. Liu, A. Patnaik, Mouse Models for Cancer Immunotherapy Research, Cancer Discov, 8 (2018) 1358-1365.

[91] M. DuPage, T. Jacks, Genetically engineered mouse models of cancer reveal new insights about the antitumor immune response, Curr Opin Immunol, 25 (2013) 192-199.

[92] A. Buqué, N. Bloy, M. Perez-Lanzón, K. Iribarren, J. Humeau, J.G. Pol, S. Levesque, L. Mondragon, T. Yamazaki, A. Sato, F. Aranda, S. Durand, A. Boissonnas, J. Fucikova, L. Senovilla, D. Enot, M. Hensler, M. Kremer, G. Stoll, Y. Hu, C. Massa, S.C. Formenti, B. Seliger, O. Elemento, R. Spisek, F. André, L. Zitvogel, S. Delaloge, G. Kroemer, L. Galluzzi, Immunoprophylactic and immunotherapeutic control of hormone receptor-positive breast cancer, Nat Commun, 11 (2020) 3819.

[93] F.S. Salah, M. Ebbinghaus, V.Y. Muley, Z. Zhou, K.R. Al-Saadi, M. Pacyna-Gengelbach, G.A. O'Sullivan, H. Betz, R. König, Z.Q. Wang, R. Bräuer, I. Petersen, Tumor suppression in mice lacking GABARAP, an Atg8/LC3 family member implicated in autophagy, is associated with alterations in cytokine secretion and cell death, Cell Death Dis, 7 (2016) e2205.

[94] X.H. Liang, S. Jackson, M. Seaman, K. Brown, B. Kempkes, H. Hibshoosh, B. Levine, Induction of autophagy and inhibition of tumorigenesis by beclin 1, Nature, 402 (1999) 672-676.

[95] M. Cicchini, R. Chakrabarti, S. Kongara, S. Price, R. Nahar, F. Lozy, H. Zhong, A. Vazquez, Y. Kang, V. Karantza, Autophagy regulator BECN1 suppresses mammary tumorigenesis driven by WNT1 activation and following parity, Autophagy, 10 (2014) 2036-2052.

[96] V. Cianfanelli, C. Fuoco, M. Lorente, M. Salazar, F. Quondamatteo, P.F. Gherardini, D. De Zio, F. Nazio, M. Antonioli, M. D'Orazio, T. Skobo, M. Bordi, M. Rohde, L. Dalla Valle, M. Helmer-Citterich, C. Gretzmeier, J. Dengjel, G.M. Fimia, M. Piacentini, S. Di Bartolomeo, G. Velasco, F. Cecconi, AMBRA1 links autophagy to cell proliferation and tumorigenesis by promoting c-Myc dephosphorylation and degradation, Nat Cell Biol, 17 (2015) 20-30.

[97] L.D. Cassidy, A.R. Young, P.A. Pérez-Mancera, B. Nimmervoll, A. Jaulim, H.C. Chen, D.J.O. McIntyre, R. Brais, T. Ricketts, S. Pacey, M. De La Roche, R.J. Gilbertson, D.C. Rubinsztein, M. Narita, A novel Atg5-shRNA mouse model enables temporal control of Autophagy in vivo, Autophagy, 14 (2018) 1256-1266.

[98] S. Rao, L. Tortola, T. Perlot, G. Wirnsberger, M. Novatchkova, R. Nitsch, P. Sykacek, L. Frank, D. Schramek, V. Komnenovic, V. Sigl, K. Aumayr, G. Schmauss, N. Fellner, S. Handschuh, M. Glösmann, P. Pasierbek, M. Schlederer, G.P. Resch, Y. Ma, H. Yang, H. Popper, L. Kenner, G.

Kroemer, J.M. Penninger, A dual role for autophagy in a murine model of lung cancer, Nat Commun, 5 (2014) 3056.

[99] A.M. Strohecker, J.Y. Guo, G. Karsli-Uzunbas, S.M. Price, G.J. Chen, R. Mathew, M. McMahon, E. White, Autophagy sustains mitochondrial glutamine metabolism and growth of BrafV600E-driven lung tumors, Cancer Discov, 3 (2013) 1272-1285.

[100] M.T. Rosenfeldt, J. O'Prey, J.P. Morton, C. Nixon, G. MacKay, A. Mrowinska, A. Au, T.S. Rai, L. Zheng, R. Ridgway, P.D. Adams, K.I. Anderson, E. Gottlieb, O.J. Sansom, K.M. Ryan, p53 status determines the role of autophagy in pancreatic tumour development, Nature, 504 (2013) 296-300.

[101] Z. Zhong, E. Sanchez-Lopez, M. Karin, Autophagy, Inflammation, and Immunity: A Troika Governing Cancer and Its Treatment, Cell, 166 (2016) 288-298.

[102] B. Levine, N. Mizushima, H.W. Virgin, Autophagy in immunity and inflammation, Nature, 469 (2011) 323-335.

[103] Q. Zhu, R. Wang, D. Nemecio, C. Liang, How autophagy is tied to inflammation and cancer, Mol Cell Oncol, 7 (2020) 1717908.

[104] V. Deretic, T. Saitoh, S. Akira, Autophagy in infection, inflammation and immunity, Nat Rev Immunol, 13 (2013) 722-737.

[105] J. Moscat, M. Karin, M.T. Diaz-Meco, p62 in Cancer: Signaling Adaptor Beyond Autophagy, Cell, 167 (2016) 606-609.

[106] J. Moscat, M.T. Diaz-Meco, p62 at the crossroads of autophagy, apoptosis, and cancer, Cell, 137 (2009) 1001-1004.

[107] R. Mathew, C.M. Karp, B. Beaudoin, N. Vuong, G. Chen, H.Y. Chen, K. Bray, A. Reddy, G. Bhanot, C. Gelinas, R.S. Dipaola, V. Karantza-Wadsworth, E. White, Autophagy suppresses tumorigenesis through elimination of p62, Cell, 137 (2009) 1062-1075.

[108] T. Monkkonen, J. Debnath, Inflammatory signaling cascades and autophagy in cancer, Autophagy, 14 (2018) 190-198.

[109] T.O. Crisan, T.S. Plantinga, F.L. van de Veerdonk, M.F. Farcas, M. Stoffels, B.J. Kullberg, J.W. van der Meer, L.A. Joosten, M.G. Netea, Inflammasome-independent modulation of cytokine response by autophagy in human cells, PLoS One, 6 (2011) e18666.

[110] R. Lock, C.M. Kenific, A.M. Leidal, E. Salas, J. Debnath, Autophagy-dependent production of secreted factors facilitates oncogenic RAS-driven invasion, Cancer Discov, 4 (2014) 466-479.

[111] M. Lamkanfi, V.M. Dixit, Mechanisms and functions of inflammasomes, Cell, 157 (2014) 1013-1022.

[112] O. Kepp, L. Galluzzi, G. Kroemer, Mitochondrial control of the NLRP3 inflammasome, Nat Immunol, 12 (2011) 199-200.

