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Autophagy and Hallmarks of Cancer

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Abstract

Autophagy is a catabolic program that is responsible for the degradation of dysfunctional or unnecessary proteins and organelles to maintain cellular homeostasis. Mechanistically, it involves the formation of double-membrane autophagosomes that sequester cytoplasmic material and deliver it to lysosomes for degradation. Eventually, the material is recycled back to the cytoplasm. Abnormalities of autophagy often lead to human diseases, such as neurodegeneration and cancer. In the case of cancer, increasing evidence has revealed the paradoxical roles of autophagy in both tumor inhibition and tumor promotion. Here, we summarize the context-dependent role of autophagy and its complicated molecular mechanisms in the hallmarks of cancer. Moreover, we discuss how therapeutics targeting autophagy can counter malignant transformation and tumor progression. Overall, the findings of studies discussed here shed new light on exploiting the complicated mechanisms of the autophagic machinery and relevant small-molecule modulators as potential antitumor agents to improve therapeutic outcomes.

Keywords

therapy; autophagosomes; ATGs; cancer; macroautophagy

I. INTRODUCTION

Macroautophagy (hereafter referred to as autophagy) is a conserved process by which eukaryotic cells sequester intracellular material including damaged organelles, redox-active protein aggregates, and foreign matter within double-membraned vesicles (also known as autophagosomes). These vesicles are then transported to the lysosome for degradation.[1,2] The autophagic network is a multilayer cellular process that is tightly controlled by a set of

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autophagy-relevant factors, including (but not limited to) ATG5, ATG7, and BECN1.[3] Under normal physiological conditions, baseline levels of autophagy mediate a key homeostatic function, essentially operating as an intracellular quality control system. Autophagy can be upregulated in response to a variety of intrinsic or extrinsic stimuli: starvation, growth factor deprivation, hypoxia, pathogens, and many others.[4,5] Autophagy is a critical regulator of cellular homeostasis, and autophagic dysfunction is associated with human diseases, including Alzheimer's disease, Parkinson's disease, and cancers.[6,7] Of note, autophagy has complex and context-dependent roles in cancer. In some contexts, autophagy has a preventive role during cancer development. Moreover, in most contexts autophagy promotes tumorigenesis.[7,8] In this review, we summarize the mechanism of autophagy and its paradoxical roles in cancer. Importantly, we discuss the molecular and cellular mechanisms whereby the autophagic network interfaces with multiple hallmarks of cancer. Finally, we illustrate a series of molecules and agents targeting autophagy executors for potential cancer treatments.

II. MECHANISMS OF AUTOPHAGY

The autophagic process involves the sequential formation of the phagophore (also known as the isolation membrane), autophagosome, and autolysosome, ultimately leading to the degradation and recycling of autophagic cargo.[9] The molecular machinery of autophagy is highly conserved from yeasts to mammals and executed by a group of autophagy-related proteins (ATGs) that associate with other proteins to form different complexes in autophagic flux.[9]

A. Autophagy Initiation and Phagophore Nucleation

In yeast, autophagy is initiated at the phagophore assembly site (PAS).[10] Contrarily in mammals, phagophores are nucleated at an endoplasmic reticulum (ER) -emanating membrane domain enriched for the lipid phosphatidylinositol 3-phosphate (PI3P), known as the omegasome.[11] Signals that activate the autophagic process typically originate from various stressors, including energy or nutrient shortage, hypoxia, oxidative stress, and other cytotoxic insults. The best characterized triggers for autophagy induction include inactivation of mammalian target of rapamycin complex 1 (mTORC1) under amino acid deprivation[12,13] and activation of AMP-activated protein kinase (AMPK), which senses changes in the AMP:ATP ratio resulting from energy starvation.[14,15] These two kinases regulate autophagy initiation by controlling the activation of the unc-51-like autophagy-activating kinase 1 (ULK1) complex (known as the Atg1 complex in yeast), which consists of serine/threonine kinase ULK1, scaffolding subunit FIP200 (FAK family-interacting protein of 200 kDa), and regulatory subunits ATG13 and ATG101.[16] In the absence of starvation (hereafter referred to as fed), mTORC1 binds the ULK1 complex and phosphorylates both ULK1[17] and ATG13,[18] thereby suppressing the ULK1 complex function. Upon energy depletion, AMPK directly activates the ULK1 complex by phosphorylation at multiple sites in the central intrinsically disordered region (IDR).[17,19,20] Additionally, AMPK indirectly induces autophagy by inhibiting mTORC1 through phosphorylation of the regulatory-associated protein of mTOR (RAP-TOR).[21]

