Beyond self-eating: Emerging autophagy-independent functions for the autophagy molecules in cancer (Review)

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Abstract. Autophagy is a conserved catabolic process that controls organelle quality, removes misfolded or abnormally aggregated proteins and is part of the defense mechanisms against intracellular pathogens. Autophagy contributes to the suppression of tumor initiation by promoting genome stability, cellular integrity, redox balance and proteostasis. On the other hand, once a tumor is established, autophagy can support cancer cell survival and promote epithelial-to-mesenchymal transition. A growing number of molecules involved in autophagy have been identified. In addition to their key canonical activity, several of these molecules, such as ATG5, ATG12 and Beclin-1, also exert autophagy-independent functions in a variety of biological processes. The present review aimed to summarize autophagy-independent functions of molecules of the autophagy machinery and how the activity of these molecules can influence signaling pathways that are deregulated in cancer progression.

Contents

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Abbreviations: AMM, autophagy machinery molecule; PI3P, phosphatidylinositol-3-phosphate; NER, nucleotide excision repair; NHEJ, non-homologous end joining; MEF, mouse embryonic fibroblast; EMT, epithelial-to-mesenchymal transition; SA, secretory autophagy; LAP, LC-3-associated phagocytosis; ROS, reactive oxygen species

Key words: cancer, autophagy, autophagy-independent, cancer progression, proliferation, cell death, survival, metastasis, genome instability

1. Introduction

Macroautophagy, hereafter referred to as autophagy, is a catabolic process where cytoplasmic materials are sequestered by double-membrane-bound vesicles, called autophagosomes, to be degraded via fusion with lysosomes. Autophagy, from the Greek *autóphagos*, meaning 'self-eating', is a process that is highly conserved from yeast to humans and is necessary for maintenance of cellular homeostasis under nutrient deprivation and other stress conditions (1). It is also involved in physiological processes such as defense against intracellular pathogens, organelle quality control and removal of misfolded or aggregated proteins (2).

Numerous studies demonstrate that autophagy acts as a double-edged sword in cancer. Namely, it can inhibit tumor initiation by removing damaged proteins and organelles and preventing genome instability (3-6). Tissue-specific deletion of key autophagic molecules (such as autophagy related genes ATG7 and ATG5) restricts cancer development in several mouse models of inducible cancer such as melanoma and pancreatic cancer (7-12). On the other hand, when a tumor has already developed, autophagy can support cancer cell survival under stressful conditions such as hypoxia and metabolic stress, promoting the persistence of tumor cells in hostile environment (13-16). Autophagy affects anchorage to the extracellular matrix, cytoskeletal remodeling and epithelial-to-mesenchymal transition (EMT), further supporting its involvement in cancer progression (17).

The autophagy machinery consists of a number of molecules, involved in the different steps of autophagy: Initiation, nucleation, elongation, autophagosome-lysosome fusion and degradation of substrates (18). A group of ~20 molecules, called autophagy-related genes, was initially discovered through genetic studies in yeast and found to be necessary for the control of several key phases of the autophagy

process (19,20). The group of autophagic molecules has been studied in humans and gradually expanded to include other proteins; The Autophagy Project of the BioGRID repository contains information on ~200 human proteins involved in autophagy (thebiogrid.org/project/6/autophagy.html; accessed on October 2023) (21) (Table SI).

Numerous autophagy machinery molecules (AMMs) have been reported to extend their functions beyond autophagy. Non-canonical autophagy-related processes have been described (22-25). For example, molecules involved in autophagic vesicle elongation are also involved in a form of exocytosis termed secretory autophagy (22). In addition, there is increasing evidence that individual AMMs exert autophagy-independent functions in various types of diseases, including cancer (23-25). The present review aimed to discuss the autophagy-independent functions of AMMs with a particular focus on cancer progression.

2. Autophagic cascade

The steps involving AMMs in the typical autophagic cascade have been explored (26). The present review briefly outlines the autophagic role of those AMMs that have also been reported to have autophagy-independent functions.

Nutrient shortage and stress conditions are the main triggers for the autophagy process (Fig. 1). One of the key sensors of energy, nutrient and redox status is the mTORC1 protein complex, which consists of the Ser/Thr kinase mTOR and other regulatory components (27). Under nutrient-limited conditions, the amount of ATP decreases and increased AMP/ATP ratio triggers the activation of AMPK, which in turn restrains mTORC1 and its inhibitory activity towards Unc-51-like autophagy-activating kinase 1 (ULK1). ULK1 can form a complex with autophagy related proteins ATG101, ATG13 and RB1CC1 (family kinase-interacting protein 200/RB1 Inducible Coiled-Coil 1), which initiates the autophagy cascade (28) by phosphorylating components of PI3K complex I (PIK3C3, Beclin-1, ATG14 and PIK3R4) (29). This complex is essential for the nucleation phase of autophagy. Activated PI3K complex I phosphorylates phosphatidylinositol (PI) to form PI-3-phosphate (PI3P) (29), which binds to the nascent phagophore membrane (30). PI3K complex I is positively regulated by the ultraviolet radiation resistance-associated gene (UVRAG) (31) and autophagy and Beclin-1 regulator 1 (AMBRA1) (32). The process is supported by ATG9, a lipid scramblase that is incorporated into vesicles involved in the nucleation of phagophores and subsequently assists the elongation process (33,34). Two ubiquitin-like conjugation systems are then activated: The phagophore elongation complexes ATG5-ATG12-ATG16L1 and the LC3 system. The ATG5-ATG12-ATG16L1 complex is formed by a reaction cascade involving ATG7 (E1-like enzyme) and ATG10 (E2-like enzyme), which mediate covalent binding between ATG5 and ATG12. Subsequently, the ATG5-ATG12 conjugate binds ATG16L1 and forms a ternary complex located at the autophagosomal membrane (35). Studies propose an alternative model for the formation of the ATG5-ATG12-ATG16L1 complex, which first requires an interaction between ATG5 and ATG16L1. Then, the transient ATG5-ATG16L1 duplet allows recruitment of ATG12 and the formation of a stable trimeric structure via formation of a covalent bond between ATG12 and ATG5 (36-38). The ATG5-ATG12-ATG16L1 complex serves as a scaffold and promotes LC3 lipidation (35). Microtubule-associated protein 1-light chain 3 (MAP1LC3) is the ortholog of Atg8 in yeast. LC3 is first cleaved at its carboxy terminus by ATG4 to form LC3 I. Following ATG4-mediated cleavage, LC3 is activated by ATG7 (E1-like enzyme) and ATG3 (E2-like enzyme) and finally conjugated to phosphatidylethanolamine (PE) to form the active LC3 (LC3-II) (39). Lipidated LC3, together with the ATG5-ATG12-ATG16L1 complex, enables elongation of the autophagic phagophore membrane (40).