[113] 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.

[114] K. Nakahira, J.A. Haspel, V.A. Rathinam, S.J. Lee, T. Dolinay, H.C. Lam, J.A. Englert, M. Rabinovitch, M. Cernadas, H.P. Kim, K.A. Fitzgerald, S.W. Ryter, A.M. Choi, Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome, Nat Immunol, 12 (2011) 222-230.

[115] T. Yamazaki, A. Kirchmair, A. Sato, A. Buque, M. Rybstein, G. Petroni, N. Bloy, F. Finotello, L. Stafford, E. Navarro Manzano, F. Ayala de la Pena, E. Garcia-Martinez, S.C. Formenti, Z. Trajanoski, L. Galluzzi, Mitochondrial DNA drives abscopal responses to radiation that are inhibited by autophagy, Nat Immunol, 21 (2020) 1160-1171.

[116] D.S. Chen, I. Mellman, Oncology meets immunology: the cancer-immunity cycle, Immunity, 39 (2013) 1-10.

[117] L. Spel, J.J. Boelens, S. Nierkens, M. Boes, Antitumor immune responses mediated by dendritic cells: How signals derived from dying cancer cells drive antigen cross-presentation, Oncoimmunology, 2 (2013) e26403.

[118] Y.S. Lee, K.J. Radford, The role of dendritic cells in cancer, Int Rev Cell Mol Biol, 348 (2019) 123-178.

[119] J. Sprooten, P. Agostinis, A.D. Garg, Type I interferons and dendritic cells in cancer immunotherapy, Int Rev Cell Mol Biol, 348 (2019) 217-262.

[120] S. Iurescia, D. Fioretti, M. Rinaldi, Targeting Cytosolic Nucleic Acid-Sensing Pathways for Cancer Immunotherapies, Front Immunol, 9 (2018) 711.

[121] C. Münz, Antigen Processing for MHC Class II Presentation via Autophagy, Front Immunol, 3 (2012) 9.

[122] D.S. Oh, H.K. Lee, Autophagy protein ATG5 regulates CD36 expression and anti-tumor MHC class II antigen presentation in dendritic cells, Autophagy, 15 (2019) 2091-2106.

[123] J.D. Mintern, C. Macri, W.J. Chin, S.E. Panozza, E. Segura, N.L. Patterson, P. Zeller, D. Bourges, S. Bedoui, P.J. McMillan, A. Idris, C.J. Nowell, A. Brown, K.J. Radford, A.P. Johnston, J.A. Villadangos, Differential use of autophagy by primary dendritic cells specialized in cross-presentation, Autophagy, 11 (2015) 906-917.

[124] L. You, Z. Wang, H. Li, J. Shou, Z. Jing, J. Xie, X. Sui, H. Pan, W. Han, The role of STAT3 in autophagy, Autophagy, 11 (2015) 729-739.

[125] S. Rao, K. Gharib, A. Han, Cancer Immunosurveillance by T Cells, Int Rev Cell Mol Biol, 342 (2019) 149-173.

[126] S. Aits, M. Jäättelä, Lysosomal cell death at a glance, J Cell Sci, 126 (2013) 1905-1912.

[127] P.K. Ziegler, J. Bollrath, C.K. Pallangyo, T. Matsutani, Ö. Canli, T. De Oliveira, M.A. Diamanti, N. Müller, J. Gamrekelashvili, T. Putoczki, D. Horst, A.K. Mankan, M.G. Öner, S. Müller, J. Müller-Höcker, T. Kirchner, J. Slotta-Huspenina, M.M. Taketo, T. Reinheckel, S. Dröse, A.C. Larner, W.S. Wels, M. Ernst, T.F. Greten, M.C. Arkan, T. Korn, D. Wirth, F.R. Greten, Mitophagy in Intestinal Epithelial Cells Triggers Adaptive Immunity during Tumorigenesis, Cell, 174 (2018) 88-101.e116.

[128] A. Das Mohapatra, I. Tirrell, A.P. Benechet, S. Pattnayak, K.M. Khanna, P.K. Srivastava, Cross-dressing of CD8alpha(+) Dendritic Cells with Antigens from Live Mouse Tumor Cells Is a Major Mechanism of Cross-priming, Cancer Immunol Res, 8 (2020) 1287-1299.

[129] S. Campana, C. De Pasquale, P. Carrega, G. Ferlazzo, I. Bonaccorsi, Cross-dressing: an alternative mechanism for antigen presentation, Immunol Lett, 168 (2015) 349-354.

[130] X. Xu, K. Araki, S. Li, J.H. Han, L. Ye, W.G. Tan, B.T. Konieczny, M.W. Bruinsma, J. Martinez, E.L. Pearce, D.R. Green, D.P. Jones, H.W. Virgin, R. Ahmed, Autophagy is essential for effector CD8(+) T cell survival and memory formation, Nat Immunol, 15 (2014) 1152-1161.

[131] H.H. Pua, I. Dzhagalov, M. Chuck, N. Mizushima, Y.W. He, A critical role for the autophagy gene Atg5 in T cell survival and proliferation, J Exp Med, 204 (2007) 25-31.

[132] D.J. Puleston, H. Zhang, T.J. Powell, E. Lipina, S. Sims, I. Panse, A.S. Watson, V. Cerundolo, A.R. Townsend, P. Klenerman, A.K. Simon, Autophagy is a critical regulator of memory CD8(+) T cell formation, Elife, 3 (2014).

[133] L. DeVorkin, N. Pavey, G. Carleton, A. Comber, C. Ho, J. Lim, E. McNamara, H. Huang, P. Kim, L.G. Zacharias, N. Mizushima, T. Saitoh, S. Akira, W. Beckham, A. Lorzadeh, M. Moksa, Q. Cao, A. Murthy, M. Hirst, R.J. DeBerardinis, J.J. Lum, Autophagy Regulation of Metabolism Is Required for CD8(+) T Cell Anti-tumor Immunity, Cell Rep, 27 (2019) 502-513.e505.

[134] V.V. Parekh, L. Wu, K.L. Boyd, J.A. Williams, J.A. Gaddy, D. Olivares-Villagómez, T.L. Cover, W.X. Zong, J. Zhang, L. Van Kaer, Impaired autophagy, defective T cell homeostasis, and a wasting syndrome in mice with a T cell-specific deletion of Vps34, J Immunol, 190 (2013) 5086-5101.

[135] J. Brummelman, K. Pilipow, E. Lugli, The Single-Cell Phenotypic Identity of Human CD8(+) and CD4(+) T Cells, Int Rev Cell Mol Biol, 341 (2018) 63-124.

[136] C. Tanchot, M. Terme, H. Pere, T. Tran, N. Benhamouda, M. Strioga, C. Banissi, L. Galluzzi, G. Kroemer, E. Tartour, Tumor-infiltrating regulatory T cells: phenotype, role, mechanism of expansion in situ and clinical significance, Cancer Microenviron, 6 (2013) 147-157.