The activated ULK1 complex then triggers nucleation of the phagophore by activating downstream the Class III phosphoinositide 3-kinase complex I (PI3KC3-C1). PI3KC3-C1 is another pivotal autophagy-initiating complex, and consists of phosphoinositide (PI) kinase vacuolar protein sorting 34 (VPS34), regulatory subunit BECN1 (Atg6 in yeast), scaffold protein VPS15, and ER-targeting protein ATG14L.[16] ULK1 directly phosphorylates VPS34 and BECN1,[22] thereby activating the PI3KC3-C1 complex, and in turn generates local phosphatidylinositol-3-phosphate (PI3P) in the phagophore.[23] This autophagosome-specific pool of PI3P is essential for phagophore nucleation.[24,25] PI3P promotes recruitment of additional autophagy-specific PI3P effectors, such as WD-repeat domain PI-interacting protein 2 (WIPI2). WIPI2 subsequently recruits the ATG12–ATG16L conjugation complex for phagophore expansion.[26]

B. Phagophore Elongation and Autophagosome Completion

From initiation at the PAS or omegasome, the phagophore elongates into a cup-shaped structure and begins to engulf cellular material. In the expansion stage, two ubiquitin-like protein (UBL) conjugation systems are required for the elongation of the phagophore membrane: the ATG12–ATG5 UBL and the microtubule-associated light-chain B (LC3B, the mammalian orthologue of yeast Atg8)-phosphatidylethanolamine (PE) UBL.[27] ATG12 is a ubiquitin-like protein, which covalently attaches to substrates via the carboxyl group of its C-terminal glycine.[28] The ATG12–ATG5 conjugation is mediated by the E1-like enzyme ATG7 and the E2-like enzyme ATG10.[29,30] The ATG12–ATG5 conjugate then forms a supermolecular complex with AT-G16L1. This complex is recruited to the phagophore by WIPI2,[26] where it acts as an E3-like enzyme for the LC3-PE UBL.[31] Nascent pro-LC3 is cleaved by the cysteine protease ATG4B, thereby exposing a glycine residue for its conjugation with PE.[32,33] The processed LC3 is then conjugated to membrane-associated PE by the E1-like enzyme ATG7 and the E2-like enzyme ATG3 in concert with the ATG12–ATG5–ATG16L complex, converting it from a diffuse form (LC3-I) to a membrane-anchored, lipidated form (LC3-II).[34,35] LC3 lipidation is required for phagophore expansion and closure[36,37] and is widely used as an autophagosome marker. The autophagasome maturation involves the clearance of LC3/Atg8 and PI3P from the autophagasome outer membrane by ATG4 and YMR1, respectively. Following this dissociation, the autophagosome can fuse with the lysosome.[38]

C. Lysosomal Fusion and Degradation of Cargo

After formation of the autophagosome is complete, its outer membrane fuses with the lysosome (vacuole in yeast) to form the structure known as the autolysosome.[39] The autophagosome–lysosome fusion involves the function of three protein families: Rab GTPases, membrane-tethering factors (such as HOPS and EPG5), and soluble N-ethylmaleimide-sensitive factor attachment proteins (SNAREs). Rab GTPases are located at specific membranes, which then recruit tethering complexes that act as bridges to tether the opposing lipid bilayers. These tethering complexes in turn recruit and promote SNARE proteins to physically drive fusion of the autophagosome with the lysosome.[40] Additionally, recent studies have revealed the critical roles of ATG8 family members in the positioning of autophagosomes near lysosomes. Moreover, these proteins assist in the assembly of the fusion machinery, which highlights them as possible hubs for the coordination of the final

fusion stages of autophagy.[41] Degradation of the autophagic cargo is dependent on a series of lysosomal acid hydrolases. Salvaged nutrients are then released back to the cytoplasm for protein synthesis and maintenance of cellular homeostasis.

III. EPIGENETIC, TRANSCRIPTIONAL, AND POST-TRANSCRIPTIONAL REGULATION OF AUTOPHAGY

A. Epigenetic Regulation of Autophagy

Accumulating evidence indicates that epigenetic modifications are involved in the control of autophagy.[42–53] Post-translational modifications of histones and DNA methylation may affect the chromatin structure, which leads to the dysregulation of a series of autophagy-related genes.[43–45,48,49] Several histone modifications, including H3R17 dimethylation (me2),[54] H3K9me2,[45,55,56] H3K27 trimethylation (me3),[48] and H4K16 deacetylation,[57] are linked to autophagy in human cancers.