The nascent phagophore sequesters specific cargo material via simultaneous interaction between LC3-II molecules and cargo receptors such as sequestrosome-1 (SQSTM1 or p62), toll-interacting Protein), and neighbor Of BRCA1 Gene 1) (41). SQSTM1 oligomerizes via its PB1 domain and forms filaments that interact with polyubiquitinated cargoes and LC3-II via LC3-interacting regions. These interactions enable autophagy-mediated degradation of specific cargo material (42).

In the late stages of the autophagic process, the phagophore closes and fuses with the lysosome to form the autophagolysosome. This phase relies on soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins, which are found in both membranes (43). The activity of the two known SNARE complexes (TX17-SNAP29-VAMP7/VAMP812 and STX7-SNAP29-YKT6 complexes) is facilitated by the tethering factors such as the homotypic fusion and protein sorting) complex, pleckstrin Homology And RUN Domain Containing M1) and EPG5 (Ectopic P-Granules 5 Autophagy Tethering Factor), which promote close interaction between the membranes. In the autophagolysosome, acidic hydrolases degrade sequestered material and generate metabolites that are released into the cytoplasm (44). The nutrients obtained via the autophagy pathway stimulate mTOR activation. A negative feedback mechanism stops autophagy when availability of nutrients is restored (44).

3. Autophagy-independent role of AMMs and cancer

During tumor transformation and progression, several biological functions are altered (45). Cancer cells acquire genome instability, which gives them selective advantages. The aggressiveness of the transformed clones is characterized by sustained proliferation and death resistance. Cancer cells have invasive behavior determined by the activation of molecular invasion programs and the ability to control the tumor microenvironment by sending signals to surrounding cells, including immune cells (45). Increasing evidence suggests that AMMs may serve functions that are not exclusive to lysosomal degradation of autophagy substrates (22-24). AMMs are involved in the processes of cancer initiation and progression (Table I).

4. Non-autophagic functions of AMMs in genome stability and cell proliferation

Normal cells control DNA integrity to ensure genome stability. Following DNA damage, cell cycle progression is delayed or blocked by a number of cell cycle control mechanisms to allow repair of DNA damage and prevent abnormal cell division (45).

Impaired autophagy has been recognized as a trigger for chromosome instability (46). In addition, numerous AMMs

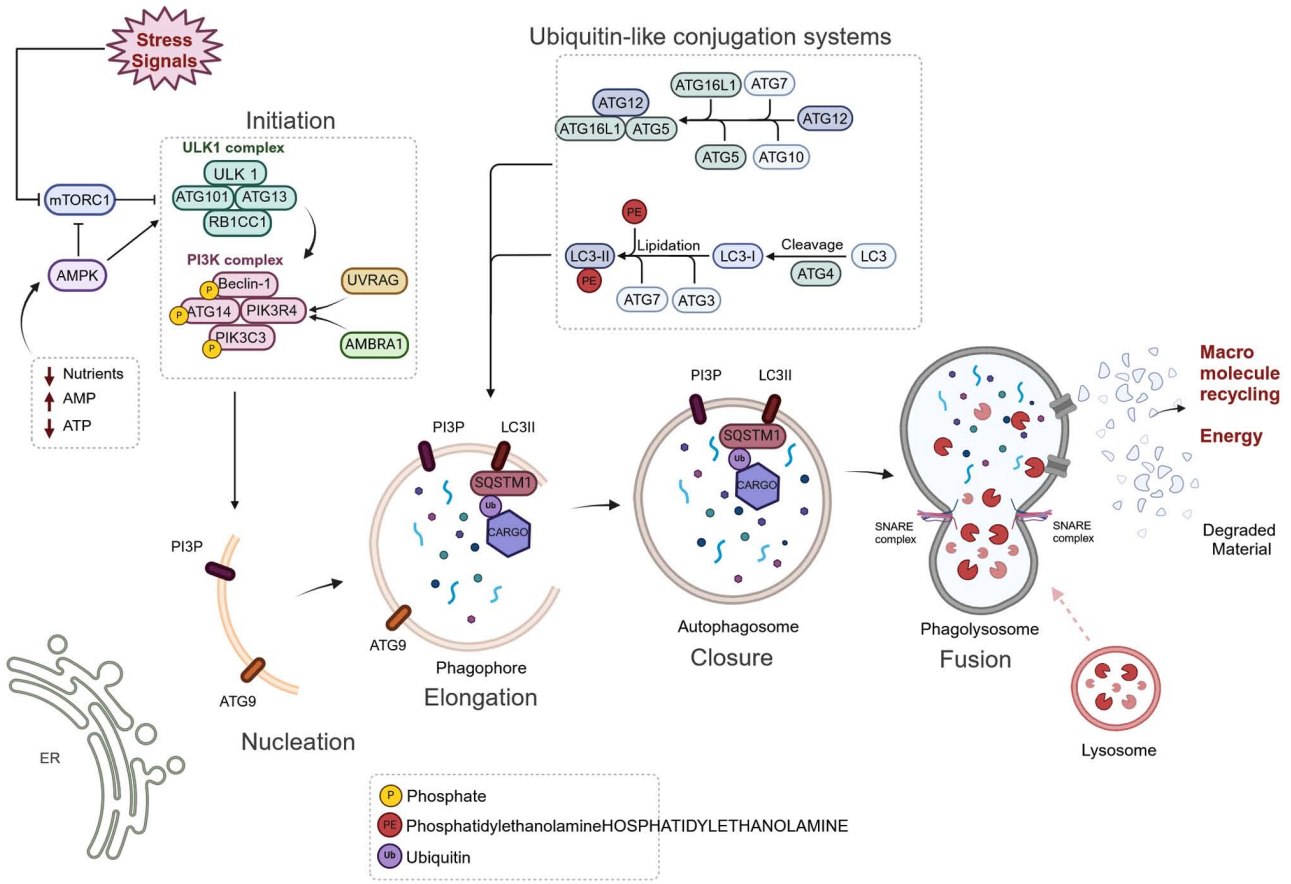

Figure 1. Autophagic machinery. An overview of the autophagic process showing the signaling pathways that regulate autophagy and molecular circuitry involved in the key steps of phagolysosome formation: Nucleation, elongation, closure and fusion. Created with BioRender.com. ULK1, Unc-51-like autophagy-activating kinase 1; ATG, autophagy related genes; RB1CC1, RB1 Inducible Coiled-Coil 1; UVRAG, ultraviolet radiation resistance-associated gene; AMBRA1, autophagy and Beclin-1 regulator 1; ER, endoplasmic reticulum; PI3P, phosphatidylinositol-3-phosphate; SQSTM1, sequestrosome-1.