[137] E. Jacquin, L. Apetoh, Cell-Intrinsic Roles for Autophagy in Modulating CD4 T Cell Functions, Front Immunol, 9 (2018) 1023.

[138] J. Wei, L. Long, K. Yang, C. Guy, S. Shrestha, Z. Chen, C. Wu, P. Vogel, G. Neale, D.R. Green, H. Chi, Autophagy enforces functional integrity of regulatory T cells by coupling environmental cues and metabolic homeostasis, Nat Immunol, 17 (2016) 277-285.

[139] N. Gammoh, J. Fraser, C. Puente, H.M. Syred, H. Kang, T. Ozawa, D. Lam, J.C. Acosta, A.J. Finch, E. Holland, X. Jiang, Suppression of autophagy impedes glioblastoma development and induces senescence, Autophagy, 12 (2016) 1431-1439.

[140] H. Wei, S. Wei, B. Gan, X. Peng, W. Zou, J.L. Guan, Suppression of autophagy by FIP200 deletion inhibits mammary tumorigenesis, Genes Dev, 25 (2011) 1510-1527.

[141] N.N. Khodarev, Intracellular RNA Sensing in Mammalian Cells: Role in Stress Response and Cancer Therapies, Int Rev Cell Mol Biol, 344 (2019) 31-89.

[142] J. Lévy, W. Cacheux, M.A. Bara, A. L'Hermitte, P. Lepage, M. Fraudeau, C. Trentesaux, J. Lemarchand, A. Durand, A.M. Crain, C. Marchiol, G. Renault, F. Dumont, F. Letourneur, M. Delacre, A. Schmitt, B. Terris, C. Perret, M. Chamaillard, J.P. Couty, B. Romagnolo, Intestinal inhibition of Atg7 prevents tumour initiation through a microbiome-influenced immune response and suppresses tumour growth, Nat Cell Biol, 17 (2015) 1062-1073.

[143] A. Yang, N.V. Rajeshkumar, X. Wang, S. Yabuuchi, B.M. Alexander, G.C. Chu, D.D. Von Hoff, A. Maitra, A.C. Kimmelman, Autophagy is critical for pancreatic tumor growth and progression in tumors with p53 alterations, Cancer Discov, 4 (2014) 905-913.

[144] U. Santanam, W. Banach-Petrosky, C. Abate-Shen, M.M. Shen, E. White, R.S. DiPaola, Atg7 cooperates with Pten loss to drive prostate cancer tumor growth, Genes Dev, 30 (2016) 399-407.

[145] X. Xie, J.Y. Koh, S. Price, E. White, J.M. Mehnert, Atg7 Overcomes Senescence and Promotes Growth of BrafV600E-Driven Melanoma, Cancer Discov, 5 (2015) 410-423.

[146] L. Poillet-Perez, E. White, Role of tumor and host autophagy in cancer metabolism, Genes Dev, 33 (2019) 610-619.

[147] J.L. Guerriero, Macrophages: Their Untold Story in T Cell Activation and Function, Int Rev Cell Mol Biol, 342 (2019) 73-93.

[148] A. Yang, G. Herter-Sprie, H. Zhang, E.Y. Lin, D. Biancur, X. Wang, J. Deng, J. Hai, S. Yang, K.K. Wong, A.C. Kimmelman, Autophagy Sustains Pancreatic Cancer Growth through Both Cell-Autonomous and Nonautonomous Mechanisms, Cancer Discov, 8 (2018) 276-287.

[149] L. Galluzzi, T.A. Chan, G. Kroemer, J.D. Wolchok, A. Lopez-Soto, The hallmarks of successful anticancer immunotherapy, Sci Transl Med, 10 (2018) eaat7807.

[150] K. Yamamoto, A. Venida, J. Yano, D.E. Biancur, M. Kakiuchi, S. Gupta, A.S.W. Sohn, S. Mukhopadhyay, E.Y. Lin, S.J. Parker, R.S. Banh, J.A. Paulo, K.W. Wen, J. Debnath, G.E. Kim, J.D. Mancias, D.T. Fearon, R.M. Perera, A.C. Kimmelman, Autophagy promotes immune evasion of pancreatic cancer by degrading MHC-I, Nature, 581 (2020) 100-105.

[151] T. Lamark, V. Kirkin, I. Dikic, T. Johansen, NBR1 and p62 as cargo receptors for selective autophagy of ubiquitinated targets, Cell Cycle, 8 (2009) 1986-1990.

[152] L. Poillet-Perez, D.W. Sharp, Y. Yang, S.V. Laddha, M. Ibrahim, P.K. Bommareddy, Z.S. Hu, J. Vieth, M. Haas, M.W. Bosenberg, J.D. Rabinowitz, J. Cao, J.-L. Guan, S. Ganesan, C.S. Chan, J.M. Mehnert, E.C. Lattime, E. White, Autophagy promotes growth of tumors with high mutational burden by inhibiting a T-cell immune response, Nature Cancer, 1 (2020) 923-934.

[153] N. Bloy, P. Garcia, C.M. Laumont, J.M. Pitt, A. Sistigu, G. Stoll, T. Yamazaki, E. Bonneil, A. Buqué, J. Humeau, J.W. Drijfhout, G. Meurice, S. Walter, J. Fritsche, T. Weinschenk, H.G. Rammensee, C. Melief, P. Thibault, C. Perreault, J. Pol, L. Zitvogel, L. Senovilla, G. Kroemer, Immunogenic stress and death of cancer cells: Contribution of antigenicity vs adjuvanticity to immunosurveillance, Immunol Rev, 280 (2017) 165-174.

[154] E. Caron, K. Vincent, M.H. Fortier, J.P. Laverdure, A. Bramoullé, M.P. Hardy, G. Voisin, P.P. Roux, S. Lemieux, P. Thibault, C. Perreault, The MHC I immunopeptidome conveys to the cell surface an integrative view of cellular regulation, Mol Syst Biol, 7 (2011) 533.

[155] A.D. Garg, D.V. Krysko, P. Vandenabeele, P. Agostinis, Extracellular ATP and P_2X_7 receptor exert context-specific immunogenic effects after immunogenic cancer cell death, Cell Death Dis, 7 (2016) e2097.

[156] M. Michaud, I. Martins, A.Q. Sukkurwala, S. Adjemian, Y. Ma, P. Pellegatti, S. Shen, O. Kepp, M. Scoazec, G. Mignot, S. Rello-Varona, M. Tailler, L. Menger, E. Vacchelli, L. Galluzzi, F. Ghiringhelli, F. di Virgilio, L. Zitvogel, G. Kroemer, Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice, Science, 334 (2011) 1573-1577.

[157] F. Di Virgilio, A.C. Sarti, S. Falzoni, E. De Marchi, E. Adinolfi, Extracellular ATP and P2 purinergic signalling in the tumour microenvironment, Nat Rev Cancer, 18 (2018) 601-618.

