BBA - Reviews on Cancer 1876 (2021) 188565

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

journal homepage: www.elsevier.com/locate/bbacan

Review

Cross talk between autophagy and oncogenic signaling pathways and implications for cancer therapy

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ARTICLE INFO

Keywords:
Autophagy
EMT
Cancer metastasis
Oncogenic proteins
Anticancer therapy

ABSTRACT

Autophagy is a highly conserved metabolic process involved in the degradation of intracellular components including proteins and organelles. Consequently, it plays a critical role in recycling metabolic energy for the maintenance of cellular homeostasis in response to various stressors. In cancer, autophagy either suppresses or promotes cancer progression depending on the stage and cancer type. Epithelial-mesenchymal transition (EMT) and cancer metastasis are directly mediated by oncogenic signal proteins including SNAI1, SLUG, ZEB1/2, and NOTCH1, which are functionally correlated with autophagy. In this report, we discuss the crosstalk between oncogenic signaling pathways and autophagy followed by possible strategies for cancer treatment via regulation of autophagy. Although autophagy affects EMT and cancer metastasis, the overall signaling pathways connecting cancer progression and autophagy are still illusive. In general, autophagy plays a critical role in cancer cell survival by providing a minimum level of energy via self-digestion. Thus, cancer cells face nutrient limitations and challenges under stress during EMT and metastasis. Conversely, autophagy acts as a potential cancer suppressor by degrading oncogenic proteins, which are essential for cancer progression, and by removing damaged components such as mitochondria to enhance genomic stability. Therefore, autophagy activators or inhibitors represent possible cancer therapeutics. We further discuss the regulation of autophagy-dependent degradation of oncogenic proteins and its functional correlation with oncogenic signaling pathways, with potential applications in cancer therapy.

1. Background

Autophagy, a highly evolutionarily conserved process in all eukaryotes, can result in the degradation of cytoplasmic materials such as damaged organelles, proteins, pathogens, and lipids in a lysosome-dependent manner. The newly formed double-membrane structure (called "autophagosome") specifically sequesters these cytoplasmic materials, followed by fusion with lysosome for degradation [1–4]. The degradation via autophagy recycles the cellular components and provides the energy necessary for maintaining homeostasis during metabolic stress. Autophagy plays an essential role in many cellular events such as survival and death, development, and in responding to various stressors. Therefore, the dysregulation of autophagy occurs in a wide range of diseases including, cancer, neurodegenerative and metabolic

Abbreviations: ATGs, Autophagy-related genes; AMPK, Adenosine monophosphate-activated protein kinase; BCL2, B-cell lymphoma protein 2; BNIP3, BCL2-interacting protein 3; EMT, Epithelial-to-mesenchymal transition; ERK, extracellular signal-regulated kinase; FAK, Focal adhesion kinase; GSK3β, Glycogen synthase kinase 3β; JAK, Janus kinase; LC3, Microtubule-associated protein light chain 3; LKB1, Liver kinase B1; MHC-I, major histocompatibility complex class I; MTORC1, Mammalian target of rapamycin complex 1; MMPs, matrix metalloproteinases; NBR1, neighbor of BRCA1 gene 1; NICD, NOTCH1 intracellular domain; NFκB, nuclear transcription factor κB; PE, Phosphatidylethanolamine; PI3K, Phosphoinositide-3-kinase; PKA, cAMP-dependent protein kinase; RKIP, Raf kinase inhibitory protein; ROSs, Reactive oxygen species; SQSTM1, sequestosome 1; STAT, signal transducer and activator of transcription; TAMs, tumor associated macrophages; T_{reg}, regulatory T cells; TGF-β, Tumor growth factor-beta; ULK1/2, Unc-51-like kinase 1 and 2; TSC1/2, Tuberous Sclerosis complex 1 and 2; ZEB1/2, Zinc-finger *E*-box-binding homeobox 1 and 2.

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https://doi.org/10.1016/j.bbcan.2021.188565
Received 9 April 2021; Received in revised form 5 May 2021; Accepted 8 May 2021
Available online 13 May 2021

disorders, and infections.

Autophagy is extensively involved in cancer initiation, epithelial-mesenchymal transition (EMT), and metastasis [5–9]. In general, the toxic components or damaged organelles in cells can induce carcinogenesis unless they are promptly removed by cellular mechanisms [10–13]. Therefore, autophagy as a self-digesting process is critical in removing intracellular debris and maintaining cellular homeostasis in normal conditions [14–17]. In addition, autophagy promotes cancer survival. Autophagy is triggered when cancer cells encounter stressors such as metabolic deprivation or oxidative stress progression [18–21]. Also, autophagy regulates multiple transcription factors that are vital for cancer progression [22–27]. Although autophagy plays a critical role in cancer, the connection between it and oncogenic signals remains unclear. In this review, we investigated and integrated a number of oncogenic pathways functionally linked to autophagy. We also discussed the functional roles in immune responses and the selective degradation of oncogenic proteins during cancer progression. Finally, we suggested a few potential therapeutic applications in cancer.

2. The general molecular machinery of autophagy

Autophagy is divided into three major types: macroautophagy, microautophagy and chaperone-mediated autophagy. Many autophagy-related genes (*ATGs*) are involved in the autophagic process [28–31]. Macroautophagy (commonly known as "autophagy") is the primary process in removing protein aggregates and damaged organelles. It involves a stepwise process in which ATG proteins play a key role. During the phagophore (also called "isolation membrane") formation initiation cytoplasmic materials are selectively or non-selectively engulfed into the lumen of autophagosomes and subsequently degraded by proteases after fusion with lysosomes [28–32]. Selective autophagy encampasses mitophagy (mitochondria), lipophagy (lipids), peroxophagy (peroxisomes), ribophagy (RNA), and other types [1–3,28,31]. In microautophagy, cytoplasmic proteins are directly engulfed by the lysosomes via invagination of lysosomal membrane or cellular protrusions and eventually degraded by lysosomal proteases [1–3,28,31]. Chaperone-mediated autophagy (CMA) is a specific lysosomal degradation pathway in which the hsc70-containing complex is involved in protein recognition and unfolding. Finally, the proteins crossing the lysosomal membrane are removed by the lysosomal enzymes [1–3,28,31].

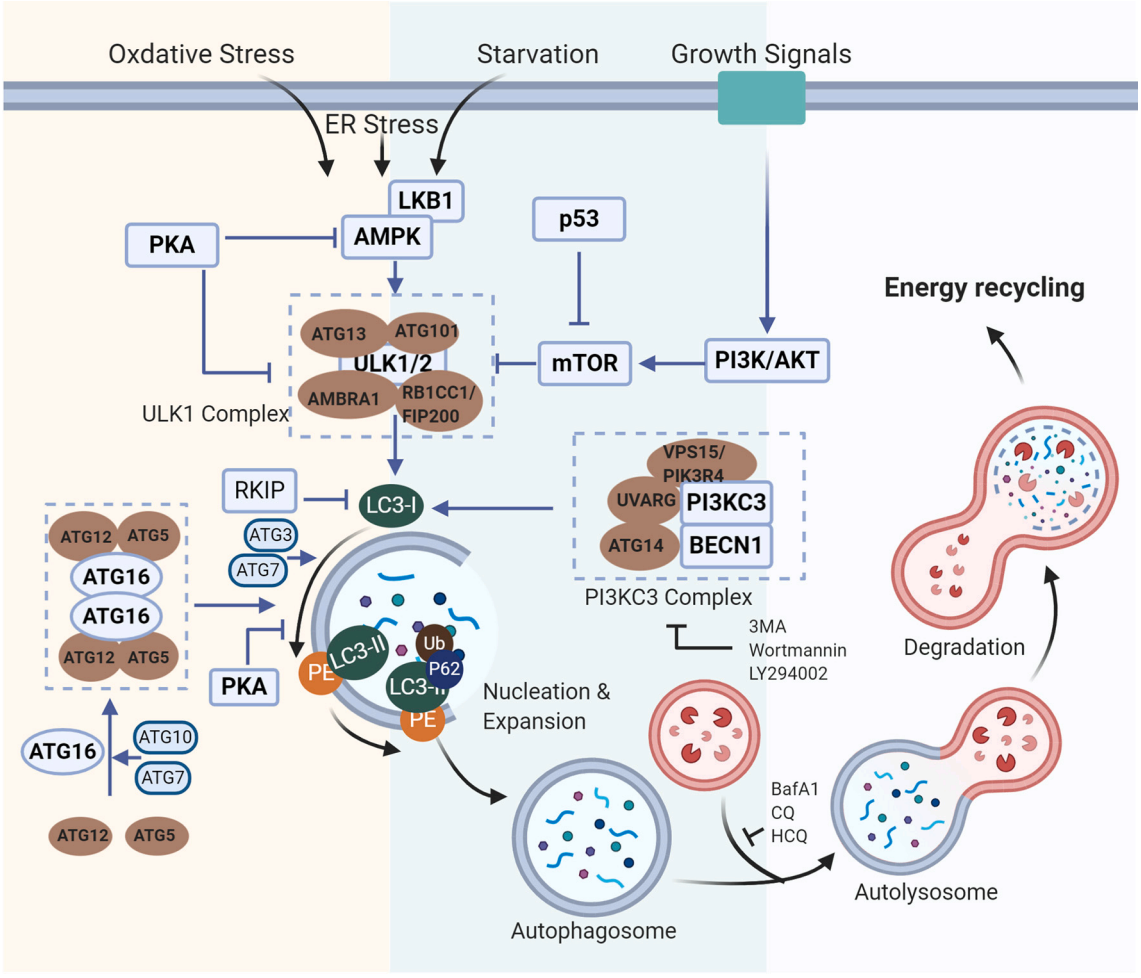

Fig. 1. Autophagy involves multiple steps: induction, nucleation, vesical expansion, and lysosomal fusion. A few critical signal complexes are involved in the regulation of autophagy induction. The ULK1/2 complex regulates the initiation of autophagy together with the PI3KC3 (class III PIK3) complex. It is composed of several proteins, including ATG13, ATG101, AMBRA1, and FIP200. The ULK1/2 complex is controlled by either activator (e.g., AMPK) or inhibitor signals (e.g., mTOR pathway or PKA). The PI3KC3 complex, comprising class III PIK3 with BECN1, UVRAG, PIK3R4, and ATG14 proteins, is specifically inhibited by chemical compounds such as 3-methyladenine (3-MA) and wortmannin, as well as proteins such as BCL2 or RUBICON. LC3 is lipidated to phosphatidylethanolamine (PE) via two ubiquitin-like conjugation proteins. PE-conjugated LC3s (LC3-II form) are formed via nucleation and vesical expansion resulting in autophagosomes, followed by fusion with lysosomes facilitated by other proteins such as SNARE or Rabs to degrade its contents for energy recycling. The fusion with lysosomes is inhibited by compounds such as chloroquine (CQ), hydroxychloroquine (HCQ), and bafilomycin A1 (Baf-A1). Created with BioRender.com.