have been shown to play a role in genomic stability independent of autophagy (Fig. 2). Some of these proteins were originally identified because of their function in maintaining genome stability rather than their link to autophagy. For example, UVRAG was originally discovered because of its involvement in nucleotide excision repair (NER) (47). UVRAG interacts with the UV sensor damage Specific DNA Binding Protein 1) and mediates the assembly of the NER complex at damaged DNA foci. Accordingly, UVRAG expression is associated with a lower UV mutation rate in cutaneous melanoma, where UV radiation is the main factor for tumorigenesis and progression (48). UVRAG also promotes repair of DNA double-strand breaks by interacting with the DNA-dependent protein kinase complex DNA-PKcs in the non-homologous end joining (NHEJ) DNA repair system (49). In colon cancer model, DNA double-strand breaks repair requires interaction between UVRAG and Beclin-1 to regulate DNA damage response and centrosome stability (50). UVRAG physically associates with the centrosome component centrosomal protein 63) to control proper chromosome segregation and prevent aneuploidy (49). Truncating UVRAG mutations were detected in a significant proportion of colon carcinoma cases with a defective DNA mismatch repair system (51). The truncated UVRAG protein loses the ability to repair DNA and exhibits autophagy-independent oncogenic properties, although conflicting data on autophagy activation have been reported (51,52).

Following treatment with 5-fluorouracil (5-FU), ATG5 translocates to the nucleus independently of its autophagic function and interacts with Mis18α (MIS18 kinetochore Protein A), a protein localized in the centromere and involved in methylation of the underlying chromatin. This binding increases the levels of promoter methylation of MLH1 (MutL Homolog 1) gene (a component of DNA mismatch repair), thereby downregulating MLH1 expression and enhancing mismatch repair defects and resistance to 5-FU (53). Similarly, following DNA-damaging treatment, ATG5 interacts with survivin in the nucleus, disrupting chromosome segregation and triggering an abnormal mitotic process known as mitotic catastrophe (54). This suggests control of cell cycle progression by ATG5 independent of autophagy.

AMBRA1 is another AMM that controls cell cycle progression by mediating degradation of cyclin D, which regulates the G1/S phase transition. A defective AMBRA1/cyclin D axis leads to premature entry into S phase, resulting in replication stress and genome instability (55). In addition, ATG4B down-regulation in colorectal cancer has been shown to decrease expression and activity of cyclin D1 (56). The aforementioned study demonstrated an inhibition of mTOR and induction of autophagy in ATG4B-silenced cells; however it is unclear how this fits with the hypothesis that ATG4B can prime LC3B for lipidation and autophagy induction (56). ATG7 promotes CDKN1A (p21) expression and cell cycle arrest by directly

Table I. Autophagy-independent functions of the autophagy machinery.

AMM	Autophagic function	Cancer-associated function	(Refs.)
AMBRA1	PI3K complex I positive regulation	MYC and cyclin D regulation involved in G1/S transition	(55)
		Induction of apoptosis via BH3-like domain	(66)
ATG3	LC3 activation	Control of mitochondrial fission and fusion and apoptotic cell death	(71)
ATG4B	LC3 priming for lipidation	mTOR phosphorylation and promotion of G1/S phase transition	(56)
		Mitochondrial respiration (mitochondrial function impairment and Warburg effect)	(73)
ATG4D	LC3 activation/inactivation	Induction of apoptosis via BH3-like domain	(67)
ATG5	Phagophore elongation	Interaction with ATP6V1E1 causing exosome production	(24,92)
		Clathrin membrane regulation with endocytic trafficking	(37)
		Interacts with Mis18α inducing microsatellite instability	(53)
		Interaction with AuroraB and induction of mitotic catastrophe	(54)
		Cleaved N-terminal portion inducer of apoptosis	(68)
		ERK activation	(83)
ATG7	ATG12 activation for conjugation with ATG5	Binding with p53 and DNA damage-driven cell cycle arrest	(57)
ATG9B	Autophagosomal membrane expansion	Stabilization of MYH9 and boost of focal adhesion formation	(89)
ATG12	Phagophore elongation	Clathrin membrane regulation with endocytic trafficking	(37)
		Controls mitochondrial fission and fusion and apoptotic cell death	(38,69,71)
		Block of oncosis	(72)
		ERK activation	(83)
ATG16L1	Phagophore elongation	Interacts with Rab33A for vesicular release	(91)
Beclin-1	Autophagic nucleation (PI3K complex I component)	Controls STAT3 downstream signaling	(25)
		Controls NHEJ and regulation of centrosome stability	(50)
		Kinetocore stability by interaction with KMN complex for mitotic progression	(58)
		Nuclear localization for cytokinesis completion	(59)
		Cleaved C-terminal portion inducer of apoptosis	(61,64,65)
		Growth factor receptor endosomal signaling	(84)
		Controls E-cadherin and α-catenin membrane localization	(85)
		Regulation of tight junction permeability via endocytosis of occludin	(86)
LC3B/LC3	Phagophore elongation	Interacts with ATP6V1E1 causing exosome production	(24,92)
		Apoptosis and anoikis induction	(76)
		ERK activation	(83)
		Regulates Rho signaling and actin stress fiber formation	(88)
		LC3-associated phagocytosis	(97)
ULK1	Autophagy initiation complex	TNF-induced cell death, PARP regulation and necrosis	(74,75)
UVRAG	PI3K complex I positive regulation	Chromosome stability and DNA repair	(48-50,52)

AMM, autophagy machinery molecule; AMBRA1, autophagy and Beclin-1 regulator 1; ATG, autophagy related genes; ULK1, Unc-51-like autophagy-activating kinase 1; UVRAG, ultraviolet radiation resistance-associated gene; ATP6V1E1, ATPase H+ Transporting V1 Subunit E1; NHEJ, Non-Homologous End Joining; KMN, KNL-1/Mis12/Ndc80; Rab33A, Member RAS Oncogene Family 33A; MYH9, myosin heavy chain 9; Mis18α, MIS18 Kinetochore Protein A.

binding to p53, a master keeper of cell cycle, apoptosis and CDKN1A (p21) expression. The effect of ATG7 on this process is enhanced by nutrient starvation, which is known to stimulate autophagy (57). Nevertheless, the E1-like enzymatic activity of ATG7, which is central to its autophagic involvement, is not required for this cell cycle arrest (57).