[158] Y. Ma, S. Adjemian, S.R. Mattarollo, T. Yamazaki, L. Aymeric, H. Yang, J.P. Portela Catani, D. Hannani, H. Duret, K. Steegh, I. Martins, F. Schlemmer, M. Michaud, O. Kepp, A.Q. Sukkurwala, L. Menger, E. Vacchelli, N. Droin, L. Galluzzi, R. Krzysiek, S. Gordon, P.R. Taylor, P. Van Endert, E. Solary, M.J. Smyth, L. Zitvogel, G. Kroemer, Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-presenting cells, Immunity, 38 (2013) 729-741.

[159] G. Karsli-Uzunbas, J.Y. Guo, S. Price, X. Teng, S.V. Laddha, S. Khor, N.Y. Kalaany, T. Jacks, C.S. Chan, J.D. Rabinowitz, E. White, Autophagy is required for glucose homeostasis and lung tumor maintenance, Cancer Discov, 4 (2014) 914-927.

[160] Y. Zhao, T. Wu, S. Shao, B. Shi, Y. Zhao, Phenotype, development, and biological function of myeloid-derived suppressor cells, Oncoimmunology, 5 (2016) e1004983.

[161] T.M. Grzywa, A. Sosnowska, P. Matryba, Z. Rydzynska, M. Jasinski, D. Nowis, J. Golab, Myeloid Cell-Derived Arginase in Cancer Immune Response, Front Immunol, 11 (2020) 938.

[162] A.R. Lim, W.K. Rathmell, J.C. Rathmell, The tumor microenvironment as a metabolic barrier to effector T cells and immunotherapy, Elife, 9 (2020).

[163] C.H. Chang, J. Qiu, D. O'Sullivan, M.D. Buck, T. Noguchi, J.D. Curtis, Q. Chen, M. Gindin, M.M. Gubin, G.J. van der Windt, E. Tonc, R.D. Schreiber, E.J. Pearce, E.L. Pearce, Metabolic Competition in the Tumor Microenvironment Is a Driver of Cancer Progression, Cell, 162 (2015) 1229-1241.

[164] V.M. Ngwa, D.N. Edwards, M. Philip, J. Chen, Microenvironmental Metabolism Regulates Antitumor Immunity, Cancer Res, 79 (2019) 4003-4008.

[165] R.J. Kishton, M. Sukumar, N.P. Restifo, Metabolic Regulation of T Cell Longevity and Function in Tumor Immunotherapy, Cell Metab, 26 (2017) 94-109.

[166] Y. Botbol, I. Guerrero-Ros, F. Macian, Key roles of autophagy in regulating T-cell function, Eur J Immunol, 46 (2016) 1326-1334.

[167] S.D. Dowling, F. Macian, Autophagy and T cell metabolism, Cancer Lett, 419 (2018) 20-26.

[168] D. Murera, F. Arbogast, J. Arnold, D. Bouis, S. Muller, F. Gros, CD4 T cell autophagy is integral to memory maintenance, Sci Rep, 8 (2018) 5951.

[169] S.K. Vodnala, R. Eil, R.J. Kishton, M. Sukumar, T.N. Yamamoto, N.H. Ha, P.H. Lee, M. Shin, S.J. Patel, Z. Yu, D.C. Palmer, M.J. Kruhlak, X. Liu, J.W. Locasale, J. Huang, R. Roychoudhuri, T. Finkel, C.A. Klebanoff, N.P. Restifo, T cell stemness and dysfunction in tumors are triggered by a common mechanism, Science, 363 (2019).

[170] Y. Lu, Q. Wang, G. Xue, E. Bi, X. Ma, A. Wang, J. Qian, C. Dong, Q. Yi, Th9 Cells Represent a Unique Subset of CD4(+) T Cells Endowed with the Ability to Eradicate Advanced Tumors, Cancer Cell, 33 (2018) 1048-1060.e1047.

[171] T. Rivera Vargas, Z. Cai, Y. Shen, M. Dosset, I. Benoit-Lizon, T. Martin, A. Roussey, R.A. Flavell, F. Ghiringhelli, L. Apetoh, Selective degradation of PU.1 during autophagy represses the differentiation and antitumour activity of T(H)9 cells, Nat Commun, 8 (2017) 559.

[172] Y. Guo, Y. Feng, X. Cui, Q. Wang, X. Pan, Autophagy inhibition induces the repolarisation of tumour-associated macrophages and enhances chemosensitivity of laryngeal cancer cells to cisplatin in mice, Cancer Immunol Immunother, 68 (2019) 1909-1920.

[173] T. Alissafi, A. Hatzioannou, K. Mintzas, R.M. Barouni, A. Banos, S. Sormendi, A. Polyzos, M. Xilouri, B. Wielockx, H. Gogas, P. Verginis, Autophagy orchestrates the regulatory program of tumor-associated myeloid-derived suppressor cells, J Clin Invest, 128 (2018) 3840-3852.

[174] L.D. Cunha, M. Yang, R. Carter, C. Guy, L. Harris, J.C. Crawford, G. Quarato, E. Boada-Romero, H. Kalkavan, M.D.L. Johnson, S. Natarajan, M.E. Turnis, D. Finkelstein, J.T. Opferman, C. Gawad, D.R. Green, LC3-Associated Phagocytosis in Myeloid Cells Promotes Tumor Immune Tolerance, Cell, 175 (2018) 429-441.e416.

[175] I. Vitale, G. Manic, L.M. Coussens, G. Kroemer, L. Galluzzi, Macrophages and Metabolism in the Tumor Microenvironment, Cell Metab, 30 (2019) 36-50.

[176] H. Salmon, R. Remark, S. Gnjatic, M. Merad, Host tissue determinants of tumour immunity, Nat Rev Cancer, 19 (2019) 215-227.

[177] M.D. Vesely, M.H. Kershaw, R.D. Schreiber, M.J. Smyth, Natural innate and adaptive immunity to cancer, Annu Rev Immunol, 29 (2011) 235-271.

[178] D. Bruni, H.K. Angell, J. Galon, The immune contexture and Immunoscore in cancer prognosis and therapeutic efficacy, Nat Rev Cancer, 20 (2020) 662-680.

[179] L. Galluzzi, J. Humeau, A. Buque, L. Zitvogel, G. Kroemer, Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors, Nat Rev Clin Oncol, 17 (2020) 725-741.

[180] A. Brandmaier, S.C. Formenti, The Impact of Radiation Therapy on Innate and Adaptive Tumor Immunity, Semin Radiat Oncol, 30 (2020) 139-144.

[181] E. Deutsch, C. Chargari, L. Galluzzi, G. Kroemer, Optimising efficacy and reducing toxicity of anticancer radioimmunotherapy, Lancet Oncol, 20 (2019) e452-e463.

[182] G. Petroni, S.C. Formenti, S. Chen-Kiang, L. Galluzzi, Immunomodulation by anticancer cell cycle inhibitors, Nat Rev Immunol, 20 (2020) 669-679.