The overall mechanism of autophagy includes several distinct steps: induction, vesicle nucleation, elongation, closure, and maturation followed by fusion with lysosomes and degradation. These steps are executed by ATGs and other autophagy-associated proteins as shown in Fig. 1 [1–3,28,31]. Under metabolic stress, including nutrient or growth factor deprivation, signaling pathways such as mTOR or AMPK activate the Unc-51-like kinases 1 and 2 (ULK1 and ULK2) complex [33–36]. The cytosolic LC3 proteins conjugate with phosphatidylethanolamine (PE) via two ubiquitin-like conjugation mechanisms, leading to vesicle nucleation [37–39]. Also, the complete autophagosome formation requires the activity of Atg1-Atg13-Atg17-Atg31-Atg29 complex kinase in yeast [1–3,28–32]. In mammalian cells, this complex is composed of the Atg1 homolog, ULK1 and ULK2, the mammalian homolog of Atg13 (ATG13), and RB1-inducible coiled-coil 1 (RB1CC1/FIP200) [34–36,40–46]. The ULK1/2 complex is also functionally linked to class III phosphatidylinositol 3-kinase (PI3K) complex comprising several proteins such as PIK3C3/VPS34, PIK3R4/p150, UVRAG and BECN1 [36,37,41,42,47]. The action of this PI3K complex is necessary for autophagic vesicle expansion and maturation. Indeed, treatment with class III PI3K inhibitors such as LY294002, wortmannin, and 3-methyladenine (3-MA) results in the failure of autophagosome formation [40–42,47].

WIPI I and WIPI II (Atg18 and Atg 21 in yeast), and PtdIns3P-binding proteins also regulate the phagophore formation by modulating the PI3K activity [48–52]. Furthermore, two ubiquitin-like conjugation systems are necessary for the elongation process. ATG5 proteins are conjugated to ATG12 by the sequential action of ATG3 and ATG7 [37–39]. The ATG5-ATG12 conjugates combined with ATG16L mediate the lipidation of microtubule-associated light chain 3 (MAP-LC3/LC3) with PE, facilitating the localization of LC3 to both sides of the double-membraned autophagosomes [37–39,53,54]. Finally, the autophagosomes fuse with lysosomes, resulting in the degradation of cellular cargo by lysosomal enzymes. The fusion step is specifically blocked by inhibitors such as chloroquine (CQ), hydroxychloroquine (HCQ), or bafilomycin A1 (Baf-A1) [1–4,55–58]. Also, other proteins such as RAB7, and SNAREs (VAM7, VAM8 and syntaxin17) involved in membrane trafficking play a critical role in autophagy [42,59–61]. The components of autophagy pathway are presented in Fig. 1.

3. The central regulatory pathway

Autophagy is mainly regulated by several serine/threonine kinase kinases, including MTORC1, cAMP-dependent protein kinase A (PKA), and AMP-dependent protein kinase (AMPK) [62,63]. Both MTORC1 and PKA inhibit autophagy under nutrient-rich conditions, and the deactivation of these kinases under starvation induces autophagy [62–65]. In mammals, this inhibition occurs at least partially via the phosphorylation of LC3 by PKA [66]. Also, the functional interaction between PKA and MTORC1 is associated with the inhibition of cellular events [67,68]. By contrast, the activation of AMPK at lower levels of energy promotes autophagy. Indeed, decreased AMPK activity induces activation of MTORC1 either by PKA or indirectly [69]. AMPK, a major energy-sensing kinase, regulates a variety of cellular processes including autophagy [70,71]. At low energy levels, the activated AMPK phosphorylates the TSC1/2 complex, leading to the inhibition of MTORC1 and autophagy induction [72,73]. AMPK can induce autophagy via a direct inhibition of MTORC1 or the activation of ULK1/2 [74,75]. Moreover, autophagy is positively regulated by LKB1 upon nutrient deprivation [76]. Our previous studies suggested that Raf kinase inhibitory protein (RKIP), which inhibits the ERK pathway, suppresses the starvation-induced autophagy via a direct interaction with cytosolic LC3 but not the lipidated membrane-associated LC3. However, this RKIP-associated inhibition of autophagy is dependent on MTORC1 and not ERK activation [77]. Additionally, RKIP displayed functional associations with several other autophagy-related protein genes including class III PI3K (PI3KC3) in cancer cells [78]. The PI3KC3 complex comprising PI3KC3, BECN1, ATG14, VPS15, and UVRAG controls the initiation of autophagy together with the ULK1/2 complex (ULK1/2, ATG13, ATG101, AMBRA1, and RB1CC1) and is specifically inhibited by compounds such as 3-methyladenine, wortmannin, and LY294002. The regulatory pathway of autophagy is shown in Fig. 1.

Autophagy is selectively regulated by p53, depending on the cellular localization of the p53 protein. In the cytosol, p53 inhibits autophagy, while in nucleus, it enhances autophagy through the transcriptional activation of core autophagy genes [79–83]. This feedback mechanism is tightly regulated during autophagy in a context-dependent manner under different cellular conditions. Furthermore, many autophagy genes are regulated by some master transcription factors, including the transcription factor EB (TFEB) forkhead family of transcriptional factors (FOXO1 and FOXO3), peroxisome proliferator-activated receptor gamma (PPARG), and others. Indeed, stimulating these transcription factors greatly enhances autophagy by increasing the expression of autophagy genes [22,84–87]. By contrast, bromodomain-containing protein 4 (BRD4) represses autophagy genes through binding with G9a on their promoter regions [88].

4. The dual role of autophagy in cancer

Since autophagy is associated with many biological pathways, it is widely implicated in a variety of cellular processes, including tumorigenesis [14,89,90]. In particular, autophagy plays a context-dependent role in cancer [91–94]. It protects the cell by eliminating damaged cellular components, maintaining genomic stability, limiting inflammation, viral infection, and maintaining homeostasis [13–16,89,90]. The accumulation of damaged mitochondria results in reactive oxygen species, leading to genomic instability, which is associated with many types of cancer. Autophagy protects the healthy cells and prevents them from turning cancerous. However, the same cytoprotective effect can help the cancer cells to survive once they develop.

Autophagy may promote cancer when cancer cells encounter nutrient deprivation during EMT and cancer metastasis. Self-digestion by autophagy provides the minimum level of energy for cancer cell survival [23–27]. Autophagy also protects cancer cells from immune responses and Anoikis during cancer progression [95,96]. It additionally provides many metabolites necessary for the maintenance of cancer cells and resistance to death by apoptosis or necrosis [97–102]. Moreover, autophagy plays an essential role in maintaining cancer stem cells (CSCs). Autophagy maintenance and homeostasis are fundamental requirements for the conservation of pluripotency in several pathophysiological conditions [103–106]. The dormancy and other essential CSCs characteristics were described in detail by Rahman et al. in their recent review [103]. In addition, the activation of autophagy in cancer cells increases resistance to cancer drugs [106–111]. Autophagy also regulates the cancer microenvironment promoting cancer metastasis and resistance to stressors, treatments, and apoptosis in advanced stages of tumorigenesis. The dual role of autophagy in cancer is depicted in Fig. 2.

Autophagy plays multiple stage or context-dependent roles during cancer progression depending on the metabolic needs of the cancer cells [91–94]. As a result, targeted modulation of autophagy represents a potentially effective strategy for treating malignant tumors [7,111,112]. Indeed, in many types of cancer, autophagy blockers have been used as cancer therapy [113–116]. The detailed role of autophagy inhibitors and activators in cancer therapy will be described later in this review. However, because the role of autophagy varies with cancer type or stage, thus the clinical and therapeutic implications in cancer remain to be investigated.

5. The functional linkage between autophagy and EMT/cancer metastasis

Epithelial-mesenchymal transition (EMT) is a multistep process in which cells lose their epithelial characteristics and reversibly acquire

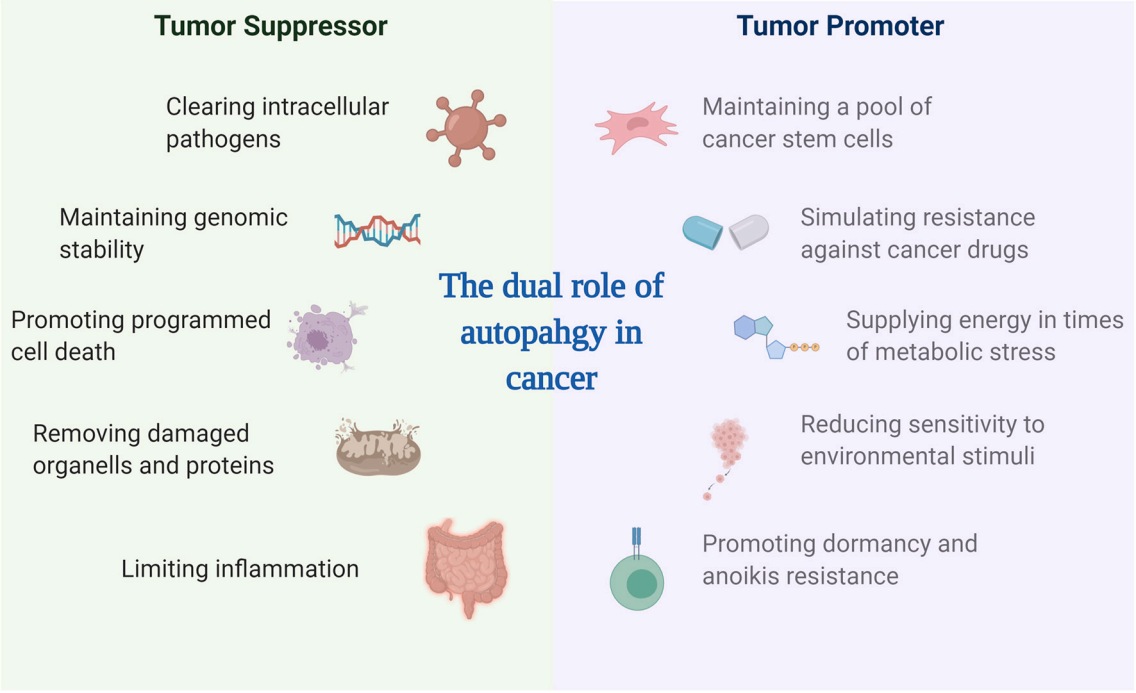

Fig. 2. The dual role of autophagy in cancer progression. Autophagy plays a dual role in tumorigenesis by suppressing or promoting cancer progression depending on the cancer type or stage. The specific role of autophagy in cancer is individually described. Created with BioRender.com.

mesenchymal characteristics. This process suppresses the level of epithelial proteins such as *E*-Cadherin, Claudin, and Desmoplakin [117–122]. Inversely, it increases the levels of several mesenchymal proteins, including N-Cadherin, Vimentin, and Fibronectin [120–126]. EMT promotes the acquisition by cancer cells of additional properties (e.g., Anoikis resistance, anti-apoptosis, drug resistance, invasion and migration, and cancer stemness), which promote cancer metastasis [120–128].