The component of the PI3K complex Beclin-1 is crucial for mitotic progression as it interacts with the KNL-1/Mis12/Ndc80

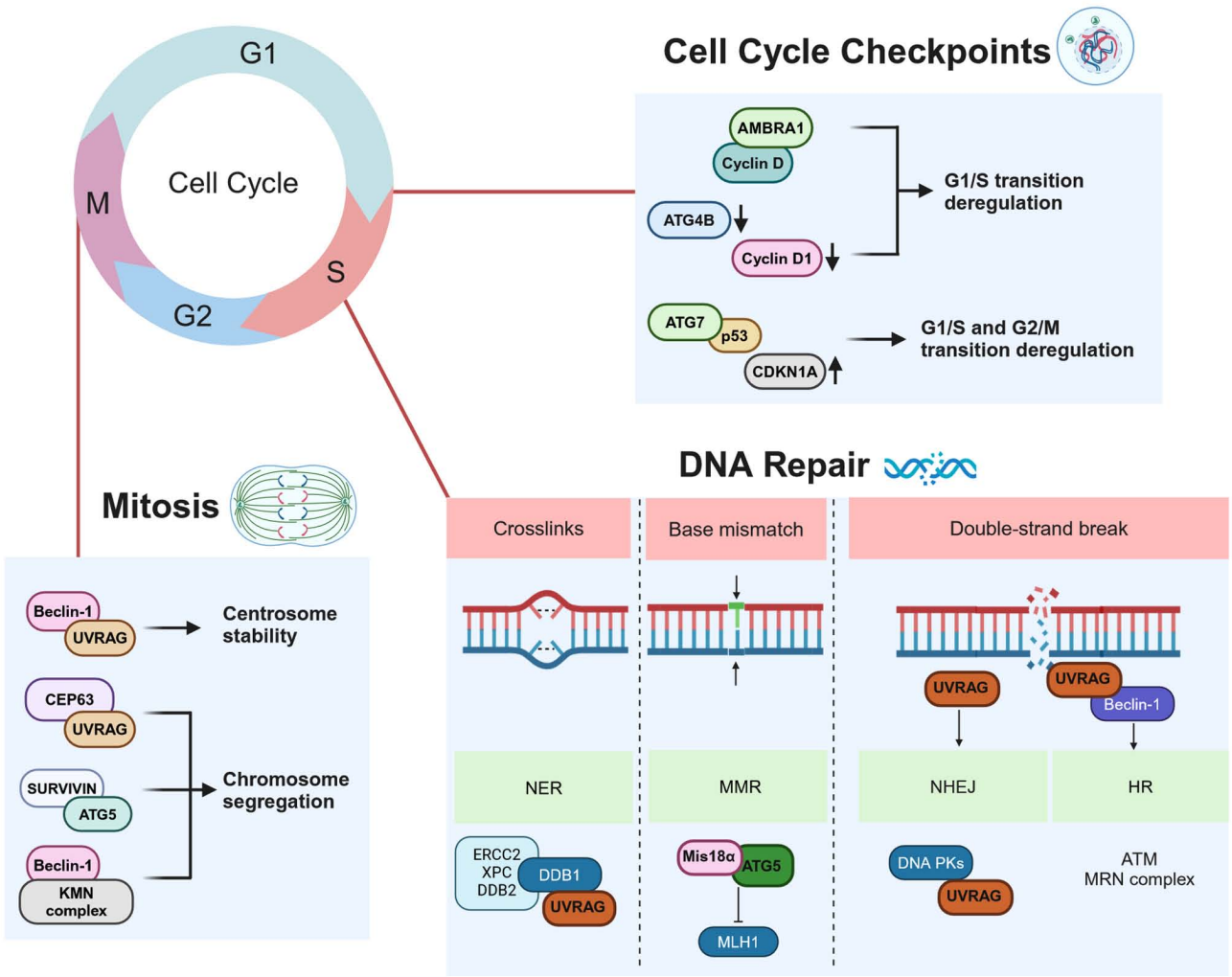

Figure 2. AMMs affecting genome stability and cell cycle progression. At G1/S checkpoint, AMBRA1 and ATG4B interact with cyclins controlling replication stress and genome instability whereas ATG7 interacts with p53 and promotes CDKN1A expression governing G1/S and G2/M checkpoints. A number of AMMs (UVRAG, ATG5 and Beclin-1) intervene in the processes of DNA repair involved in maintaining genome stability throughout the cell cycle. UVRAG interacts with DDB1, a component of the NER complex, to resolve DNA cross-links. ATG5, together with Mis18α, controls expression of MLH1 and impairs the mismatch repair system. UVRAG is involved in the response to double strand breaks by both NHEJ and HR. Beclin-1 interacts with UVRAG to regulate HR. Certain AMMs (Beclin-1, UVRAG, ATG5) interact with kinetochore structures that affect proper chromosomal segregation. Created with BioRender.com. AMM, autophagy machinery molecule; AMBRA1, autophagy and Beclin-1 regulator 1; ATG, Autophagy related genes; CDKN1A, Cyclin Dependent Kinase Inhibitor 1A; UVRAG, ultraviolet radiation resistance-associated gene; DDB1, Damage Specific DNA Binding Protein 1; NER, Nucleotide Excision Repair; Mis18α, MIS18 kinetochore Protein A; MLH1, MutL Homolog 1; NHEJ, Non-Homologous End Joining; HR, homologous Recombination; CEP63, Centrosomal Protein 63; ERCC2, Excision Repair Cross-Complementing Rodent Repair Deficiency, Complementation Group 2; XPC, Xeroderma Pigmentosum, Complementation Group C; DNA PK, Protein Kinase, DNA-Activated; ATM, Ataxia Telangiectasia Mutated; MMR, Mismatch Mediated Repair.

complex involved in the precise anchoring of the kinetochore to the mitotic spindle (58). Moreover, a variant of the PI3K complex, which includes Bax-Interacting Factor 1), is involved in cytokinesis, and thus exerts a tumor suppressor function distinct from its role in the early steps of autophagy (59). PI3P generated by the activated PI3K complex mediates contact with proteins of the centrosome and regulates completion of cytokinesis (60).