Nutrient starvation activates the AMPK-fork-head box protein O3a (FOXO3a) axis to suppress SKP2. SKP2 repression upregulates protein arginine methyltransferase CARM1 protein levels.[54] The stabilization of CARM1 induces global H3R17me2 levels in nutrient starvation–induced autophagy.[54] Recent studies have indicated that H3K9me2[45,56,58] and H3K27me3[48] act as repressors of autophagy. Following autophagy induction, the G9a methyltransferase and G9a-mediated H3K9me2 are removed from the target gene promoters, leading to upregulation of autophagy regulators such as LC3B and sequestosome 1 (SQSTM1/p62).[45] EZH2-mediated H3K27me3 epigenetically represses autophagy by downregulating mTOR pathway suppressors such as TSC2, RGS16, GPI, and RHOA.[48] Moreover, EZH2 inhibitors such as GSK343[59] and UNC1999[60] significantly induce autophagy in cancer cells. In addition to methylation, histone acetylation contributes to autophagy in tumorigenesis. Downregulation of H4K16ac is associated with autophagy induction in human cancer cells, which is mediated by the histone acetyltransferase hMOF.[57] Deacetylation of H4K16 widely affects autophagy-related gene expression.[57] Other histone modifications such as H2BK120 monoubiquitination,[51] H3K56 acetylation,[43,61] and H4K20 methylation[43,62] are also involved in autophagy regulation.

B. Transcriptional Regulation of Autophagy

Emerging studies have demonstrated the key role played by transcription factors in regulating autophagy in cancer cells.[54,63–69] STAT3 is the one of the most important transcriptional regulators of autophagy-related genes. STAT3 represses BECN1 expression by directly binding to its promoter and recruiting HDAC3.[70] STAT3 also regulates autophagy through PIK3R1 regulation. STAT3 suppresses autophagy by transcriptionally upregulating the PIK3R1 gene products p55α and p50α, which inhibit p85α-mediated autophagy.[71] Recent studies have demonstrated that STAT3 also acts as a transcriptional activator of *BCL2*, *BCL2L1*, and *MCL1*,[72,73] which are key autophagy-related regulators. Interestingly, both nuclear STAT3 and cytoplasmic STAT3 suppress autophagy in cancer cells. Cytoplasmic STAT3 directly interacts with EIF2AK2 to inhibit its enzymatic activity, resulting in decreased autophagy activator eukaryotic translation initiation factor q alpha kinase 2A (EIF2A) phosphorylation.[74,75] Furthermore, several STAT3 regulating noncoding

RNAs are involved in autophagy regulation. For example, the long noncoding RNA *HAGLROS*, a direct target of STAT3,[76,77] activates the mTOR pathway to promote autophagy suppression.[77]

Transcription factor EB (TFEB), a member of the microphthaimia family, has been reported to be a key regulator of lysosomal biogenesis and autophagy.[78] Nutrient starvation induces TFEB nuclear translocation. Nuclear-localized TFEB directly transcriptionally induces *WIPI*, *VPS11*, and *VPS18* in starvation-induced autophagy.[78] TFEB nuclear translocation upregulates autophagy-related regulators, including *ATP6V0D1*, *LAMP1*, *CTSB*, *MAP1LC3B*, and *UVRAG*.[79] Of note, emerging studies have demonstrated that TFEB serves as a bridge to mediate upstream regulators and autophagy progression in cancer cells. STUB1 regulates autophagy and mitochondrial biogenesis by modulating TFEB activity.[80] In addition, MAP4K3, a novel autophagy regulator,[81] regulates TFEB nuclear localization and transcriptional activity by phosphorylating TFEB at serine 3.[81] Several other genes, such as *PEG3*,[82] *AKT*,[83] and *BRD4*,[84] are also involved in autophagy regulation by influencing TFEB transcription activity.

C. Post-Transcriptional Regulation of Autophagy

MicroRNAs (miRNAs) are small noncoding RNAs that are 18–25 nucleotides in length. miRNAs serve as post-transcriptional regulators of protein-coding genes by binding to the 3′-untranslated region (UTR) of target messenger RNAs (mRNAs).[85] Emerging studies report that miRNAs play important roles in the regulation of autophagy.[86–90] miR-30a was the first miRNA shown to be involved in autophagy regulation by targeting *BECN1*.[91] A similar observation in human chronic myeloid leukemia cells showed that miR-30a inhibits autophagy by targeting both *BECN1* and *ATG5*.[92] miR-101 is also an autophagy suppressor.[93–95] miR-101-mediated inhibition of autophagy partially depends on three novel targets, *STMN1*, *RAB5A*, and *ATG4D*.[96] Similarly, miR376b regulates starvation and mTOR inhibition–related autophagy through inhibition of *ATG4C* and *BECN1*.[97] Finally, miR-23b regulates autophagy to promote radioresistance in pancreatic cancer cells by targeting *ATG12*.[98]