EMT is specifically regulated by several oncogenic proteins such as SLUG, SNAI1, ZEB1/2, TWIST, and NOTCH1. Upon activation of oncogenic signals, the levels of these transcription factors are strongly enhanced to either induce or repress the expression of genes coding for the EMT proteins. For example, SNAI1 directly binds along with other factors to the *E*-Cadherin promoter and represses its gene expression [120–128]. Also, the zinc-finger E-box-binding homeobox 1 (ZEB1) inhibits the expression of E-Cadherin. By contrast, NICD, a transcription factor derived from NOTCH1 signal, activates the expression of several mesenchymal proteins, such as N-Cadherin and Vimentin [120–128].

According to recent studies, autophagy regulates the intracellular level or activation of EMT transcription factors via functional association with multiple oncogenic signals. Autophagy inhibits EMT via the regulation of key transcription factors in certain cancer cells. By contrast, it stimulates EMT by regulating the level of EMT proteins in others. Indeed, defective autophagy in human skin squamous cell carcinoma and melanoma facilitates EMT by stabilizing TWIST [129–132]. Also, the activation of autophagy downregulates and degrades SNAI1 and TWIST in many cancer cells [129–136]. Furthermore, the knockdown of *ATG5* and *ATG7* genes increases SNAI1 and SLUG levels in glioblastoma cells [132–134].

Autophagy boosts EMT by stimulating cell viability during cancer migration and invasion [137]. Indeed, the silencing of *ATGs* genes suppresses EMT in hepatocellular cancer cells. In addition, autophagy plays a critical role in controlling Anoikis resistance, anti-apoptotic events, and drug resistance [95–102]. Autophagy is activated when cancer cells detach from the primary tissues, which facilitates cancer cell survival by inhibiting Anoikis [95–97]. In fact, overexpression of oncogenic H-Ras promotes cell survival via activation of detachment-dependent autophagy [26]. Conversely, autophagy suppresses cancer Ras-driven epithelial tumorigenesis by limiting the accumulation of reactive oxygen species [138]. This suggests that it is critical for Anoikis resistance in cancer cells. The overall relationship between EMT and autophagy is presented schematically in Fig. 3. Below, we describe the role of different signaling pathways in modulating the interaction between autophagy and EMT/cancer metastasis.

5.1. *PI3K/AKT/mTOR signaling pathway*

The PI3K/AKT/MTORC1 axis induced by growth factors is a major signal transduction pathway in cancer cell growth in nutrient-rich conditions. Conversely, inhibition of this pathway under nutrient-deficient conditions promotes autophagy. MTORC1, a serine/threonine kinase, regulates several cellular functions including translational regulation, protein degradation, cell metabolism, cytoskeletal dynamics and autophagy [139–145]. As shown above, in addition to the PI3K/AKT/MTORC1 axis, the MTORC1 activity is also regulated by LKB1/adenosine monophosphate–activated protein kinase (AMPK) and Ras-dependent MAPK pathways [72–76,146]. However PI3K/AKT/mTOR signaling pathway has been reported in cancer matastasis, progression, drugs resistance and also have role in other diseases [147–152]. MTORC1 activation induces phosphorylation of ribosomal protein S6 (p70S6) and eukaryotic initiation factor 4E (eIF4E)-binding proteins (4E-BPs), whose translation promotes cancer [153,154]. PI3K, a key upstream regulator of MTORC1, is directly activated by growth factor-mediated Ras signals as well as by TGF-β, nuclear transcription factor κB (NF-κB) or other cytokine signaling pathways that are essential for the control of cancer progression [155–158].

The PI3K/AKT activation induces upregulation of EMT and metastasis via WNT/β-catenin and glycogen synthase kinase 3β (GSK3β) activity [156]. Although the ERK pathway activated by TGF-β is required for EMT and metastasis, the PI3K/AKT/ERK axis is also associated with TGF-β–induced EMT and metastasis [159,160], suggesting that these signals interact with each other in a context-dependent manner during tumorigenesis.

The mTOR pathway activated by PI3K signal inhibits autophagy,

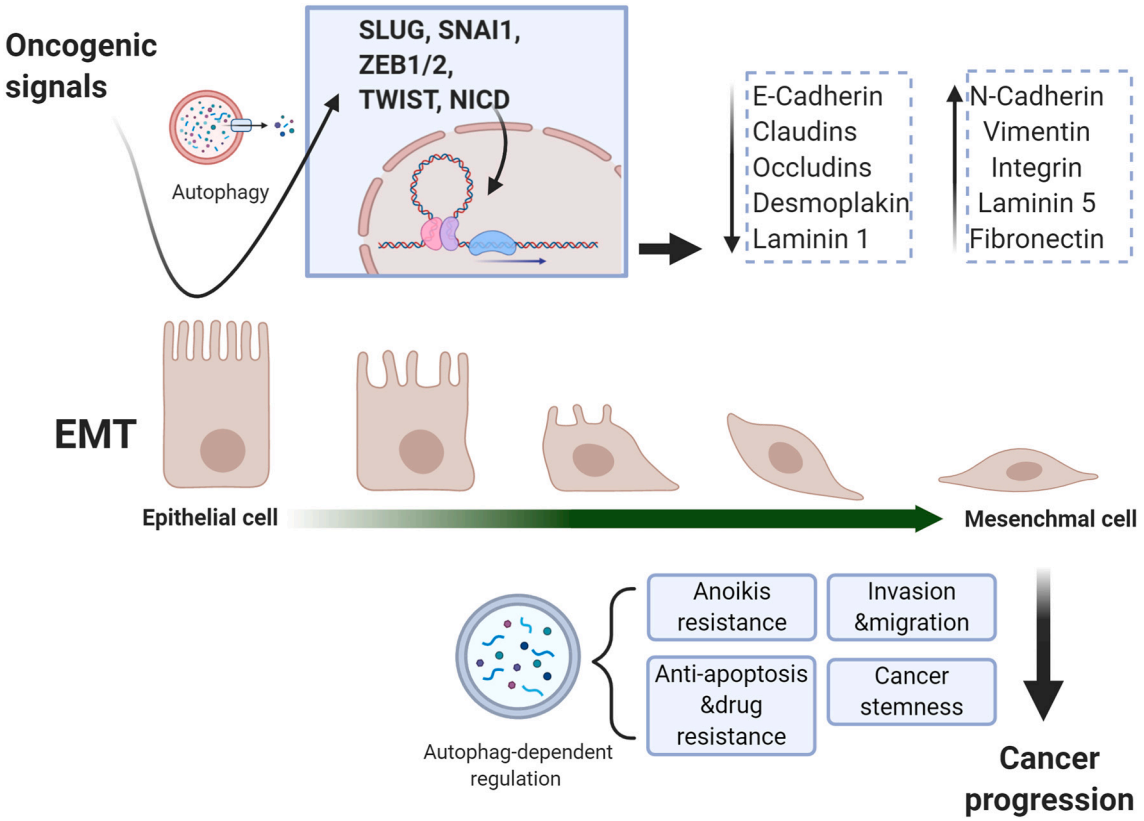

Fig. 3. EMT mediators and the functional crosstalk with autophagy. Epithelial-like cells are transformed to mesenchymal-like cells by oncogenic signals via the activation of EMT-associated transcription factors such as SNAI1, SLUG, ZEB1, TWIST, and NOTCH1. The intracellular level or activation of these mediators is partly regulated by autophagy. EMT induces an increase in mesenchymal markers such as N-Cadherin and Vimentin and a decrease in epithelial markers such as *E*-Cadherin and Claudins. Mesenchymal-like cells exhibit specific cellular properties: Anoikis resistance, invasion and migration, anti-apoptosis, drug resistance, and cancer stemness. These mesenchymal properties are functionally associated with the regulation of autophagy in cancer cells. Created with BioRender.com.

which attenuates cancer migration and invasion in certain cancers [161]. Activation of autophagy via direct inhibition of MTORC1 by metformin also inhibits the proliferation, migration, EMT and metastasis of thyroid cancer cells [162]. Autophagy activation via direct inhibition of MTORC1 activate autophagy dependent drugs resistance in cancer [163]. Similarly, autophagy activation by water stress proteins such as WSP1 that downregulate the PI3K/AKT/mTOR pathway promotes degradation of β-catenin, and suppresses EMT and cancer metastasis [164]. Indeed, autophagy inhibition by PI3K activation leads to the upregulation of SNAI1, SLUG, integrin-linked kinase (ILK), and WNT/β-catenin signaling resulting in EMT and cancer metastasis [165].

Liver kinase B1 (LKB1), a tumor suppressor, acts as an autophagy inducer [166]. Under low levels of energy, LKB1 activates AMPK to induce cell growth and proliferation by stimulating autophagy via inhibition of MTORC1 or direct activation ULK1/2, a key protein regulating autophagy [167,168]. In addition, LKB1/AMPK inhibits EMT by downregulating Smad2/3 in the TGF-β signaling pathway, and GSK-3β stimulates autophagy via activation of LKB1/AMPK and inhibition of PI3K/AKT/MTORC1 pathway [169]. GSK-3β also indirectly induces autophagy via β-catenin followed by the modulation of LKB1/AMPK [170]. Also, nesfatin-1/nucleobindin-2 (NUCB-2) regulates EMT and metastasis via the LKB1/AMPK/MTORC1 pathway in colon cancer [171]. Furthermore, activation of LKB1/AMPK inhibits TGF-β–induced cancer via suppression of Smad2/3 activity [172]. Overall, the activation of LKB1/AMPK plays a critical role in cancer cell survival under metabolic stress by stimulating autophagy via modulation of several oncogenic signaling proteins (Fig. 4).