5. Unconventional role of AMMs in cell death and survival

Autophagy is a multifaceted process that promotes either cell survival or death, depending on the physiological state of the cell and environmental conditions. Autophagy and apoptosis are closely associated processes in which AMMs can be activated by apoptotic factors and vice versa (61). For example, the autophagosome membrane and its associated autophagy machinery serve as a platform for recruitment and activation of the apoptotic caspase cascade (62). On the other hand, proapoptotic caspase-9 has been shown to interact with ATG7 and contribute to autophagy in various human cancer cell lines (63).

Under certain circumstances, autophagy and apoptosis appear to be mutually exclusive processes mediated by common players (Fig. 3). Protease-mediated cleavage of certain AMMs inhibits autophagy and promotes apoptosis. For example, under unfavorable conditions, such as cell starvation and drug treatment, cleavage of Beclin-1 by caspase-3 or caspase-8 results in formation of an autophagy-impaired Beclin-1 fragment that localizes to mitochondria and promotes apoptosis (61,64,65).

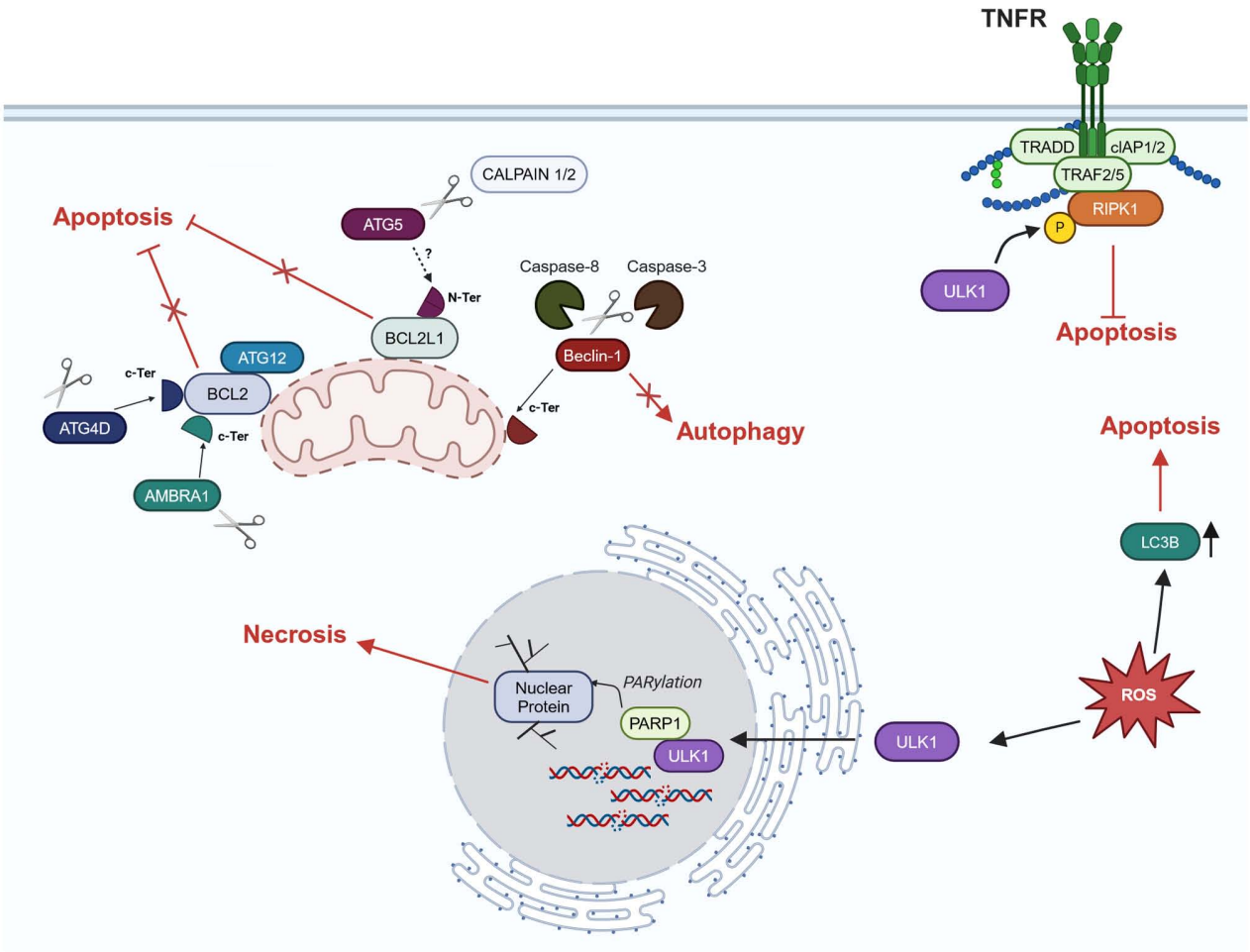

Figure 3. AMMs in cell death. Molecules that activate apoptosis, such as the caspase family, cleave AMMs, which act on mitochondrial homeostasis and apoptosis. ULK1 is involved in the control of cell death mediated by the TNFR. Upon activation TNFR forms a trimer and recruits a number of molecules in the intracellular compartment, including TRADD, TRAF2 and TRAF5, RIPK1 and cIAP1 and cIAP2. This core signaling complex leads to apoptotic cell death. ULK1 is also involved in necrosis, which is stimulated by increased ROS. Through its nuclear translocation, ULK1 potentiates activity of PARP1 and the PARylation of nuclear proteins. ROS are also responsible for the increase in LC3B production, which stimulates the expression of apoptotic molecules and the induction of anoikis. Created with BioRender.com. AMM, autophagy machinery molecules; ULK1, Unc-51-like autophagy-activating kinase 1; TNFR, Tumor Necrosis Factor Receptor; TRADD, tumor Necrosis Factor Receptor Type 1-Associated DEATH Domain Protein; TRAF, TNF Receptor Associated Factor; RIPK1, Receptor Interacting Serine/Threonine Kinase 1; cIAP, Cellular inhibitor of apoptosis protein; ROS, Reactive oxygen species; ATG, Autophagy related genes; AMBRA1, autophagy and Beclin-1 regulator 1; P, Phosphate; c-Ter, C-terminal.