[183] P. Sharma, J.P. Allison, The future of immune checkpoint therapy, Science, 348 (2015) 56-61.

[184] P. Sharma, J.P. Allison, Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential, Cell, 161 (2015) 205-214.

[185] J. Tang, J.X. Yu, V.M. Hubbard-Lucey, S.T. Neftelinov, J.P. Hodge, Y. Lin, Trial watch: The clinical trial landscape for PD1/PDL1 immune checkpoint inhibitors, Nat Rev Drug Discov, 17 (2018) 854-855.

[186] T. Okazaki, S. Chikuma, Y. Iwai, S. Fagarasan, T. Honjo, A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application, Nat Immunol, 14 (2013) 1212-1218.

[187] L. Galluzzi, J.M. Bravo-San Pedro, B. Levine, D.R. Green, G. Kroemer, Pharmacological modulation of autophagy: therapeutic potential and persisting obstacles, Nat Rev Drug Discov, 16 (2017) 487-511.

[188] R. Amaravadi, A.C. Kimmelman, E. White, Recent insights into the function of autophagy in cancer, Genes Dev, 30 (2016) 1913-1930.

[189] M.D. Arensman, X.S. Yang, W. Zhong, S. Bisulco, E. Upeslacis, E.C. Rosfjord, S. Deng, R.T. Abraham, C.H. Eng, Anti-tumor immunity influences cancer cell reliance upon ATG7, Oncoimmunology, 9 (2020) 1800162.

[190] Y.P. Yang, L.F. Hu, H.F. Zheng, C.J. Mao, W.D. Hu, K.P. Xiong, F. Wang, C.F. Liu, Application and interpretation of current autophagy inhibitors and activators, Acta Pharmacol Sin, 34 (2013) 625-635.

[191] F. Cuomo, L. Altucci, G. Cobellis, Autophagy Function and Dysfunction: Potential Drugs as Anti-Cancer Therapy, Cancers (Basel), 11 (2019).

[192] G. Manic, F. Obrist, G. Kroemer, I. Vitale, L. Galluzzi, Chloroquine and hydroxychloroquine for cancer therapy, Mol Cell Oncol, 1 (2014) e29911.

[193] H. Maes, A. Kuchnio, A. Peric, S. Moens, K. Nys, K. De Bock, A. Quaegebeur, S. Schoors, M. Georgiadou, J. Wouters, S. Vinckier, H. Vankelecom, M. Garmyn, A.C. Vion, F. Radtke, C. Boulanger, H. Gerhardt, E. Dejana, M. Dewerchin, B. Ghesquière, W. Annaert, P. Agostinis, P. Carmeliet, Tumor vessel normalization by chloroquine independent of autophagy, Cancer Cell, 26 (2014) 190-206.

[194] H. Vakifahmetoglu-Norberg, H.G. Xia, J. Yuan, Pharmacologic agents targeting autophagy, J Clin Invest, 125 (2015) 5-13.

[195] F. Pietrocola, J. Pol, E. Vacchelli, S. Rao, D.P. Enot, E.E. Baracco, S. Levesque, F. Castoldi, N. Jacquelot, T. Yamazaki, L. Senovilla, G. Marino, F. Aranda, S. Durand, V. Sica, A. Chery, S. Lachkar, V. Sigl, N. Bloy, A. Buque, S. Falzoni, B. Ryffel, L. Apetoh, F. Di Virgilio, F. Madeo, M.C. Maiuri, L. Zitvogel, B. Levine, J.M. Penninger, G. Kroemer, Caloric Restriction Mimetics Enhance Anticancer Immunosurveillance, Cancer Cell, 30 (2016) 147-160.

[196] V. Le Noci, M. Sommariva, F. Bianchi, T. Triulzi, E. Tagliabue, A. Balsari, L. Sfondrini, Local Administration of Caloric Restriction Mimetics to Promote the Immune Control of Lung Metastases, J Immunol Res, 2019 (2019) 2015892.

[197] S. Lévesque, J. Le Naour, F. Pietrocola, J. Paillet, M. Kremer, F. Castoldi, E.E. Baracco, Y. Wang, E. Vacchelli, G. Stoll, A. Jolly, P. De La Grange, L. Zitvogel, G. Kroemer, J.G. Pol, A synergistic triad of chemotherapy, immune checkpoint inhibitors, and caloric restriction mimetics eradicates tumors in mice, Oncoimmunology, 8 (2019) e1657375.

[198] B.A. Simone, A. Palagani, K. Strickland, K. Ko, L. Jin, M.K. Lim, T.D. Dan, M. Sarich, D.A. Monti, M. Cristofanilli, N.L. Simone, Caloric restriction counteracts chemotherapy-induced inflammation and increases response to therapy in a triple negative breast cancer model, Cell Cycle, 17 (2018) 1536-1544.

[199] A.D. Saleh, B.A. Simone, J. Palazzo, J.E. Savage, Y. Sano, T. Dan, L. Jin, C.E. Champ, S. Zhao, M. Lim, F. Sotgia, K. Camphausen, R.G. Pestell, J.B. Mitchell, M.P. Lisanti, N.L. Simone, Caloric restriction augments radiation efficacy in breast cancer, Cell Cycle, 12 (2013) 1955-1963.

[200] B.A. Simone, T. Dan, A. Palagani, L. Jin, S.Y. Han, C. Wright, J.E. Savage, R. Gitman, M.K. Lim, J. Palazzo, M.P. Mehta, N.L. Simone, Caloric restriction coupled with radiation decreases metastatic burden in triple negative breast cancer, Cell Cycle, 15 (2016) 2265-2274.

[201] S. Eikawa, M. Nishida, S. Mizukami, C. Yamazaki, E. Nakayama, H. Udono, Immune-mediated antitumor effect by type 2 diabetes drug, metformin, Proc Natl Acad Sci U S A, 112 (2015) 1809-1814.

[202] Y. Liu, L. Wang, J. Predina, R. Han, U.H. Beier, L.C. Wang, V. Kapoor, T.R. Bhatti, T. Akimova, S. Singhal, P.K. Brindle, P.A. Cole, S.M. Albelda, W.W. Hancock, Inhibition of p300 impairs Foxp3(+) T regulatory cell function and promotes antitumor immunity, Nat Med, 19 (2013) 1173-1177.

[203] C. Lee, L. Raffaghello, S. Brandhorst, F.M. Safdie, G. Bianchi, A. Martin-Montalvo, V. Pistoia, M. Wei, S. Hwang, A. Merlino, L. Emionite, R. de Cabo, V.D. Longo, Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy, Sci Transl Med, 4 (2012) 124ra127.

[204] S. Di Biase, C. Lee, S. Brandhorst, B. Manes, R. Buono, C.W. Cheng, M. Cacciottolo, A. Martin-Montalvo, R. de Cabo, M. Wei, T.E. Morgan, V.D. Longo, Fasting-Mimicking Diet Reduces HO-1 to Promote T Cell-Mediated Tumor Cytotoxicity, Cancer Cell, 30 (2016) 136-146.