5.2. *Class III PI3K signaling pathway*

BECN1, a prominent autophagy gene, specifically binds to VPS34/PI3KC3 proteins in the class III PI3K complex, resulting in autophagy induction [36]. BECN1 also acts as a tumor suppressor. It deactivates ZEB1, WNT1, and NF-κB in cancer, resulting in the inhibition of EMT [173–176]. Therefore, BECN1 expression has been used as a biomarker to predict overall survival and progression in gastric and liver cancer patients. Indeed, the allelic loss of *BECN1* gene stimulates tumor progression in many cancers [173,174]. In addition, the heterozygous BECN1-deficient mice show an increase of tumorigenicity by limiting the chromosomal instability [11,12,177]. Furthermore, most mutations on the *BECN1* gene are functionally associated with genetic mutations of *BRCA1* gene [178,179].

Together with BECN1, AMBRA1 is one of core components in the class III PI3K complex and considered as a tumor suppressor [180]. UV irradiation resistance-associated gene (UVRAG), another BECN1-interacting partner, is also monoallelically mutated in many colon cancers [181]. Bif-1 (also known as Endophilin B1) specifically interacts with BECN1, and knockout of *Bif-1* gene causes spontaneous tumor development in mice [182], suggesting that these BECN1-associating proteins in the PI3K complex are essential for not only the function of autophagy but also tumor suppression. However, the function of BECN1 in cancer is a context-dependent [183,184]. In fact, the overexpression of BECN1 in cancer cells stimulates cell death, suggesting anticancer effect [185]. Knockdown of the *BECN1* gene in cancer cells increases EMT and metastasis in thyroid cancer by stabilizing *ZEB1* mRNA [186]. Furthermore, *BECN1* deficiency strongly activates WNT1 and NF-κB in some cancer cells [175,187]. Interestingly, *BECN1* knockdown inhibits

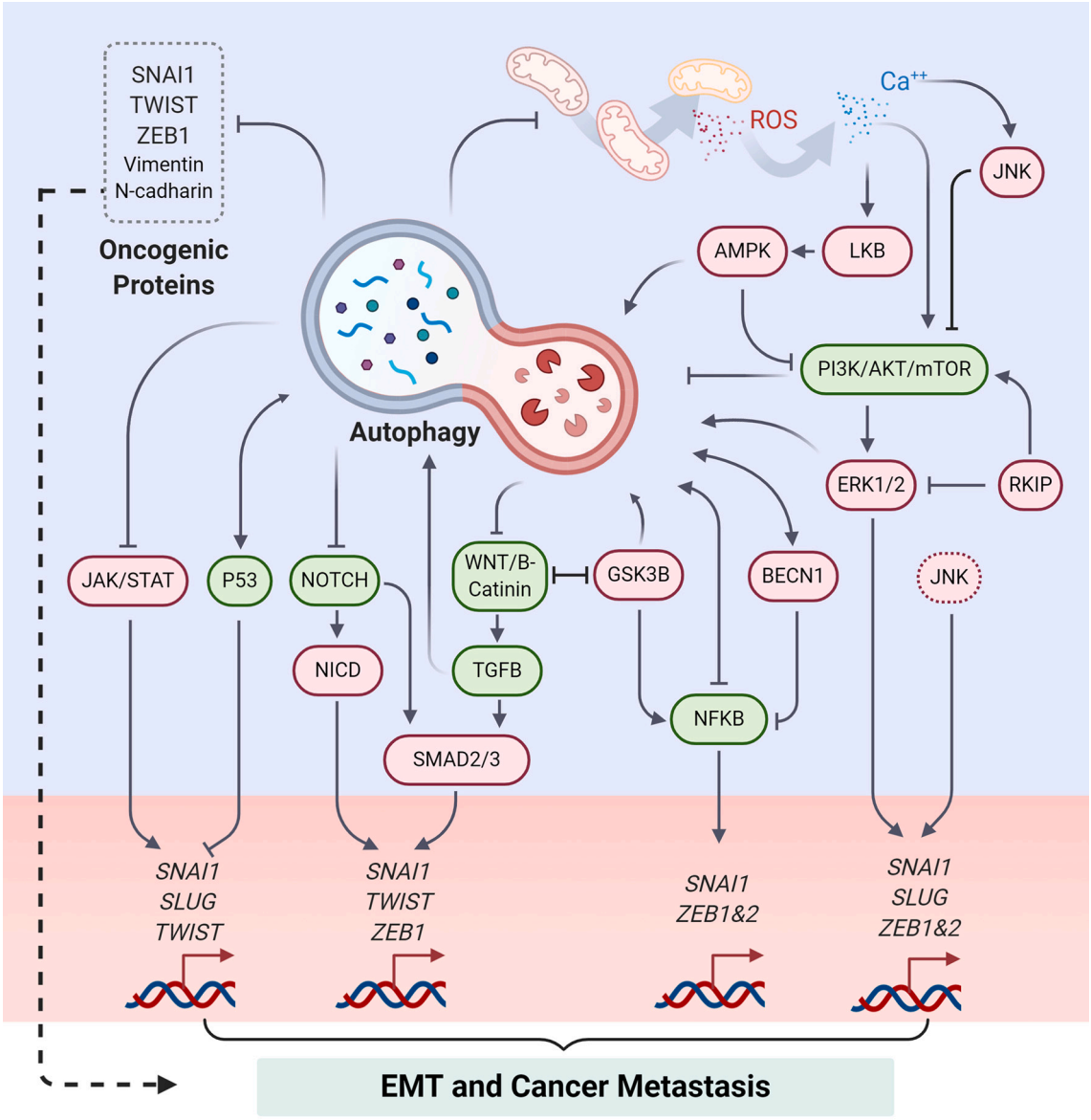

Fig. 4. The crosstalk between autophagy and cancer-associated signaling pathways in cancer. During cancer progression (EMT and cancer metastasis), many signaling pathways are functionally connected during the inhibition or activation of autophagy. Activation and inhibition of proteins or pathways is indicated by arrows and bar-heads, respectively. Created with BioRender.com.

rapamycin-induced autophagy, and suppresses EMT and invasion via downregulation of Vimentin and TWIST proteins and upregulation of E-cadherin in colon cancer [188]. These studies suggest that BECN1 is essential in the interaction between autophagy and regulation of cancer progression, indicating an effective strategy for the development of anti-cancer drugs in the future.

5.3. *p53 signaling pathway*

p53, a well-known cancer suppressor, is highly activated upon DNA damage. It plays an essential role in controlling cell cycle and programmed cell death following DNA damage [189–191]. It also regulates autophagy by stimulating the expression of specific ATGs [176–180,191–193]. In addition, p53 inhibits the PI3K/AKT/MTORC1 pathway and consequently decreases the expression of cancer proteins such as ZEB1, ZEB2, or SNAI1. As a result, it suppresses EMT and cancer metastasis [201–203]. Interestingly, in *p53*-mutant cancer cells, the increase of EMT and mitochondrial fission also promotes autophagy [194,195]. suggesting that dysfunction of specific intracellular pathways induces autophagy in the absence of p53 activity.

p53 regulates autophagy in a location-dependent and context dependent manner [176–180,191–193]. The cytoplasmic p53 generally inhibits autophagy although the specific mechanism of inhibition still remains to be elucidated. Conversely, the nuclear p53 promotes autophagy by downregulating the PI3K/AKT/mTOR signal pathway via direction interaction with PTEN [176–180,191–193]. Additionally, the nuclear p53 enhances the expression of several autophagy-related genes including *ATG7, ATG4, ATG10* and *ULK1/2*. Moreover, the increased autophagy dramatically contributes to p53-dependent apoptosis and cancer suppression but promotes cancer in cells with impaired p53 [196,197]. Besides, p53 suppresses the expression of oncogenes (e.g., *SNAI1, ZEB1* and *ZEB2*) by modulating the microRNAs in the nucleus [198,199]. Furthermore, inactivation of the *p53* gene largely upregulates the expression of *SNAI1, ZEB1* and *ZEB2* genes via mir-200a or miR130b [200–202]. However autophagy also dually regulated p53 in a context dependent manner [203,204]. These reports suggest that p53 is

a key mediator linking oncogenic signals to autophagy during the cancer progression.

5.4. NOTCH signaling pathway

The NOTCH signaling mechanism involves a variety of cellular events such as cell differentiation, development, and cancer progression via interaction with other signaling pathways. Activation of the NOTCH signal strongly induces the expression of several proteins involved in EMT and resistance to apoptosis by inhibiting p53 during tumorigenesis [205–209]. The NOTCH signaling is initiated by the binding of Notch to Deltex, which is located on the membrane of neighbouring, followed by subsequent cleavage via metalloproteinases (ADAM17 or ADAM10) and presenilin-dependent gamma secretase complex (S1, S2, S3 and S4), resulting in synthesis of NOTCH intracellular domain (NICD) in cytosol [206]. The nuclear translocation of NICD leads to transcriptional activation of target genes including *$p27^{cip1/waf1}$, SNAI1, VEGF, AKT, mTOR, NF-κB, c-Myc* and *cyclins* [205–209]. The NOTCH signal interacts with multiple oncogenic proteins such as platelet-derived growth factor (PDGF), SNAI1, hedgehog, WNT, AKT, mTOR, RAS, NF-κB, and sonic hedgehog (Shh). Furthermore, NOTCH signaling is associated with EMT under hypoxia, resulting in increased tumor aggressiveness. Therefore, cancer patients with a high level of NOTCH-1 expression generally show poor prognosis.

Autophagy is also linked to NOTCH signaling. Upon activation of autophagy, the signal is significantly inhibited via degradation of intracellular NICD. Indeed, impaired autophagy inhibits cell differentiation and often leads to hematological malignancies and neurological disorders [210–214] In addition, activation of autophagy in cancer cells interferes with cancer progression by regulating the intracellular level of NICD (our unpublished data). These results indicate the functional connection between autophagy and NOTCH signal (Fig. 4), control of which represents a strong strategy for the development of new drugs against hematological diseases or cancers.

5.5. WNT signaling pathway

The WNT pathway consists of classical and non-classical signals, which are crucial for control of EMT and other cellular processes. In the non-classical WNT pathway, two WNT proteins WNT51 and WNT11 promote EMT via decreased p38 (MAPK14) phosphorylation in tumorigenesis [215]. In the classical pathway (a typical WNT pathway), the WNT/β-catenin directly stimulates HIF-1α–induced EMT via downregulation of E-cadherin and transformation of actin cytoskeleton. This WNT/β-catenin-dependent EMT requires TWIST activation and upregulation of SNAI1 and SLUG [216,217]. Further, the EGF-induced EMT depends on the repression of E-cadherin and activation of SNAI1, SLUG and TWIST [218]. The WNT signaling is also connected with PI3K/AKT and TGF-β pathways during cancer progression [219–222].