AMBRA1 carries a BH3 motif that, after being released by caspase-mediated cleavage, binds and blocks BCL2, one of the key inhibitors of apoptosis (66). Overexpression of ATG4D and a form of ATG4D cleaved by caspase-3 leads to their recruitment to mitochondria, where they contribute to apoptosis. Again, this pro-apoptotic function of ATG4D relies on its C-terminal BH3 domain, which specifically interacts with members of the BCL2 family (67). Similarly, ATG5 is specifically cleaved by calpains 1/2 during apoptosis, independently of cell type and apoptotic stimulus. Truncated ATG5 translocates to the mitochondria, associates with BCL2-like protein 1 (BCL2L1) and triggers caspase activation via an autophagy-independent mechanism (68). The ATG5 partner ATG12 can control apoptosis independently of the other AMMs by interacting with BCL2 protein family via the BH3 motif (69). ATG12 is an unstable protein that, when not conjugated to ATG5, is subject to proteasomal degradation (36). Due to aberrant proteasomal blockade, ATG12 accumulates in osteosarcoma cells, antagonizes BCL2 and activates apoptosis (38). In colorectal cancer cell lines, oncogenic Ras promotes cancer cell survival by decreasing ATG12 levels and thus ATG12-mediated inhibition of apoptosis (70). ATG12 also serves a role in the control of mitochondrial homeostasis. It interacts with ATG3 in a complex that does not affect autophagy, but is critical for controlling mitochondrial fission and fusion and regulating the function of mitochondria-mediated cell death pathways (71).

Not only apoptosis, but also other forms of cell death are influenced by AMMs. Lung and breast cancer cell lines in which ATG12 expression is reduced undergo oncosis, a caspase-independent cell death triggered by energy deficiency (72). In this condition, the imbalance of mitochondrial ions and impaired metabolism cause changes in osmotic pressure, leading to organelle swelling and cytoplasmic blebs that disrupt cellular function. Similarly, Ni *et al* (73) identified a novel phosphorylation site in ATG4B that, once phosphorylated, allows binding with the soluble catalytic core F1, and the membrane-spanning component, Fo, subunits of ATP synthase.

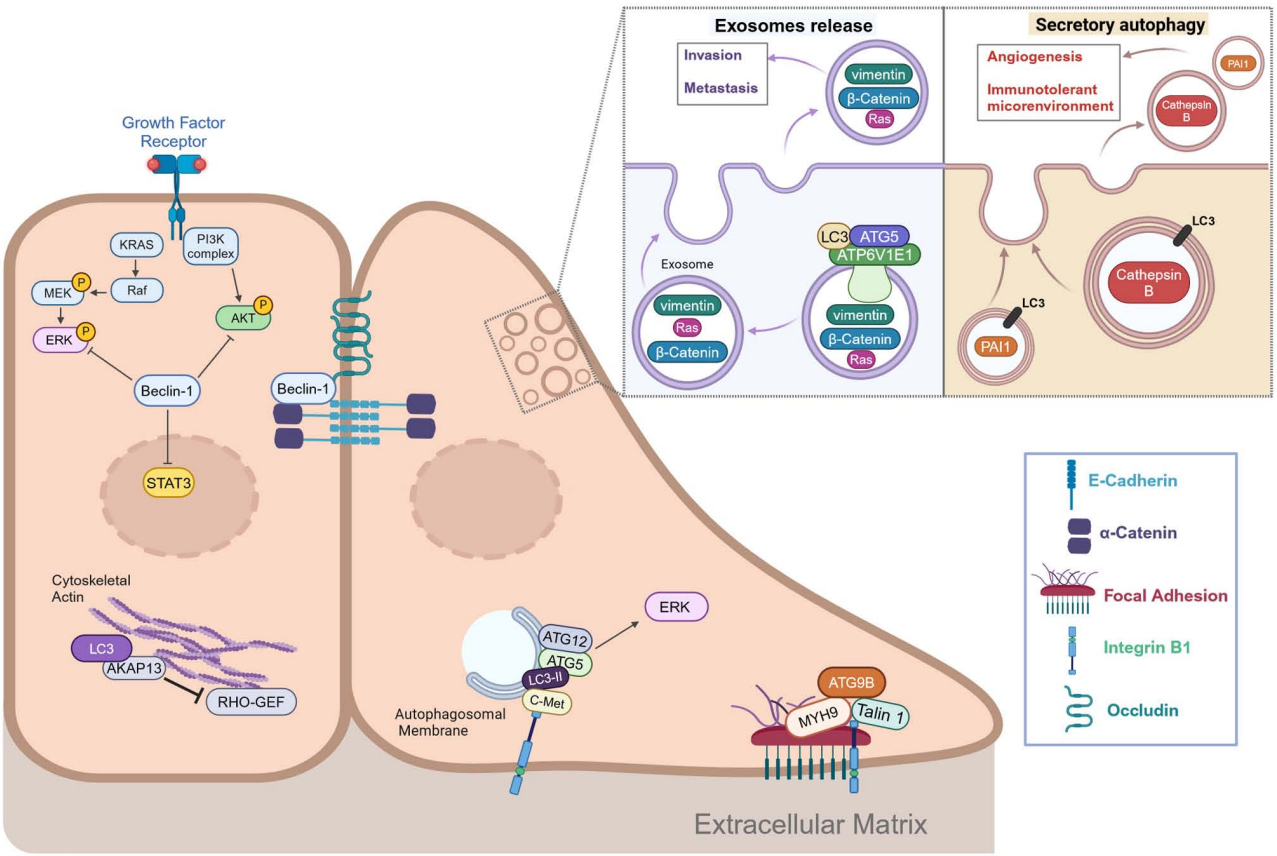

Figure 4. Role of AMMs in invasiveness and tumor microenvironment. Beclin-1 acts independently of autophagy to control mediators of proliferation ERK, AKT and transcription factor STAT3. Beclin-1 is involved in the stability of epithelial junctions by interacting with α-catenin and E-cadherin. LC3 impairs actin cytoskeleton rearrangements by controlling RHO-GEF activation via interaction with AKP13 scaffold protein. The invasive behavior of cancer cells is supported by the upregulation of focal adhesions. ATG9B interacts with MYH9, stabilizing integrin B1 and talin 1, favoring the invasive behavior of cancer cells. ERK is activated by a number of AMMs when located on the autophagosomal membrane (LC3, ATG5, ATG12) upon colocalization with B1 integrin and c-Met. Cancer cells communicate with the tumor microenvironment by secretory autophagy to stimulate angiogenesis (releasing cathepsin B) or immune tolerance (via PAI1). Alternatively, cancer cells release exosomes containing mediators for invasion and metastasis (RAS, vimentin, β-catenin). Created with BioRender.com. AMM, autophagy machinery molecule; RHO-GEF, Rho family of GTPases; AKP13, A-Kinase Anchoring Protein 13; ATG, Autophagy-related genes; P, Phosphate; MYH9, myosin heavy chain 9; PAI1, plasminogenactivator-inhibitor; ATP6V1E1, ATPase H+ Transporting V1 Subunit E1.