[205] O. Lo Re, C. Panebianco, S. Porto, C. Cervi, F. Rappa, S. Di Biase, M. Caraglia, V. Pazienza, M. Vinciguerra, Fasting inhibits hepatic stellate cells activation and potentiates anti-cancer activity of Sorafenib in hepatocellular cancer cells, J Cell Physiol, 233 (2018) 1202-1212.

[206] M. Di Tano, F. Raucci, C. Vernieri, I. Caffa, R. Buono, M. Fanti, S. Brandhorst, G. Curigliano, A. Nencioni, F. de Braud, V.D. Longo, Synergistic effect of fasting-mimicking diet and vitamin C against KRAS mutated cancers, Nat Commun, 11 (2020) 2332.

[207] I. Caffa, V. Spagnolo, C. Vernieri, F. Valdemarin, P. Becherini, M. Wei, S. Brandhorst, C. Zucal, E. Driehuis, L. Ferrando, F. Piacente, A. Tagliafico, M. Cilli, L. Mastracci, V.G. Vellone, S. Piazza, A.L. Cremonini, R. Gradaschi, C. Mantero, M. Passalacqua, A. Ballestrero, G. Zoppoli, M. Cea, A. Arrighi, P. Odetti, F. Monacelli, G. Salvadori, S. Cortellino, H. Clevers, F. De Braud, S.G. Sukkar, A. Provenzani, V.D. Longo, A. Nencioni, Fasting-mimicking diet and hormone therapy induce breast cancer regression, Nature, 583 (2020) 620-624.

[208] Z.L. Li, H.L. Zhang, Y. Huang, J.H. Huang, P. Sun, N.N. Zhou, Y.H. Chen, J. Mai, Y. Wang, Y. Yu, L.H. Zhou, X. Li, D. Yang, X.D. Peng, G.K. Feng, J. Tang, X.F. Zhu, R. Deng, Autophagy deficiency promotes triple-negative breast cancer resistance to T cell-mediated cytotoxicity by blocking tenascin-C degradation, Nat Commun, 11 (2020) 3806.

[209] A. Ko, A. Kanehisa, I. Martins, L. Senovilla, C. Chargari, D. Dugue, G. Mariño, O. Kepp, M. Michaud, J.L. Perfettini, G. Kroemer, E. Deutsch, Autophagy inhibition radiosensitizes in vitro, yet

reduces radioresponses in vivo due to deficient immunogenic signalling, Cell Death Differ, 21 (2014) 92-99.

[210] X. Liang, M.E. De Vera, W.J. Buchser, A. Romo de Vivar Chavez, P. Loughran, D. Beer Stolz, P. Basse, T. Wang, B. Van Houten, H.J. Zeh, 3rd, M.T. Lotze, Inhibiting systemic autophagy during interleukin 2 immunotherapy promotes long-term tumor regression, Cancer Res, 72 (2012) 2791-2801.

[211] J.Y. Lee, E. Lee, S.W. Hong, D. Kim, O. Eunju, J. Sprent, S.H. Im, Y.J. Lee, C.D. Surh, TCB2, a new anti-human interleukin-2 antibody, facilitates heterodimeric IL-2 receptor signaling and improves anti-tumor immunity, Oncoimmunology, 9 (2020) 1681869.

[212] M.Z. Noman, B. Janji, B. Kaminska, K. Van Moer, S. Pierson, P. Przanowski, S. Buart, G. Berchem, P. Romero, F. Mami-Chouaib, S. Chouaib, Blocking hypoxia-induced autophagy in tumors restores cytotoxic T-cell activity and promotes regression, Cancer Res, 71 (2011) 5976-5986.

[213] J. Sprooten, J. Ceusters, A. Coosemans, P. Agostinis, S. De Vleeschouwer, L. Zitvogel, G. Kroemer, L. Galluzzi, A.D. Garg, Trial watch: dendritic cell vaccination for cancer immunotherapy, Oncoimmunology, 8 (2019) e1638212.

[214] M.E. Rodriguez-Ruiz, A. Buqué, M. Hensler, J. Chen, N. Bloy, G. Petroni, A. Sato, T. Yamazaki, J. Fucikova, L. Galluzzi, Apoptotic caspases inhibit abscopal responses to radiation and identify a new prognostic biomarker for breast cancer patients, Oncoimmunology, 8 (2019) e1655964.

[215] A. Ablasser, Z.J. Chen, cGAS in action: Expanding roles in immunity and inflammation, Science, 363 (2019).

[216] T. Abe, S.D. Shapira, Negative Regulation of Cytosolic Sensing of DNA, Int Rev Cell Mol Biol, 344 (2019) 91-115.

[217] C. Vanpouille-Box, J.A. Hoffmann, L. Galluzzi, Pharmacological modulation of nucleic acid sensors - therapeutic potential and persisting obstacles, Nat Rev Drug Discov, 18 (2019) 845-867.

[218] M.Z. Noman, S. Parpal, K. Van Moer, M. Xiao, Y. Yu, J. Viklund, A. De Milito, M. Hasmim, M. Andersson, R.K. Amaravadi, J. Martinsson, G. Berchem, B. Janji, Inhibition of Vps34 reprograms cold into hot inflamed tumors and improves anti-PD-1/PD-L1 immunotherapy, Sci Adv, 6 (2020) eaax7881.

[219] B. Janji, M. Hasmim, S. Parpal, G. Berchem, M.Z. Noman, Firing up the cold tumors by targeting Vps34, Oncoimmunology, 9 (2020) 1809936.

[220] J. Baginska, E. Viry, G. Berchem, A. Poli, M.Z. Noman, K. van Moer, S. Medves, J. Zimmer, A. Oudin, S.P. Niclou, R.C. Bleackley, I.S. Goping, S. Chouaib, B. Janji, Granzyme B degradation by autophagy decreases tumor cell susceptibility to natural killer-mediated lysis under hypoxia, Proc Natl Acad Sci U S A, 110 (2013) 17450-17455.

[221] J. Spetz, A.G. Presser, K.A. Sarosiek, T Cells and Regulated Cell Death: Kill or Be Killed, Int Rev Cell Mol Biol, 342 (2019) 27-71.