In some cancer cells, autophagy suppresses cancer by inhibiting WNT pathway and specifically degrading TWIST1 and SNAI1 [129–132]. Indeed, autophagy inhibition stabilizes TWIST1 via accumulation of p62/SQSTM1 proteins, leading to EMT in cancers. Since TWIST1 and SNAI1 are downstream regulators of p62, the inhibition of autophagy stabilizes TWIST1 and SNAI1, and is suggested as a promising therapeutic strategy against cancer [129–136]. Disheveled (Dvl), which is a core component of the WNT signaling pathway, plays a critical role in both β-catenin–mediated canonical and β-catenin–independent noncanonical WNT signaling pathways [223]. Interestingly, autophagy negatively regulates the stability of Dvl in the late stages of cancer development [224,225]. Furthermore, autophagy accelerates Dvl2 degradation and induction of Dapper1, a WNT antagonist, resulting in the inhibition of the WNT pathway [226]. The autophagy-dependent Dvl2 degradation is mediated by GABA receptor–associated protein like 1 (GABARAPL1), which interacts with p62 [227,228]. In conclusion, the WNT signaling mechanism operates in conjunction with autophagy (Fig. 4), which provides insight into EMT and cancer metastasis.

5.6. NF-κB signaling pathway

The NF-κB pathway is associated with inflammatory response and other cellular processes including EMT and metastasis in cancer. In fact, activation of NF-κB tends to increase the aggressiveness and the metastatic potential of many cancers [229,230]. NF-κB is a transcription factor, which directly promotes the expression of cancer genes such as SLUG, SNAI1, TWIST1 and SIP1, which are associated with aggressive cancer phenotype [230]. Many other factors stimulate EMT and cancer metastasis by activating the NF-κB signal. For example, TLR4-induced NF-κB signaling induces EMT in renal tubular epithelial cells in the presence of uric acid [231]. Furthermore, MMP-3 activates NF-κB via direct binding with p65 and cRel subunits, which induces EMT by increasing SNAI1 expression [232]. Lastly, the expression of tumor necrosis factor–α (TNF-α) and the subsequent GSK3β activation promotes NF-κB signaling and increases the stability of SNAI1 protein, which is required for cancer progression [233].

The NF-κB signal and autophagy regulate each other in a context-dependent manner. In some cases, NF-κB inhibits autophagy by downregulating BECN1 expression in metastatic cancer cells [234]. Conversely, autophagy can suppress NF-κB signaling by downregulating the expression of MMPs in hepatocarcinoma cells, inhibiting EMT and cancer metastasis [235]. In cancer cells, ROS stimulates NF-κB–dependent autophagy, which triggers cell transformation and drug resistance during cancer development [233,236]. Indeed, this NF-κB–dependent autophagy inhibition enhances brazilin-induced apoptosis in head and neck squamous cell carcinoma. By contrast, autophagy activation suppresses ROS-induced NF-κB signaling via downregulation of MMP-2 and MMP-9 expression, resulting in EMT inhibition [235–237]. Thus, autophagy activators or inhibitors can be selectively used to regulate NF-κB signaling, which is functionally correlated with cancer progression (Fig. 4).

5.7. TGF-β signaling pathway

TGF-β is secreted by cancer cells and stromal fibroblasts in the cancer microenvironment. It is a primary inducer of EMT and cancer metastasis via control of SNAI1 expression, and it functionally coordinates with Wnt/β-catenin signaling [238]. The TGF-β pathway is regulated by either Smad or non-Smad signals. In general, TGF-β binding to its receptor activates the nuclear translocation of Smad3/4, followed by the formation of a transcriptional complex with other nuclear transcription factors (e.g., TFE3) to activate the expression of target genes including plasminogen activator inhibitor 1 (PAI1). This Smad-dependent TGF-β signal plays a significant role in regulating the morphological and functional phenotypes in epithelial cells and M2 macrophages [239,240]. Furthermore, TGF-β signal acts synergistically with factors such Ras, STAT3 and β-catenin to induce EMT and cancer metastasis via SNAI1 expression in the absence of Smad signal (Fig. 4) [241,242]. The TGF-β1-induced EMT process is also stimulated by miR-23a, which downregulates the expression of E-cadherin (CDH1) and activates the Wnt/β-catenin signaling in breast cancer cells [243].

Although TGF-β1 is the most effective factor in driving EMT, its effects on the occurrence and development of cancer depend on cell type and environment [244]. First, the TGF-β1 signal stimulates autophagy to promote invasive phenotype in human carcinoma, which is effectively inhibited by treatment with autophagy inhibitors [245,246]. In addition, the TGF-β signal stimulates autophagy by stimulating the expression of autophagy-related genes, such as *ATG7, ATG5* and BECN1 [247,248]. Furthermore, autophagy also promotes TGF-β1-dependent EMT in hepatocarcinoma by triggering the cAMP/PKA/CREB signaling, during the autophagy-dependent degradation of phosphodiesterase 4A (PDE4A) [249].

5.8. Other signaling pathways

Many other signal transduction pathways involved in cancer progression are also functionally connected with autophagy. First, the JAK/STAT signaling pathway mediates several cancer phenomena including cell invasion, migration, survival, metastasis, proliferation, immunity, and inflammation. For example, activation of JAK/STAT signaling by IL-6 upregulates the expression of MMP-2 and SNAI1 and thereby stimulates the proliferation of cancer cells and metastasis in human malignancies [250,251]. Also, treatment with JAK/STAT inhibitors such as WP1006 and ovatodiolide induces apoptosis in cancers, which eventually prevents EMT and cancer metastasis [252,253]. Interestingly, the activation of autophagy by chemical compounds including resveratol and quercetin inhibits JAK/STAT signaling, resulting in the inhibition of cancer progression [254–256]. Hence, autophagy-dependent suppression of JAK/STAT signaling by these compounds can be used to modulate EMT and cancer metastasis.

Second, integrin-mediated signaling pathways also play a key role in regulating cancer progression by modifying the cancer microenvironment. Signaling by epidermal growth factor (EGF) and TGF-β1 leads to the activation of focal adhesion kinase (FAK) and β-catenin promotes cancer progression via downregulation of E-cadherin [257–260]. Furthermore, ILK, a downstream regulator of TGF-β, also enhances EMT and cancer metastasis by activating WNT/ β-catenin pathway [261]. Interestingly, the activation of integrin-mediated FAK-SRC pathway and ILK inhibits autophagy, resulting in EMT and metastasis during the cancer development [262]. By contrast, autophagy also increases EMT by stimulating β-catenin and Smad signaling in some cancer cells [261], suggesting that autophagy in cancer depends on cancer type or stage.

Energy production in mitochondria is key to cancer progression. In particular, autophagy controls mitochondrial homeostasis when cancer cells encounter mitochondrial damage under metabolic stress. In fact, autophagy-dependent degradation of these damaged mitochondria provides a source of energy for cancer cell survival [263]. Furthermore, autophagy enhances mitochondrial fusion and reconstitution of mitochondrial network, which reduces mitochondrial fragmentation and subsequently inhibits cancer cell migration and EMT [264]. Indeed, B-cell lymphoma 2 (BCL-2) interacting protein 3 (BNIP3) induces mitochondrial fission and stimulates autophagy-dependent mitochondrial turnover in melanoma cells. The direct binding of BNIP3 to mitochondria via LC3 during mitophagy maintains the cellular architecture and cytoskeletal polymerization during cancer progression [265]. Also, the interaction between BNIP3 and CDH6 induces dynamin-related protein 1 (DRP1)-mediated mitochondrial fission and subsequent inhibition of autophagy leads to EMT [264].

6. Functions of autophagy in the tumor microenvironment and immunity

In the tumor microenvironment, tumor cells functionally associate with residential normal cells such as cancer-associated fibroblasts (CAFs), stromal cells and immune cells to overcome the environmental burden derived from the inflammatory, hypoxic, immunosuppressive, and metabolic stressors. The communication between tumor and residential cells stimulates cancer growth and migration and consequently leads to tumor malignancy [266,267]. The autophagy process plays a context-dependent role in the tumor microenvironment to promote the survival or death of tumor cells in response to the environmental stressors. Diverse adaptive and innate immune cells assist both pro-and anti-tumorigenic functions via modulating of autophagy [268,269]. Autophagy balances the biological functions of immune cells in the tumor microenvironment. Depending on the properties of the tumor type, autophagy can activate or suppress the immune response in the tumor microenvironment, leading to a protective effect or immune evasion, respectively [270–272].

Effective antitumor immune responses depend on the presentation of tumor antigens and the recruitment of lymphocytes ($CD4^+$ and $CD8^+$ T cells). In fact, autophagy involves in antigen processing and presentation on the MHC class I and class II molecules, and the lymphocyte development necessary for the immune response [272–274]. The cytosolic tumor antigens are degraded by autophagy and subsequently associated with MHC molecules on the cell surface. Indeed, this antigen processing and presentation via MHC-II is significantly stimulated upon induction of autophagy [275]. Autophagy, however, could disrupt and decrease the efficiency of antigen presentation by degrading MHC-I [276] and degrade tumor-associated antigens (TAA) [277] in autophagy-lysosomal pathway. Yi Wang *et. al* showed that treatment of autophagy activator conjugated to antigens triggers immune responses such as antigen cross-presentation and increases infiltrated $CD8^+$ T lymphocytes [274]. Also, genetic ablation of autophagy-related gene 5 (*ATG5*) in dendritic cells impairs antigen presentation on MHC class II, and rather increases expression of CD36, consequently leading to CD36-dependent phagocytosis [278]. In addition, autophagy has an important role in T cell development and T cell-mediated immune responses. $CD8^+$ T cells with low expression of CD57 (a senescence marker) exhibit an increased autophagic activity compared to senescent cells [279]. Similarly, the transcriptional and functional levels of autophagy genes are dramatically reduced in the T cells of old mice [280]. The function of *Atg5* gene is absolutely required for the T lymphocyte survival and proliferation [281]. Furthermore, autophagy deficiency impairs the development of $CD8^+$ T memory and B cells [282,283], indicating that autophagy is essential for the development of T and B cells by maintaining cellular energy homeostasis (Fig. 5).