This interaction results in impaired mitochondrial function, which leads to an increase in mitochondrial reactive oxygen species (ROS) and metabolic reprogramming of hepatocellular carcinoma cells towards the Warburg effect (73). Following autophagy-mediated activation, ULK1 can phosphorylate RIPK1, a component of the TNF receptor (TNFR)-mediated cell death complex, thereby improving survival of mouse embryonic fibroblasts (MEFs) (74). However, stress conditions, such as increased ROS species, relocate ULK1 to the nucleus, limiting the autophagic response and allowing nuclear ULK1 to promote PARP1-dependent necrosis (75). Similarly, pharmacological induction of ROS increases LC3B production without activating autophagic flux and enhances both expression of apoptotic molecules and induction of anoikis (76).

6. AMMs acting beyond autophagy in metastasis and immune microenvironment

The majority of cancer deaths are caused by metastasis. The metastatic process begins when cancer cells leave the primary neoplasm, invade the surrounding matrix and colonize other tissue via the bloodstream and lymphatic system. These processes, combined with the uncontrolled proliferative capacity of cancer cells, lead to the destruction of the physiological functions of distant organs (77). At the molecular level, invasive and metastatic behavior is supported by features of EMT, which is an embryonic molecular program that is abnormally activated in tumor cells (78). Several studies have demonstrated the role of autophagy in EMT (79-82). Nevertheless, AMMs have also been reported to have non-autophagic functions in EMT (25,83-85),(Fig. 4).

The metastatic potential of cancer cells is ensured by intracellular processes that enable cells to survive under stress conditions. Autophagic membranes carrying LC3-II and ATG5-ATG12 conjugates serve as scaffolds for ERK pathway activation (83). In colorectal cancer, B1 integrin can promote c-Met internalization and ERK1/2 activation, allowing cancer cells to survive to anoikis (84). c-Met and B1 integrin colocalize on autophagic membranes for their pro-survival signals and require LC3-II, Beclin-1 and ATG5 for this purpose, but not other canonical autophagy mediators. Loss of Beclin-1 impairs endosomal signaling and results in prolonged ERK and AKT activation, leading to migratory and invasive behavior in breast cancer (84). Similarly Beclin-1 suppresses

cell migration in colorectal cancer cells by interacting with transcription factor STAT3 (which is abnormally activated in numerous types of cancer) and blocking its phosphorylation by JAK2 (25).

In addition, Beclin-1 and several other AMMs influence cytoskeletal dynamics and cell-cell adhesion. Beclin-1 promotes membrane localization of the adhesion molecules E-cadherin and α-catenin in breast cancer (85). The aforementioned study also suggested a contribution of UVRAG to control of membrane localization of E-cadherin, but the molecular mechanism needs further investigation. Similarly, Beclin-1 localizes to the cell membrane surface and mediates endocytosis of tight junction protein occludin. However, it is not clear whether the downregulation of occludin mediated by Beclin-1 is dependent on autophagy (86). Autophagy mediates the degradation of E-cadherin (87).

LC3 has been reported to regulate cytoskeletal dynamics by interacting with the selective Rho-A exchange factor AKP13 and regulating Rho family of GTPases-dependent reorganization of the actin cytoskeleton (88). ATG9B is involved in regulation of cell-matrix contacts and invasiveness. In colorectal cancer, it serves a non-autophagic function that contributes to the formation of focal adhesions and promotes metastasis (89). In this context, the interaction between ATG9B and myosin heavy chain gene (MYH9) increases the stability of both proteins by preventing their degradative ubiquitination. This favors the interaction between ATG9B, integrin B1 and talin 1, two key molecules of focal adhesions. Immunohistochemical data have confirmed that high expression of ATG9B and MYH9 is associated with poor prognosis in colorectal carcinoma (89).

Endocytosis and exocytosis can be used by tumor cells to create the favorable microenvironment they need for aberrant behavior (90). The ATG5-ATG12 complex is involved in the clathrin membrane trafficking system that affects endocytosis under both normal and starvation conditions in MEFs (37). ATG16L1 has been proposed as a key regulator of several steps of the secretory machinery (especially vesicular release). Its interaction with small GTPase Rab33A has been shown to be key in the process of hormone secretion and may be an hallmark of neuroendocrine tissue (91).

Exosome release and secretory autophagy (SA) are two pathways that mediate secretion and require a number of AMMs. However, the molecular details of these two processes are not yet fully clarified. In the breast cancer cell line MDA-MB-231, ATG5 acts independently of autophagy to sort LC3 into multivesicular bodies, where it binds a component of the vacuolar ATPase H^+ Transporting V1 Subunit E1 and causes a decrease in vesicular acidification (92). The increase in pH promotes the fusion of vesicles with plasma membrane and their release as exosomes. These exosomes have been shown to contain invasion mediators (RAS, β-catenin and vimentin) and thus promote invasion and metastasis of breast cancer cells in mice (93). SA involves unconventional release of molecules into the extracellular space to affect the tumor microenvironment and is used for molecules that cannot enter the conventional endoplasmic reticulum-Golgi secretion system because they lack a signal peptide (93). In bladder cancer, cathepsin-B is released into the tumor microenvironment via SA and stimulates endothelial cells to undergo angiogenesis (94). Elevated levels of cathepsin-B are associated with invasiveness, metastasis and poor prognosis in bladder cancer (94).

In melanoma, SA is activated by pharmacological stimuli and mediates secretion of plasminogen activator inhibitor (PAI-1), which is involved in the formation of a pro-tumor immune microenvironment (95). Moreover, cancer-associated fibroblasts in head and neck cancer use part of the autophagic machinery to secrete tumor-promoting cytokines (IL-6 and IL-8) (96). Whether this mechanism of secretion is SA is not clear.

LC3-associated phagocytosis (LAP) is a process that generates anti-inflammatory and immunosuppressive signals that lead to immune tolerance. Studies show that LAP is involved in M2 macrophage polarization and helps to promote an immunosuppressive environment that favors tumor growth (97,98).

Conversely, in patients with colorectal cancer, expression of an ATG16L1 variant (T600A) is responsible for an increase in IFN-I levels (99). Via the mitochondrial antiviral signaling pathway, cancer cells produce IFN-I, which promotes host antitumor immunity and inhibits the proliferation and metastasis of cancer cells (99).