Unlike miRNAs, long noncoding RNAs (lncRNAs) are RNA transcripts longer than 200 nucleotides with no protein-coding potential.[99] Increasingly, reports show the importance of lncRNAs in tumorigenesis by regulating protein levels through transcriptional, post-transcriptional, and post-translational levels.[99] Since 2013, several studies have implicated lncRNAs in autophagy. *APF* lncRNA binds and inhibits miR-188–3p. In the absence of *APF* lncRNA, miR-188–3p functions to bind and suppress translation of *ATG7* mRNA, an autophagy-promoting gene. Thus, *APF* lncRNA works to inhibit miR-188–3p, thereby disinhibiting *ATG7* gene transcription.[100] Knockdown of *APF lncRNA* significantly suppresses *ATG7* expression and autophagy. Additionally, *lncRNA* HULC, which is highly upregulated in liver cancer, promotes autophagy via stabilizing SIRT1 in hepatocellular carcinoma.[101] Finally, *MEG3*, the most well-known lncRNA involved in autophagy regulation,[102–106] interacts with *ATG3* mRNA and protects it from degradation.[104] Taken together, these findings suggest that miRNAs and lncRNAs are important post-transcriptional regulators of autophagy and act by regulating autophagy-related genes.

IV. BIPOLAR NATURE OF AUTOPHAGY IN CANCER

A. Tumor Suppression by Autophagy

Autophagy has been universally demonstrated to play a tumor-suppressive role at the benign stage,[8] and defective autophagy has been connected with DNA damage and tumorigenesis.[7,107]

BECN1 is the mammalian orthologue of the yeast *Atg6* gene.[108] BECN1 interacts with either BCL-2 or PI3K Class III (VPS34),[109,110] playing a critical role in the regulation of both autophagy and cell death.[109,111] Adult mice having monoallelic deletion of *Becn1* (*BECN1*$^{+/-}$) showed increased DNA damage and a higher incidence of spontaneous lung cancer, liver cancer, and lymphomas.[112,113] Allelic deletion of *Becn1* has been reported in other tumor types, such as prostate, breast, and ovarian cancers.[108,114] BECN1 is positively regulated by the ultraviolet radiation resistance–associated gene (UVRAG) and Bax-interacting factor 1 (BIF-1). Both of these proteins enhance the interaction between BECN1 and VPS34, leading to increased autophagy.[115,116] Mutations in *UVRAG* and low expression of BIF-1 have been observed in several types of cancers.[116–118] Moreover, mice with system mosaic deletion of *Atg5* or liver-specific *Atg7* deficiency also develop liver tumors.[119] Together, these findings suggest that autophagy plays a key role in repressing tumorigenesis.

Mitophagy is the selective degradation of damaged mitochondria by autophagy. Dysfunctional mitochondria promote activation of PTEN-induced putative kinase 1 (PINK1), which further activates the E3 ligase parkin (encoded by *PARK2*) to ubiquitinate mitochondrial substrates, resulting in the selective degradation of damaged mitochondria by the autophagy machinery.[120,121] Mitophagy helps to maintain mitochondrial quality and reduce oxidative stress. *Park2* has been shown to function as a tumor suppressor gene.[122] Like *Becn1* deletion, *Park2* deletion in mice leads to increased hepatocellular carcinoma,[123] implying that defective mitophagy and oxidative stress contribute to tumor tumorigenesis.

p62, a prominent autophagy substrate, is an adaptor protein that possesses various binding motifs. It functions by recruiting proteins and assembling them into complexes.[124] Nuclear factor (erythroid-derived 2) -related factor 2 (NRF2) is activated by p62[125] and is responsible for activating the transcription of antioxidant defense genes.[126] In the absence of cellular stress, kelch-like ECH–associated protein 1 (KEAP1), a component of the CUL3–RBX1 E3 ligase complex, binds and inhibits NRF2 activity. However, in the presence of oxidative stress, p62 expression increases. Thus, p62 competitively binds KEAP1, thereby releasing NRF2. NRF2 then translocates to the nucleus and activates the expression of antioxidant defense genes, promoting cell survival and tumorigenesis.[125] Autophagy deficiency via liver-specific deletion of *Atg7* in mice results in p62 accumulation and NRF2 activation, increasing the expression of NRF2-target genes. Liver tumors originate from autophagy-deficient hepatocytes, which can be partially suppressed by p62 deletion.[119] Deficiency in p62 or NRF2 suppresses the development of Ras-driven non-small-cell lung cancer in mouse models.[127,128] Furthermore, activating mutations of NRF2 and inactivation mutations of its negative regulator, *KEAP1*, are found in various types of cancers, implying

that p62 and NRF2 function as oncogenes while *KEAP1* functions as a tumor suppressor.[129–131]