In the tumor microenvironment, tumor evasion from anti-cancer immunity is an essential process for the tumor cell survival [284]. The persistent hypoxia often increases the survival potential and aggressive growth of cancer cells. Autophagy promotes the selective degradation of the cytotoxic NK-derived granzyme B (GZMB) in the hypoxic condition, which leads to the evasion of tumor cells from NK-mediated killing [285,286]. Also, activation of autophagy in the tumor microenvironment often maintains an immunosuppressive state and prevents the infiltration of cytotoxic immune cells into tumor tissue [287,288]. Autophagy additionally associates with other immunosuppressive cells enriched in the tumor microenvironment such as regulatory T (T_{reg}) cells, and indeed promotes the secretion of competing cytokines with effector T cells for immunosuppression [289,290]. T_{reg} cells with defective *Atg5* or *Atg7* genes show insufficient self-tolerance and impaired lineage stability by inducing apoptotic signals [289]. Additionally, autophagy triggers the polarization of tumor-associated macrophages (TAMs), a promising strategy to establish an immunesuppressive microenvironment [291,292]. M2 macrophages support immune escape, angiogenesis, and tumor growth by secreting cytokines (such as IL-4), and autophagy inhibition with chloroquine enhances the anti-tumor responses by resetting TAMs from M2 to M1 type (Fig. 5) [293,294]. These findings suggest that autophagy is a critical factor in regulating cancer cell survival in the tumor microenvironment, depending on the context. Autophagy supports either an anti-tumor effect via activation of the immune system or tumor evasion from immune attack.

7. Regulation of oncogenic proteins by selective autophagy in cancer

Selective autophagy plays a critical role in modulating tumorigenesis and cancer progression, and it is an important target for developing new cancer therapies. Contrary to the general non-selective autophagy, selective autophagy discriminately removes cellular components, including organelles, proteins, and nucleic acids in certain conditions. Recently, several selective types of autophagy have been suggested such as xenophagy (bacteria-selective), lipophagy (lipids-selective), mitophagy (mitochondria-selective), ribophagy (ribosome-selective), reticulophagy (ER-selective), RNAphagy (RNA-selective), ferrtinophagy

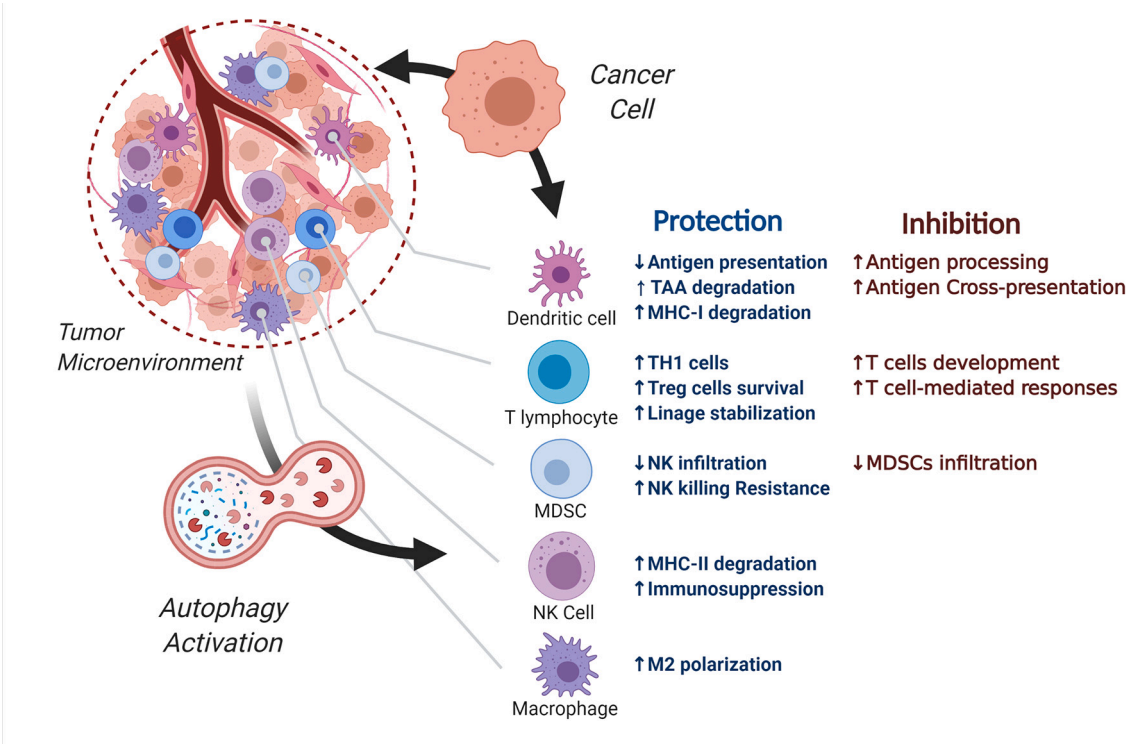

Fig. 5. Autophagy functions in immune responses between cancer and normal residential cells in tumor microenvironment. Autophagy activation in tumor microenvironment influences the residential cells (dendritic cell, T lymphocyte, myeloid-derived suppressor cell (MDSC), natural killer (NK) cell, and macrophage) through either increase (up arrow) or decrease (down arrow) of their cellular functions, consequently resulting in tumor protection or inhibition via their functional interactions with cancer cells. Created with BioRender.com.

(ferritin-selective) and others [295]. In addition, proteins that are involved in tumorigenesis can be selectively degraded by autophagy via specific interaction with autophagy receptors (e.g., SQSTM1/p62, neighbor of BRCA1 gene 1 (NBR1)). Indeed, the selective regulation of oncogenic proteins such as NICD, SNAI1, or MHC1 inhibits cancer growth and metastasis.

As discussed earlier, NOTCH signaling is a key pathway to regulate cancer progression. In particular, this signaling pathway is a major therapeutic target in various cancers, including lung, colorectal, liver, stomach, and etc [296–298]. However, targeting NOTCH signaling in these cancer cells faces difficulties due to the different characteristics of cancers and tumor microenvironments. Upon activation of NOTCH signaling, it produces the transcriptional regulator NICD, which in turn transcriptionally activates many downstream target genes that take part in EMT and cancer metastasis. Therefore, the selective degradation of the NICD protein by p62-mediated autophagy could be essential during cancer progression [299].

Major histocompatibility complex class I (MHC1), human leukocyte antigen, on the surface of cancer cells is a key factor in determining cancer evasion of the immune response. Thus, the regulatory mechanism of the MHC1 intracellular level could be a therapeutic target for cancer treatment. According to a recent article, autophagy selectively inhibits the MHC1 level in cancer through the receptor NBR1. Inhibition of autophagy with chloroquine restores of surface MHC1 level in cancer cells and consequently promotes the anti-tumor activity of $CD8^+$ T cells [276]. Similarly, genetic or pharmacological ablation of autophagy augments the surface level of MHC1 in cancer cells impeding immune evasion. In addition to the selective degradation of MHC1, NBR1 also acts as an autophagy receptor for the selective degradation of Kinesin super family 23 (KIF23) and Centrosome protein 55 (CEP55). These mitotic proteins are essential for cancer progression, and their high expression in cancers are closely associated with a poor prognosis [300,301]. In fact, NBR1-dependent autophagic degradation of KIF23 and CEP55 causes defective growth of cancer cells [302]. Also, perturbing the *NBR1* gene causes intracellular accumulation of these proteins and stimulates cancer progression due to the defect of selective autophagy [303].

Autophagy also plays an important role in the regulation of cellular iron in cancer cells through the selective degradation of ferritin, an iron-binding and storage protein. Once ferritins are degraded by autophagy in cancer cells, an increase of free irons causes non-apoptotic cell death or ferroptosis [304]. Nuclear receptor coactivator 4 (NCOA4) acts as an autophagy receptor for ferritin degradation during erastin-induced ferroptosis [305]. This is an example of several known oncogenic proteins that are specifically regulated by autophagy. Modulating selective autophagy through the novel autophagy receptors constitute an attractive strategy for cancer therapy. In particular, linking selective autophagy to the oncogenic signaling pathways could produce meaningful changes in the development cancer. Fig. 6 depicts a schematic of the degradation of oncogenic proteins by selective autophagy.

Reactive oxygen species generated in hypoxia during cancer progression activates the HIF-1α pathway. This activation enhances the survival of cancer cells by stimulating aerobic glycolysis and promotes the transition toward malignant phenotype. Also, ROS activate autophagy to control the expression of proteins such as HIF-1α and Keap1 in response to hypoxia [232,234,237,306]. Additionally, autophagy regulates the stability of other oncogenic proteins. In particular, autophagy inhibition via ATG3, ATG5 ATG7, ATG9, ATG712 or Beclin-1 silencing enhances the EMT by stabilizing intracellular SNAI1 and SLUG proteins in cancer cells. Treatment with autophagy activators significantly decreased cancer cell migration, invasion, and metastasis [307]. Death effector domain-containing DNA-binding protein (DEDD) activates autophagy via direct interaction with the class III PI3 kinase (PI3KC3)/Beclin-1, thereby promoting the degradation of SNAI1 and TWIST proteins, resulting in the inhibition of EMT and cancer metastasis in specific cancer cells [129–132]. In particular, SNAI1 proteins physically

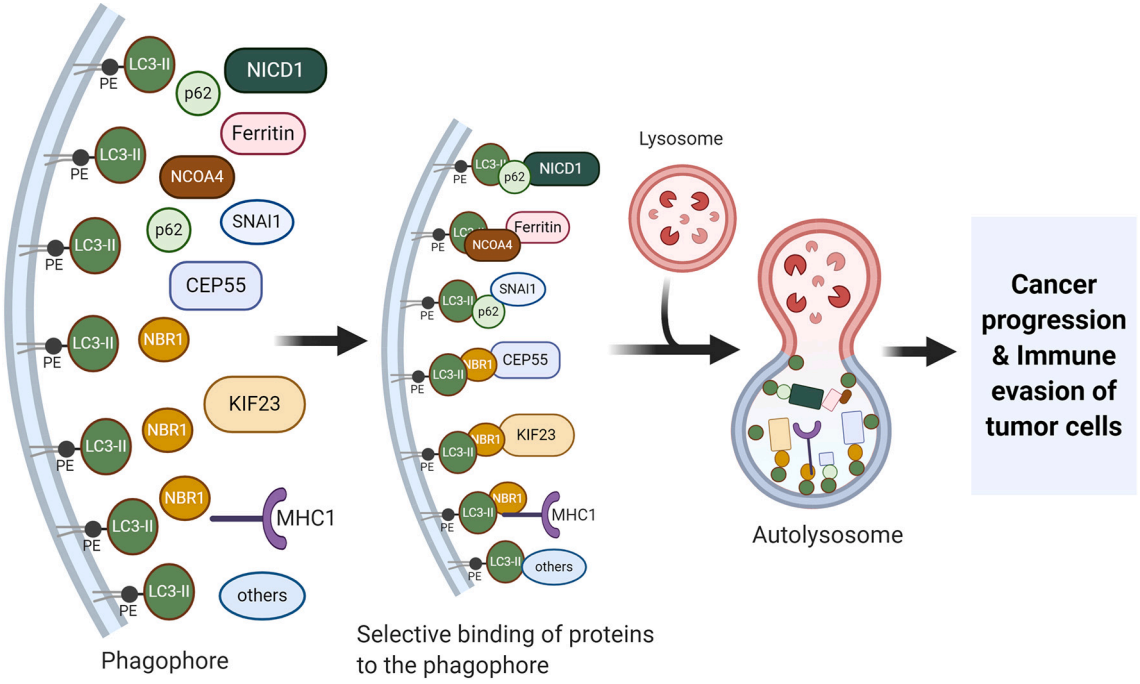

Fig. 6. A schematic illustration of degradation of oncogenic proteins by selective autophagy. LC3 is conjugated with phodphatidylethanolamine (PE) and anchored into the phagophore membrane. The oncogenic proteins (e.g., SNAI1, NICD, CEP55, KIF23, MHC1, ferritin) are selectively bound to the anchored LC3 through their specific autophagy receptors (e.g., p62, NBR1, NCOA4) within autophagosome, subsequently degraded by proteases after fusion with the lysosome. Created with BioRender.com.