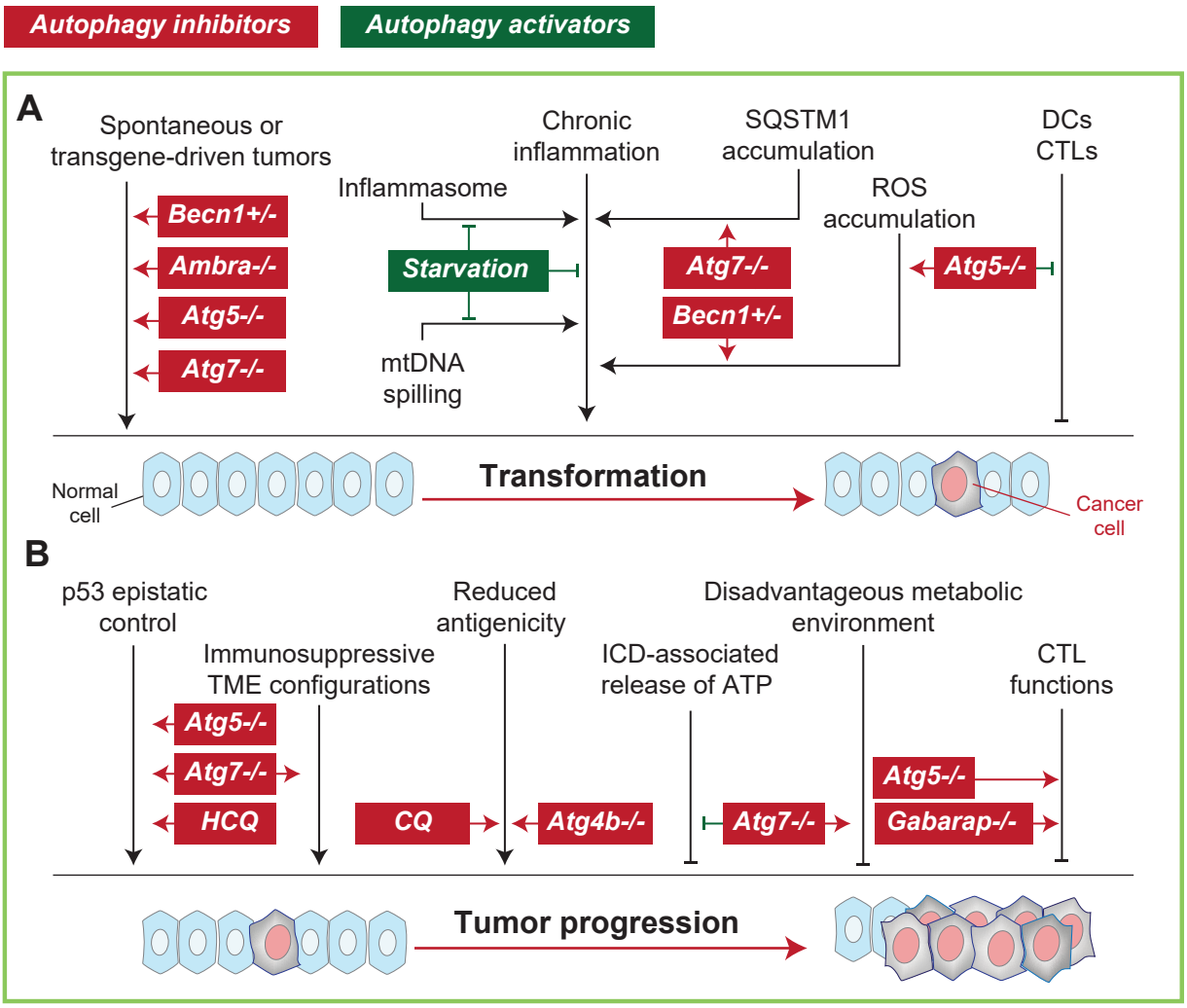
[222] A. Tittarelli, B. Janji, K. Van Moer, M.Z. Noman, S. Chouaib, The Selective Degradation of Synaptic Connexin 43 Protein by Hypoxia-induced Autophagy Impairs Natural Killer Cell-mediated Tumor Cell Killing, J Biol Chem, 290 (2015) 23670-23679.

[223] S. Khan, Y. He, X. Zhang, Y. Yuan, S. Pu, Q. Kong, G. Zheng, D. Zhou, PROteolysis TArgeting Chimeras (PROTACs) as emerging anticancer therapeutics, Oncogene, 39 (2020) 4909-4924.

[224] J. Liu, J. Ma, Y. Liu, J. Xia, Y. Li, Z.P. Wang, W. Wei, PROTACs: A novel strategy for cancer therapy, Semin Cancer Biol, (2020).

[225] X. Huang, V.M. Dixit, Drugging the undruggables: exploring the ubiquitin system for drug development, Cell Res, 26 (2016) 484-498.

[226] S. An, L. Fu, Small-molecule PROTACs: An emerging and promising approach for the development of targeted therapy drugs, EBioMedicine, 36 (2018) 553-562.


Autophagy inhibitors
Autophagy activators
A
Spontaneous or transgene-driven tumors
Chronic inflammation
SQSTM1 accumulation
DCs CTLs
Inflammasome
ROS accumulation
Becn1+/-
Ambra-/-
Atg5-/-
Atg7-/-
Starvation
mtDNA spilling
Atg7-/-
Becn1+/-
Atg5-/-
Normal cell
Transformation
Cancer cell
B
p53 epistatic control
Reduced antigenicity
Disadvantageous metabolic environment
Immunosuppressive TME configurations
ICD-associated release of ATP
CTL functions
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HCQ
CQ
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Atg7-/-
Atg5-/-
Gabarap-/-
Tumor progression

