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# 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<sub>REG</sub> cells.

## **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<sup>+</sup> cytotoxic T lymphocytes (CTLs) and CD4<sup>+</sup> helper T cells [68-72]; and (4) the development, survival and effector functions of various immune cells including CD8<sup>+</sup> 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*<sup>+/-</sup> 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*<sup>+/-</sup> 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*<sup>+/-</sup> 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-1 $\beta$  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<sup>+</sup> 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<sup>+</sup> 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<sup>+</sup> 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<sup>+</sup> DCs or CD8<sup>+</sup> 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<sup>+</sup>CD25<sup>+</sup>FOXP3<sup>+</sup> regulatory T (T<sub>REG</sub>) 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<sup>G12D</sup> are prone to transition to lung carcinomas upon deletion of *Atg5* from the lung epithelium, which is accompanied by accrued recruitment of T<sub>REG</sub> 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<sup>+/-</sup>* 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<sup>G12D</sup>- or BRAF<sup>V600E</sup>- driven lung cancer [98, 99], KRAS<sup>G12D</sup>-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<sup>V600E</sup> 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<sup>G12D</sup>-driven lung cancers (which culminates in the aberrant accumulation of mitochondria and development of benign oncocytoomas) 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<sup>G12D</sup> 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<sup>+</sup> and CD8<sup>+</sup> 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<sub>REG</sub> cells (resulting in limited immunosuppression and superior anticancer immunity by CTLs) [138] as well as CD4<sup>+</sup> cells in general (resulting in the acquisition of a robust T<sub>H</sub>9 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<sup>+</sup> 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<sub>REG</sub> 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<sup>+</sup> 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 discussed 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.

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## 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<sup>+</sup> 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.

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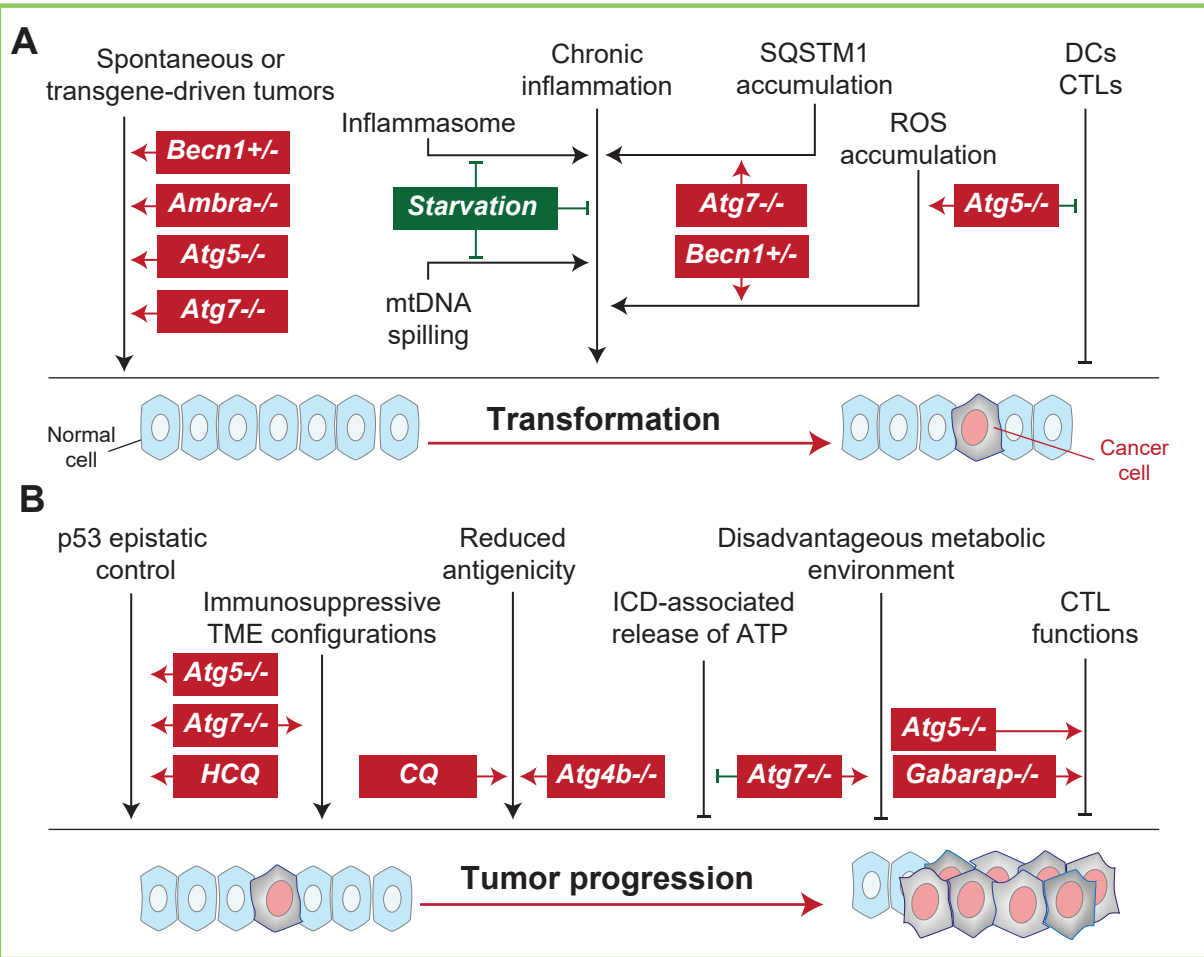