associate with LC3 and SQSTM1/p62, and are selectively sequestered into autophagosomes; their intracellular levels are plummet upon activation of autophagy such as starvation or ATG7 knockdown [132]. In addition, NICD, an essential transcription factor in the regulation of tumorigenesis, is specifically degraded by autophagy (unpublished data). Accordingly, autophagy plays a pro-survival role in cancer patients by inhibiting EMT via the regulation of key oncogenic proteins. Autophagy activators represent potential therapeutic agents despite the observations showing that autophagy promotes cancer cell survival under the metabolically challenging environment. The role of autophagy in tumorigenesis likely depends on cell type and the stage of cancer [95–102].

8. Targeting autophagy and EMT for cancer therapy

Amaravadi et al. reviewed the recent advances in targeting autophagy for cancer therapy [7]. Here, we briefly describe the molecular mechanisms common to the drug's action. Besides, Table 1 lists several autophagy-related drugs that are most promising in preclinical studies. More importantly, the review identified three tendencies among these studies. First, most are targeting advanced cancer. Second, the drugs target bulk autophagy rather than selective forms of autophagy. Third, the focus of these drugs is the upstream parts of the autophagy pathway. Targeting epithelial-mesenchymal transition, by contrast, means that cancer can be inhibited earlier. Therefore, studying therapeutics that inhibit EMT through autophagy holds the promise to not only reduce the tumor growth but do it early in the course of the disease.

Autophagy inhibitors as adjuvants is the most tried strategy of targeting autophagy in cancer. Several studies used autophagy to potentiate established cancer drugs, sensitize cancer cells to their effect, or reduce resistance to others (Fig. 7A). Chloroquine, hydroxychloroquine and VPS34-IN1 were found to favor apoptosis when used with quercetin, lidamycin, bevacizumab, GDC-0941, or everolimus in different cancer types [308–312]. Other autophagy inhibitors such as 3-methyladenine, resveratrol, and nelfinavir stimulated cancer cell death when used alone [313]. Three small molecules equivalently resulted in cell death by inhibiting ULK1 upstream of autophagy [314–320]. Same chloroquine compounds in addition to bafilomycin A1 and metformin sensitized cancer cells to drug action and chemotherapy [321–323]. A similar effect was achieved by several potent chloroquine derivatives [324–327]. Finally, autophagy inhibitors, notably chloroquine derivatives, reduced resistance to cancer drugs [328]. By contrast, leveraging autophagy to inhibit EMT is independent of the above and takes place earlier in cancer development, which we discuss next.

Metformin was found to arrest cancer cells' cell cycle, reduce their proliferation, and increase their death rate. This effect was accompanied by the inhibition of mTOR and subsequent induction of autophagy. Inhibiting autophagy by silencing *ATG7*, bafilomycin A1 or wortmannin treatment reduced that effect of Metformin [323,329,330]. More recently, Cathelicidin and Nafarine treatment also triggered autophagic cell death; an effect that was reduced by blocking autophagy [331–334]. Resveratrol can also block the activation of mTOR or accelerate the degradation of p62 to induce autophagy and promotes apoptosis in cancer cells. Tian and colleagues reviewed the recent observations in that regard [335]. Although Resveratrol and Nelfinavir themselves induce autophagy, inhibiting autophagy increases the drug cytotoxicity in some studies [336,337]. Quinacrine is an antimalarial drug similar to Chloroquine but they don't share the property of inhibiting autophagy. Among other ways, this drug inhibited cancer cell cycle and growth through the induction of autophagy [338,339].

Autophagy degrades key transcription factors of EMT in transitioning cells. Therefore, active autophagy might reduce the transition to mesenchymal phenotype, migration, and invasion of cancer cells [136]. Autophagy induction by starvation and chemical compounds resulted in down-regulated SNAI1 and SLUG and their downstream EMT proteins in glioblastoma cells. Silencing *BECN1* had the opposite effect on cell motility. Another study found that overexpressing death effector domain-containing (DEDD) promoted SNAI1 and TWIST degradation through PI3K and inhibited EMT [129]. Recent work from our laboratory showed that mesenchymal and metastatic protein levels decreased

Table 1
Autophagy regulators as cancer therapeutics.

Chemical	Function	Cancer types	Ref.
Chloroquine	Inhibit SNAI1 degradation	Cervical, Lung	[132]
	Inhibit PKA via PDE4A	Hepatocarcinoma	[249]
	Promote ROS/HO-1	Ovarian	[306]
	Sensitize cells for chemotherapy	Breast, colon	[312]
	Normalize tumor vessels	Endothelial	[340]
	Enhance HDACi pro-apoptosis	MPNST	[341]
	Potentiate 5-FU apoptosis	Colon	[342]
	Augment quercetin-induced aptoptosis	Gastric	[311]
	Potentiate lidamycin-induced aptoptosis	Non-small cell lung cancer	[310]
	Enhance VNP20009 targeting	Melanoma	[343]
	Inhibit autophagosome-lysosome fusion	Breast, Cervical, Osteosarcoma	[55,321]
Hydroxychloroquine	Potentiating bevacizumab-induced apoptosis	Glioblastoma	[309]
	Increasing everolimus-induced cytotoxicity	Renal	[312]
	Block lysosome acidification, Increase chemotherapy sensitivity, Inhibit autophagosome-lysosome fusion	Pancreatic	[344]
Chloroquine, Hydroxychloroquine	Augemnt cell drug-resistance	Renal	[328]
Rapamycin	Inhibit disshevelled degradation	Colon	[345]
	Downregulate SNAI1 and SLUG	Glioblastoma	[136]
Everolimus	Inhibit mTOR	Renal	[312]
Hydroxychloroquine, Rapamycin	Reverse drug-resistance	Prostate, Bladder	[309,346]
Chloroquine, Bafilomycin A1	Sensitize apopotosis via FOXO3a turnover	Colorectal	[347]
Bafilomycin A1	Block HIF1A degradation via Q6, Block vacular-type H(+)-ATPase, Inhibit PI3K	Hepatocarcinoma	[322,348,349]
3-methyladenine, Chloroquine	Stimulate apoptosis	Pancreatic	[313]
AICAR*	Compromise Oleanolic acid-induced aptoptosis	Bladder	[350]
	Activating AMPK	Leukemia, Hepatocarcinoma	[351,352]
Metformin	Enhance drug-response	Glioma	[323]
	Inhibit Smad2/3 phosphorylation	Lung	[172]
	Activate AMPK, Increase everolimus-induced cytotoxicity	Colorectal	[329]
	Chemopreventive, Decrease turmorigenesis	Skin	[330,353]
Doxycycline	Inhibit cancer stem cells	Breast	[354]
	Inhibit autophagy	Pancreatic	[355]
Resveratrol	Stimulate apoptosis	Melanoma	[336]
	Increase chemotherapy sensitivity, Inhibit mTOR		[335]
Arsenic trioxide	Downregulate Survivin	Glioma	[356]
Nelfinavir	Stimulate apoptosis	Breast	[337]
Quinacrine	Downregulate p62-Skp2	Ovarian, Adenocarcinoma, Breast, Colorectal, NSCLC	[338,339]
VPS34-IN1	Promote cell death in synergy with GDC-0941	Leukemia	[308]
SBI-0206965, MRT67307, MRT68921	Trigger ULK1-modulated cell death	Renal cell carcinoma, Kidney, neuroblastoma, Lung, Breast cancer cell	[314–320]
Lys01-05	Sensitize cells to radiation, Deacidify the lysosomes	Glioblastoma, lung, Melanoma	[324–327]
Cathelicidin	Trigger autophagic cell death via AMPK	Pancreatic, Colon	[331,332]
Nafarine	Trigger autophagic cell death	Lung, Colon	[333,334]
Plasma-activated medium	Trigger autophagic cell death	Bladder, Pancreatic, melanoma	[357–359]

under starvation conditions [132]. In these lung and cervical cancer cell lines, SNAI1 was associated with LC3 and was degraded by autophagy. Fig. 7B shows a diagram of the mechanism by which autophagy reduces EMT proteins.

Studies suggested alternative explanations to the effects of targeting autophagy for cancer therapy. Studies showed that the anti-cancer effect of chloroquine and its derivatives is independent of autophagy. The sensitizing effect of chloroquine on breast cancer cells was not replicated by inhibiting autophagy by knocking down *ATG12* or *BECN1* [321]. Similarly, autophagy inhibition failed to reproduce the effect of chloroquine on vessel normalization in cancer cells [340]. As for autophagy involvement in EMT, others showed that autophagy promotes EMT. Autophagy induced transforming growth factor B (TGFB)-dependent EMT and produced more invasive hepatocarcinoma cells [249]. Metformin was found to inhibit this effect through AMPK and the phosphorylation of the downstream factor SMAD2/3 [172].

Based on ClinicalTrials.Gov, a number of modulators targeting autophagy in cancer are under investigation for clinical trials (Table 2). In particular, hydroxychloroquine (HCQ), a less toxic derivative of chloroquine (CQ) that inhibits autophagy by preventing lysosomal acidification, is widely studied in a variety of solid and blood tumors [97,360,361]. Since HCQ sensitizes cancer cells treated with chemotherapy or radiotherapy, the combination therapy of HCQ with anti-cancer agents is advantageous in patients with different cancers (Table 2). In breast cancer, palbociclib, a CDK4/6 inhibitor, effectively blocks cancer cell growth in patients treated with HCQ. Ixabepilone, which induces cell death through stabilizing microtubules, shows a similar effect when combined with HCQ [362]. In addition, termsirolimus, sorafenib, capecitabine, gemcitabine, vorinostat, and other drugs are used in combination with HCQ for treating a variety of solid tumors [363–366]. By contrast, mTOR inhibitors such as rapamycin and its analogs, which activate autophagy, are also investigated as anti-cancer drugs. For instance, everolimus is effective in patients with leukemia and hepatocellular carcinoma. Further, the combination with other chemotherapies such as alemtuzumab, and panobinostat greatly sensitizes cancer cells to chemotherapy and radiotherapy [367–369]. Although using autophagy modulators as adjuvants for anti-cancer drugs is likely beneficial, it is only effective in limited cases due to the cancer heterogeneity. Taken together, selective drugs and interventions targeting autophagy could be critical for developing precise therapies in patients because autophagy regulation is generally cell stage- or type-specific.