7. microRNAs (miRNAs or miRs) in the control of AMMs

Expression of critical AMMs is regulated by miRNAs, which are also involved in carcinogenesis (100). miRNAs are a class of small non-coding RNAs (20-24 nucleotides) that control gene expression primarily by either inhibiting the translation or promoting decay of target mRNAs (101). Downregulation of several miRNAs has been shown to promote both tumor progression and autophagy by targeting AMMs (102,103). This is the case for a number of miRNAs that directly target core autophagy molecules such as ATG5 (miR-137, miR-153-3p), ATG12 (miR-30a-3p and miR-214), ATG7 (miR-138-5p and miR-375) and Beclin-1 (miR-17-5p, miR-26a, miR-30a, miR-124-3p, miR-216a and miR-409-3p) (104-114). The downregulation of these miRNAs relieves both oncogenic signaling pathways and autophagy that usually are inhibited by them. This suggests a link between autophagy and cancer progression.

8. Diagnostic and prognostic role of AMMs in cancer

As aforementioned, AMMs play a crucial role in cancer, both dependent on autophagy and independent of it. Therefore, changes in the expression of AMMs can be associated with the prognosis of patients with cancer. Molecular AMM signatures with potential diagnostic and prognostic value have been defined in triple-negative breast cancer and sarcoma (115,116).

Moreover, several studies have investigated the prognostic role of the core LC3 family nuclear proteins and shown that their expression is associated with poor prognosis in various cancers such as lung, breast, gastric and other types of carcinomas (117-122).

Similarly, a signature based on high SQSTM1 and LC3 levels has been considered a negative prognostic factor in squamous cell carcinoma (123). It has been frequently

observed that SQSTM1 exerts a pro-tumorigenic function in cancer (124,125). In a meta-analysis, SQSTM1 was shown to serve a negative prognostic role in a number of solid tumors (126). However, it is worth noting that these AMMs are typically degraded by active autophagy and their expression is used to monitor autophagic flux. Thus, these studies may reveal the prognostic role of autophagy rather than that of AMMs. At the same time, SQSTM1 functions as a scaffold protein for multiple signaling pathways and its prognostic role may therefore be independent of autophagy (127).

Beclin-1 is considered a haploinsufficient tumor suppressor in a number of cancers. Monoallelic deletion of the BECN1 gene is frequently observed in breast and ovarian cancer (128). However, the BECN1 gene is located in proximity to the known tumor suppressor BRCA1 in both humans (chromosome 17) and mice (chromosome 11) and the two loci are simultaneously deleted in breast and ovarian cancer; therefore, the actual role of Beclin-1 in tumorigenesis has been questioned (129-131). The observation that low expression of the BECN1 transcript, but not BRCA1, is associated with poor prognosis in breast cancer supports the role of Beclin-1 as a tumor suppressor (132). In addition, Beclin-1 enhances the efficacy of chemotherapeutic agents in cervical and gastric cancer cells (133).

High levels of ATG5 are associated with poor prognosis in various solid tumors (134). ATG5 has been identified as a potential prognostic marker in cervical squamous cell carcinoma and endocervical adenocarcinoma cases obtained by The Cancer Genome Atlas (135). The aforementioned study demonstrated the involvement of ATG5 in control of markers of EMT, invasive behavior and the immune effector process of T cell-mediated immunity. Contradictory results have been obtained for AMBRA1 (136). High expression of AMBRA1 is associated with poor prognosis in patients with various malignancies, such as pancreatic ductal adenocarcinoma, cholangiocarcinoma and gastric and prostate cancer (137-140). By contrast, the expression of AMBRA1 in early-stage melanoma is associated with a better prognosis (141).

9. Conclusions and perspectives

AMMs influence tumorigenesis via canonical and non-canonical autophagy functions; however, the dominance of these functions is unclear. Certain AMMs, such as ATG12, Beclin-1 and AMBRA1, have a domain that is activated by caspase and typically prevents activity of anti-apoptotic proteins (65,66,69). These AMMs therefore may link autophagy and apoptosis. Under certain stress conditions, their levels determine the fate of cells towards survival (autophagy) or death (apoptosis). Similarly, high levels of ROS promote autophagy-independent involvement of ULK1 in triggering necrosis (74). Thus, it would be useful to clarify how AMMs are regulated in cancer. For example, the LC3 and GABA type A Receptor-Associated Protein) family consists of at least 7 proteins that have different functions in membrane management for autophagic and non-autophagic purposes (142). Furthermore, they may be regulated by different transcription factors in different tissue, which could explain the activation of tissue-specific molecular programs beyond autophagy (142). As aforementioned, expression of LC3B and LC3A is associated with poor prognosis in gastric, breast and other types of cancer (117-122).

The existence of alternative variants has been demonstrated for several AMMs and may account for novel autophagy-independent functions (143). The autophagy-incompetent ATG7 p.Arg659*, has been proposed as a cholangiocarcinoma-associated gene (144). In addition, an ATG7 splice variant has been described that is unable to lipidate LC3 and is incompetent for autophagy (145), but, it remains to be clarified whether this variant has a function in cancer. As aforementioned, an ATG16L1 variant (T600A) stimulates an anti-tumor immune response and is associated with a good prognosis (99). SQSTM1 is expressed in several variants: N-Ter truncated isoform lacking the domain responsible for SQSTM1 oligomerization and autophagic cargo sorting ability (146); splice variant affecting the p62/Keap1/NRF2 axis (147) and SQSTM1 3' untranslated region-truncated variant associated with aggressiveness and resistance to therapy in patients with breast cancer (148). Therefore, it would be of interest to determine whether these different AMMs isoforms exhibit autophagy-independent functions.

Determining the autophagy-independent function of a single AMM in cancer is challenging because autophagy is a redundant signaling pathway that can find alternative routes to function and influence other cellular processes (5). Therefore, modulation of multiple autophagy markers should be considered before claiming that AMM activity is independent of autophagy. Alternatively, it is advisable to investigate the autophagy-independent role of AMMs *in vitro* by using autophagy-incompetent mutants, such as the ATG5 variant that cannot bind its autophagic partner ATG5K130R (149).

In summary, the role of AMMs is not limited to canonical autophagy but also involves autophagy-independent functions in various biological processes. Nevertheless, further studies that elucidate the link between autophagy-dependent and -independent pathways will help to clarify the activity of AMMs in cancer progression and response to therapies as well as in the identification of novel therapeutic targets.

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Authors' contributions

GT and MS conceived the review, analyzed the literature and wrote the manuscript. GT collected and reviewed the literature and produced the figures. RM critically revised the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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