Figure 1



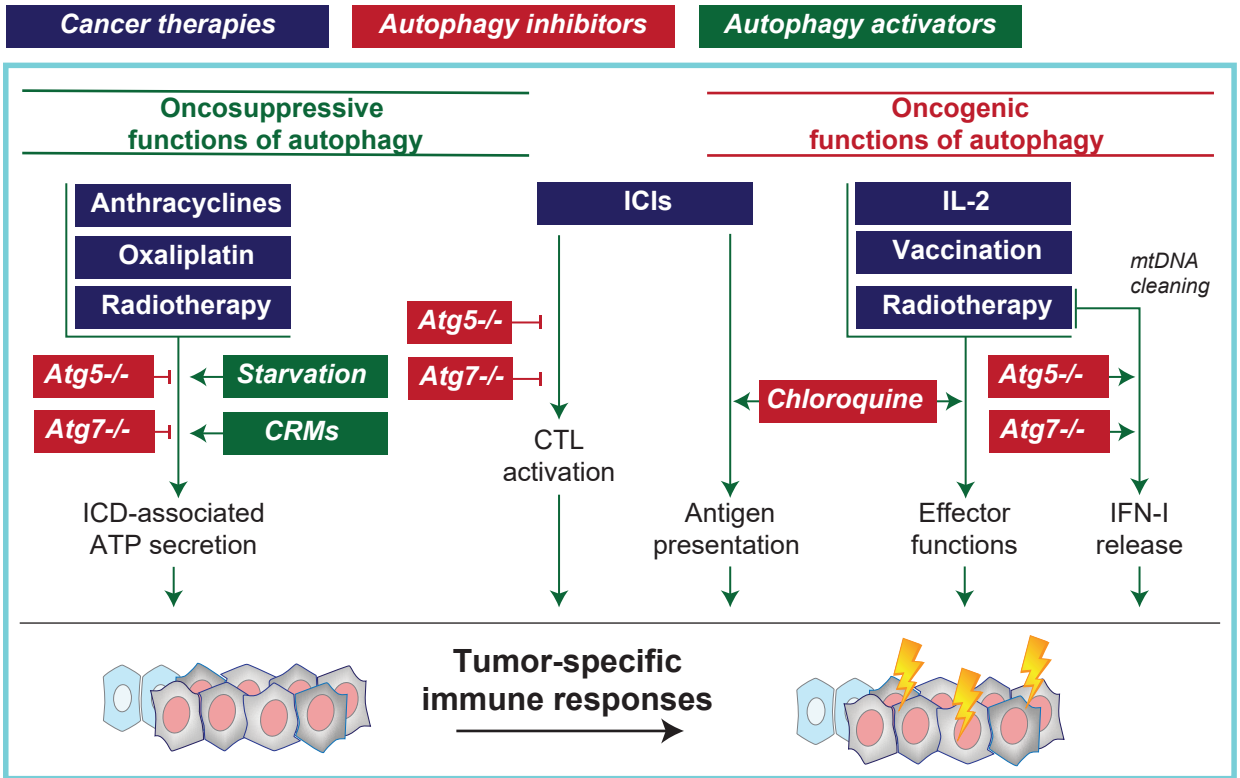


Figure 2

## Autophagy in the cancer-immunity dialogue - Effects originating from host cells

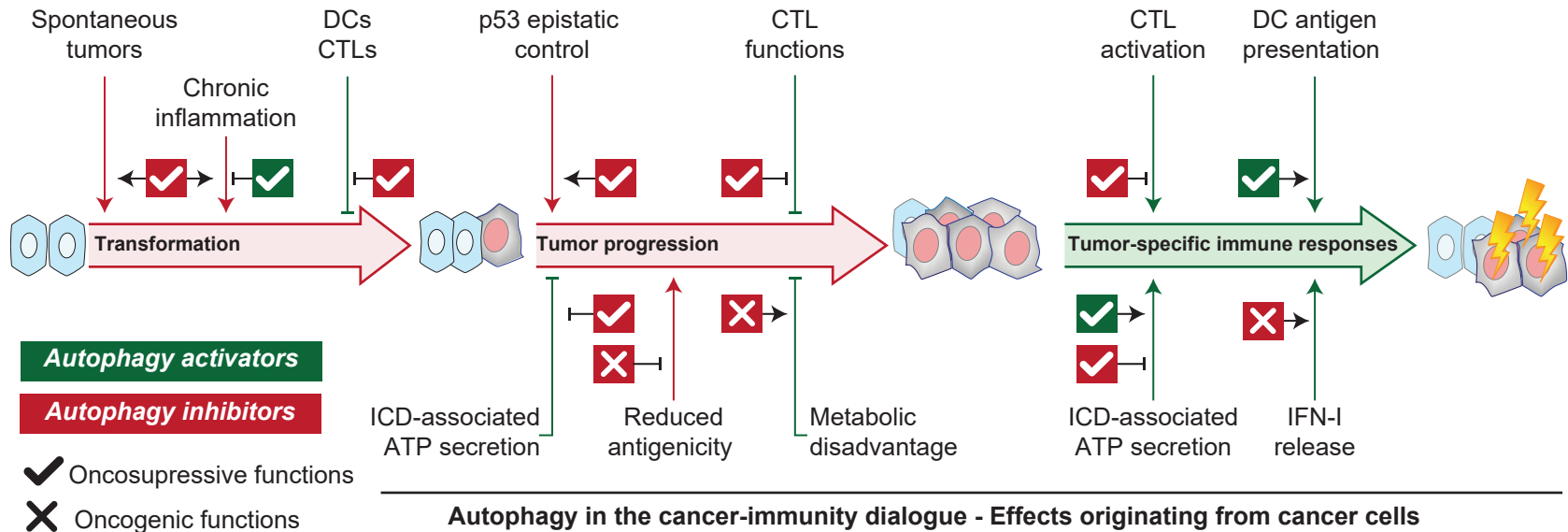


Figure 3