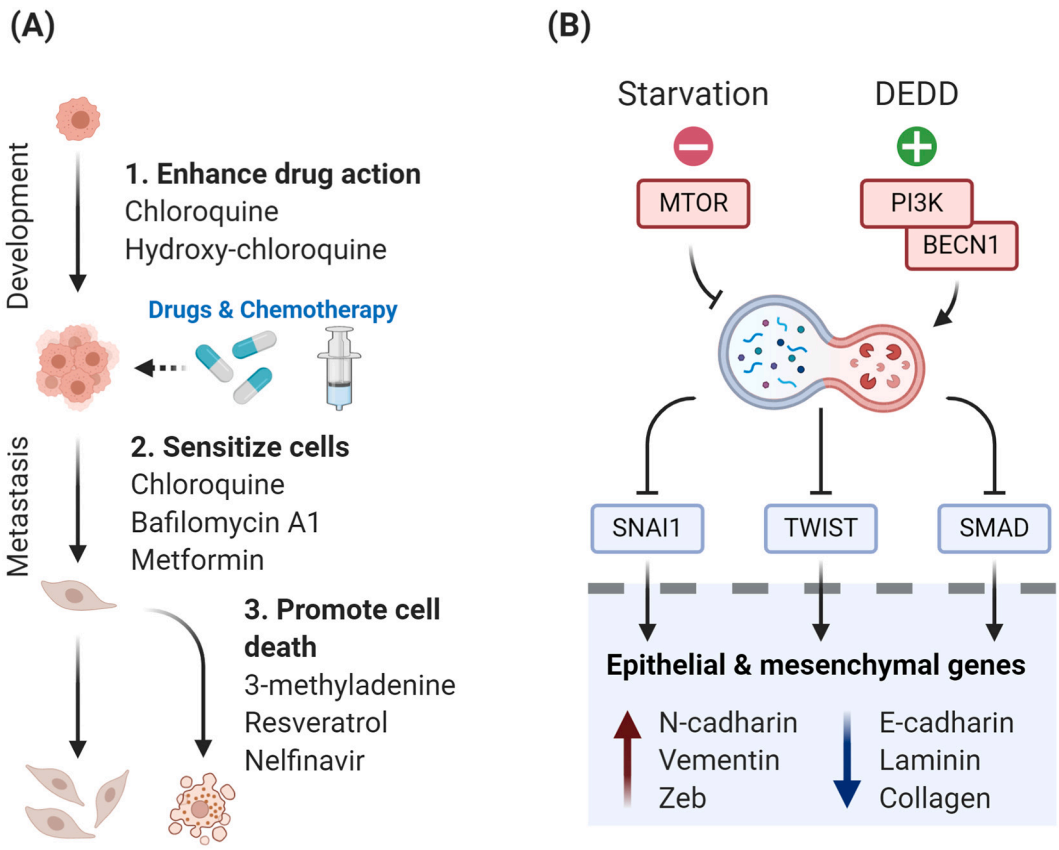

Fig. 7. Strategies for targeting autophagy in cancer therapy. A) Autophagy inhibitors work as adjuvants by enhancing the drug actions, sensitizing cancer cells to the drug effects, reducing resistance, or promoting cancer cell death. B) Autophagy induction by starvation or overexpression of death effector domain-containing (DEDD) induce autophagy, which degrades epithelial-mesenchymal transition (EMT) transcription factors and favors the expression of epithelial proteins. Created with BioRender.com.

9. Concluding remarks and future directions

This manuscript outlines the links between autophagy and cancer and how autophagy could be leveraged for developing cancer therapeutics. We started by introducing the general machinery of and regulation of autophagy to contrast it to the modification in the context of cancer. Next, we discussed the emerging picture of the dual nature of autophagy in cancer. Although by means comprehensive, it represents an appropriate introduction to the interested. We added a particular emphasis on the role of autophagy in EMT as the first step in cancer progression. We summarized the body of work on the different signaling pathways that link autophagy to EMT in transitioning cancer cells. Finally, we examined the literature on pre-clinical and clinical studies on modifying autophagy during cancer treatment. Throughout, we took liberty in conjecturing observations in the early stage and speculating on the directions of this work. In the following paragraphs, we recapitulate several points that we hope would provide insights into the massive amount of work on the topic and direct future research.

Autophagy removes damaged intracellular organelles and recycles them to build other components or generate energy. Beyond a certain point, as cells are irreparably damaged, autophagy triggers cell death. In normal cells, these functions are cytoprotective and, in the least, helps maintain the integrity of the tissue or organs by removing damaged cells. The broad span of functions lends itself to speculations about how autophagy contributes to cancer development and progression. Indeed, in the context of cancer, the same cytoprotective functions of autophagy can be harmful to the body. For instance, autophagy maintains the inside of the cell by removing damaged parts, which could help the cancerous cell divide indefinitely. Similarly, autophagy could provide energy for metabolically demanding processes such as the transitioning of cancer cells to more aggressive or metastatic forms.

Autophagy is linked to several key signaling pathways in the cell. These pathways help autophagy respond to the outside environment as well as the changes in the inside state of the cell. Several of these pathways are hijacked in cancer cells to gain independence from the outside signaling and direct the cell energy to unlimited growth. The autophagy triggered apoptosis is one example of a signaling pathway that is amenable to modifications in cancer since cancer cells can evade it continuously. Changes in metabolism in cancer cells are also a suspect for involving autophagy, which is tightly linked to the availability of nutrients. These pathways and others are among the apparent targets for modification in cancer development and therapy.

Autophagy inhibitors are the most tried class of drugs that modify autophagy to treat cancer. Several compounds have been shown in pre-clinical and clinical studies to favor cancer cell death either as a lone treatment or as an adjuvant for other drugs. The bulk of this work focused on modulating autophagy late in cancer development or preventing its progression to aggressive and metastatic disease. The drugs were also shown to reduce chemotherapy resistance and enhance the effect of drug therapeutics. Could targeting autophagy earlier in cancer development procure the same benefits? Indeed a body of work is showing that activating autophagy rather than inhibiting it would be beneficial. Leveraging the role of autophagy in degrading mesenchymal transcription factors, in particular, seem to reduce the production of the protein needed for the transition to metastatic cells. Strategies for inducing autophagy, therefore, are advantageous in an earlier stage of the disease.

Multiple drugs modify autophagy only incidentally during their course of treatment. Others have their mechanism of action in treating cancer independent of their effect on autophagy. In either case,

Table 2
Clinical trials of autophagy-targeted therapeutics in cancer.

Tumor type	Autophagy drugs and Interventions	Clinical trials	
		Phase	Identifier[a]
Chronic lymphocytic leukemia	Hydroxychloroquine (HCQ)	II	NCT00771056
	Everolimus (RAD001)	I/II	NCT01188889
	Everolimus + Alemtuzumab	I/II	NCT00935792
Chronic myeloid leukemia	HCQ + Imatinib	II	NCT01227135
Lymphoma	Vinblastine	III	NCT00059839
Multiple Myeloma	HCQ + Bortezomib	I/II	NCT00568880
	Everolimus + Panobinostat	I/II	NCT00918333
Hepatocellular carcinoma	HCQ + Sorafenib	II	NCT03037437
	HCQ	I/II	NCT02013778
	Sirolimus	II	NCT01079767
	Everolimus	III	NCT01035229
Pancreatic duck adenocarcinoma	HCQ + Gemcitabine	I/II	NCT01128296
	HCQ + Capecitabine	I/II	NCT01494155
Breast cancer	HCQ + Letrozole, palbociclib		NCT03774472
	HCQ + Ixabepilone	I/II	NCT00765765
	Chloroquine (CQ)	I/II	NCT01023477
	CQ + Taxane	I	NCT01446016
Colorectal cancer	HCQ + Vorinostat	II	NCT02316340
	HCQ + Entinostat, Regorafenib	I/II	NCT03215264
Lung cancer	HCQ	I	NCT01026844
	HCQ + Erlotinib	II	NCT00977470
Prostate cancer	HCQ sulfate	II	NCT04011410
	HCQ + SUBA-itraconazole	I/II	NCT03513211
Osteosarcoma	HCQ + Docetaxel, Gemcitabine	I/II	NCT03598595
Renal carcinoma	HCQ + Interleukin 2	I/II	NCT01550367
Brain tumor	CQ + Temozolomide	III	NCT03243461
	HCQ + Dabrafenib, Trametinib	I/II	NCT04201457
Melanoma	HCQ + Dabrafenib, Trametinib	I/II	NCT02257424
Ovarian cancer	HCQ + Itraconazole	I/II	NCT03081702

[a] Clinicaltrials.gov

deliberately stabilizing autophagy or enhancing its function could bear on the drugs' action. Studying how conventional cancer therapies modulate autophagy in their regular course of action is poignant to take advantage of autophagy features. A number of autophagy inhibitors are used as drug adjuvants to do precisely that. As several cancer drugs were found to induce autophagy, and this induction was found to be cyto-protective of the cancer cells, inhibiting autophagy seemed like a sensible strategy to boost the effectiveness of the drugs. A granular targeting of autophagy functions would seem reasonable. However, this remains speculative since few studies have explored the subtypes and selective autophagy in this context. Less is known about the role of autophagy in indirectly modifying the cancer microenvironment or the immune response that it triggers. Modifying either have succeeded as cancer therapies and, therefore, exploring how they relate to autophagy represents future research avenues.

Declarations

No ethics approval or consent to participate is needed.

Consent for publication

All authors consented to manuscript submission for publication.

Availability of data and materials

Not applicable to this manuscript.

Funding

This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Ministry of Science and ICT (MSIT) of the Korean government [2015R1A5A2008833 and 2020R1A2C2011416].

Authors' contributions

SZ, JSH and DRK designed and conceived this review. SZ, JSH, MA and DRK drafted the manuscript and prepared the Figures. MA, THL, TMP, and OM edited the manuscript. The authors read and approved the final manuscript.

Declaration of Competing Interest

The authors have no competing interests to declare.

Acknowledgments

Not applicable.

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