Figure 1

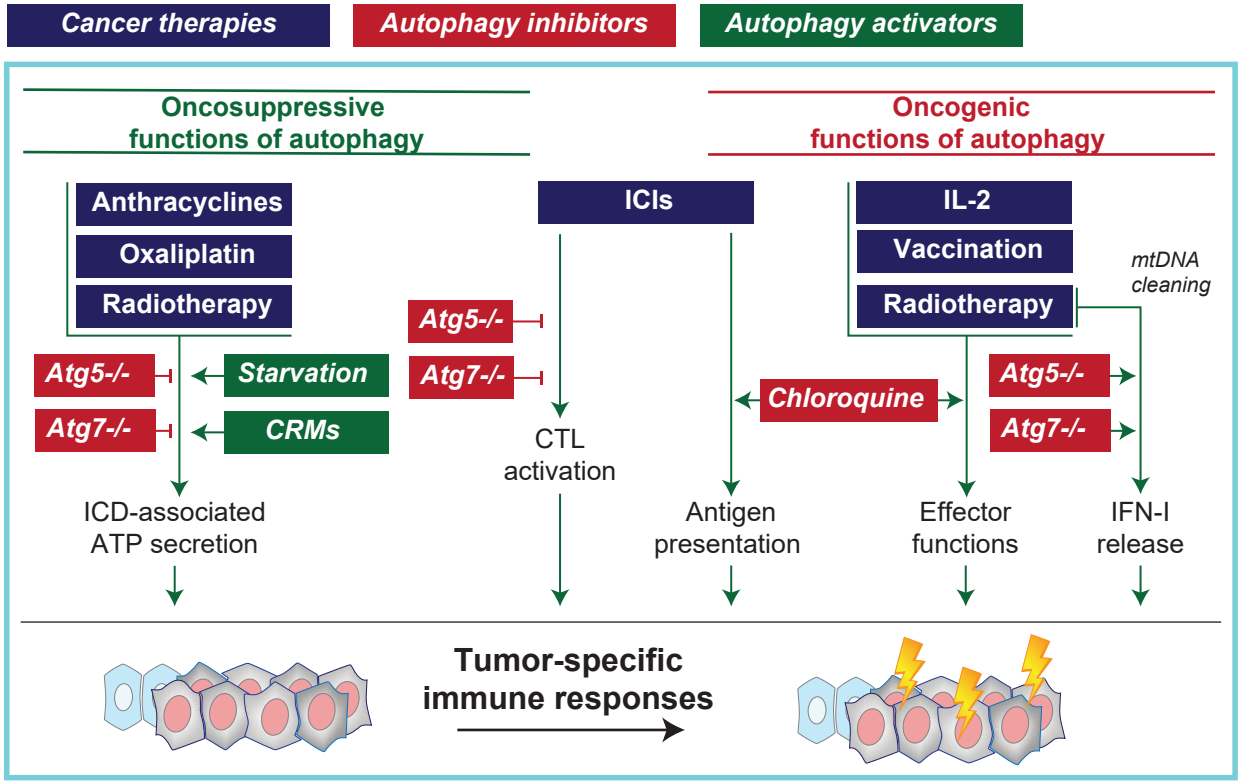

Cancer therapies
Autophagy inhibitors
Autophagy activators
Oncosuppressive functions of autophagy
Oncogenic functions of autophagy
Anthracyclines
Oxaliplatin
Radiotherapy
ICIs
IL-2
Vaccination
Radiotherapy
mtDNA cleaning
Atg5-/-
Atg7-/-
Starvation
CRMs
Atg5-/-
Atg7-/-
Chloroquine
Atg5-/-
Atg7-/-
CTL activation
ICD-associated ATP secretion
Antigen presentation
Effector functions
IFN-I release
Tumor-specific immune responses

Figure 2

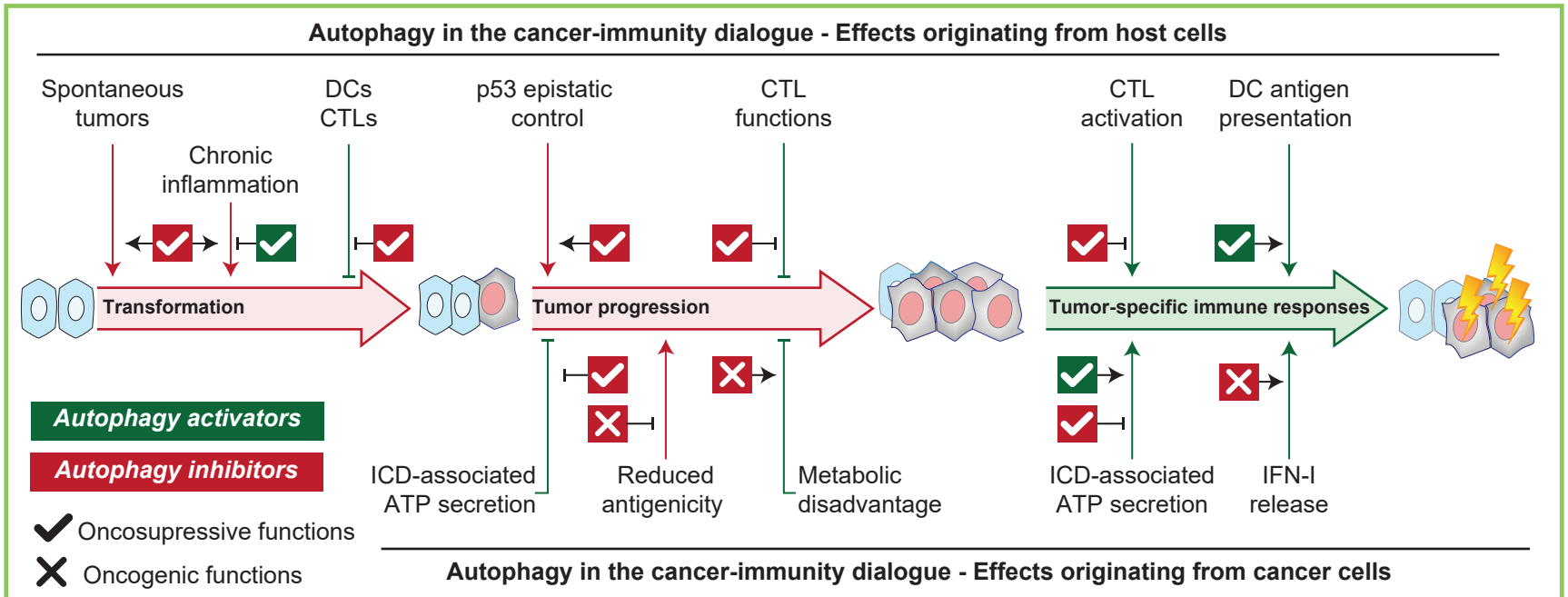
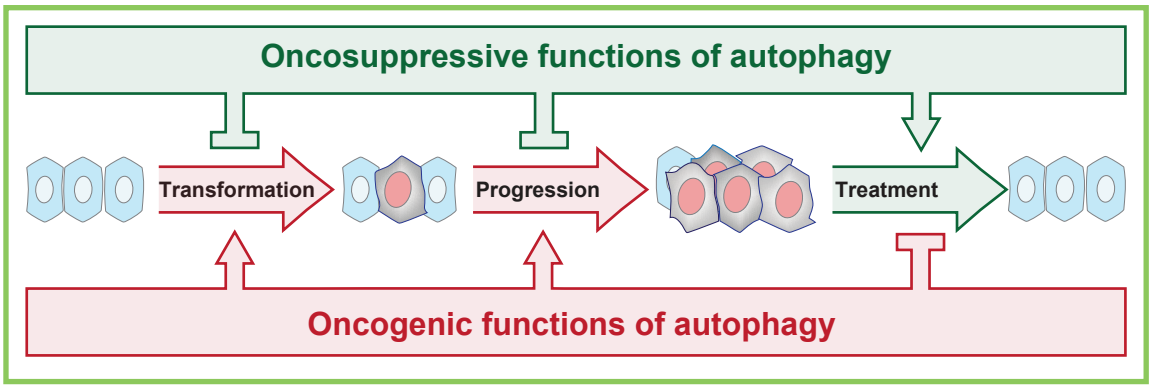

Autophagy in the cancer-immunity dialogue - Effects originating from host cells
Spontaneous tumors
Chronic inflammation
DCs
CTLs
p53 epistatic control
CTL functions
CTL activation
DC antigen presentation
Transformation
Tumor progression
Tumor-specific immune responses
Autophagy activators
Autophagy inhibitors
ICD-associated ATP secretion
Reduced antigenicity
Metabolic disadvantage
ICD-associated ATP secretion
IFN-I release
Oncosupressive functions
Oncogenic functions
Autophagy in the cancer-immunity dialogue - Effects originating from cancer cells

Figure 3


Oncosuppressive functions of autophagy
Transformation
Progression
Treatment
Oncogenic functions of autophagy