B. Tumor Promotion by Autophagy

Although autophagy inhibits early tumor initiation and growth, the principal effect of autophagy is to promote tumor growth. In many cases, cancer cells show increased autophagy dependency than normal cells. This context-dependent nature of autophagy likely results from the elevated metabolic and biosynthetic demands of dysregulated proliferating cancer cells.

Basal levels of autophagy are essential for normal tissue homeostasis.[132] Autophagy was initially shown to support the survival of yeast under starvation conditions through maintaining amino acid levels and activating the expression of genes in response to starvation.[133,134] Deletion of *Atg5* or *Atg7* in mouse brains causes polyubiquitinated protein accumulation and leads to neurodegeneration.[135,136] This suggests that clearance of abnormal proteins by autophagy is crucial for the survival of neurons. *Becn1*$^{-/-}$ mice are embryonic lethal.[112] Neonatal *Atg5*-deficient mice survive for a much shorter time than wild-type mice. Moreover, *Atg5*-deficient neonates display signs of reduced amino acid concentration and ATP levels,[137] suggesting that they suffer from a metabolic crisis. These findings support an important and conserved role for autophagy in normal cell survival in response to metabolic stress.

The major function of autophagy is to collect, degrade, and recycle intracellular material when cells are in starvation. Autophagy can supply mitochondrial substrates in the form of amino and fatty acids, further promoting tumor cell growth. Impaired autophagy in cancer cells leads to the accumulation of morphologically and functionally abnormal mitochondria.[119] Experimentally induced autophagy deficiency in tumor cells results in deficient ATP and lack of key tricarboxylic acid (TCA) -cycle intermediates, and leads to mitochondrial dysfunction. Mitochondrial dysfunction is mainly exemplified by generation of toxic reactive oxygen species (ROS) and mitochondrial damage, promoting accumulation of damaged mitochondria resulting from a failure of clearance by mitophagy.[138,139] However, the precise mechanisms of autophagy's support of mitochondrial function are still under investigation.

Autophagy is vigorously stimulated by various stressors in cancer cells to support their high metabolic demands. In conditions in which apoptosis is inhibited, autophagic cancer cells enter a state of quiescence, which allows them to survive for weeks. When metabolites and nutrients become readily available again, these cells are restored to their normal growth conditions.[140] Glucose deprivation and hypoxia, typical physiological stresses in the tumor microenvironment, activate autophagy in cancer cells to support survival.[141,142] Pharmacological inhibition of autophagy or deletion of essential autophagy genes suppresses cancer cell growth in normal and stress conditions.[142,143]

A large number of cancer cell lines have a high basal level of autophagic activities even without stressors. Several oncogenes (e.g., RAS and BRAF) that promote cancer cell growth also increase the basal level of autophagy.[144,145] It is hypothesized that both RAS and BRAF

function using similar mechanisms. Activating mutations in *RAS* and *BRAF*, although frequent in cancer, are mutually exclusive, as concurrent mutations arising in both genes are extremely rare.[146] Ras-activated cancer cells are highly dependent on autophagy to support their survival under basal and especially stressful conditions.[145] K–RAS translocates into the mitochondria and causes a disruption of Complex I. K-RAS activation significantly suppresses cancer cell mitochondrial respiration and impairs acetyl-CoA production. This results in increased dependency on autophagy to provide the necessary substrates for acetyl-CoA biosynthesis to promote TCA cycle activation.[145,147] Genetic or pharmacologic inhibition of autophagy in cancer cells with K-RAS activation causes increased ROS and DNA damage and decreased mitochondrial oxidative phosphorylation,[139,145] resulting in robust tumor suppression.[139] Human non-small-cell lung cancer cells with *BRAF* activation mutations display high levels of autophagic activity. Inhibition of autophagy through *Atg7* deficiency ($Atg7^{-/-}$) suppresses the progression of $Braf^{V600E}$-driven tumors and accumulates defective mitochondria.[144] Overall, this implies that the dysregulated mitochondrial metabolism caused by impaired autophagy promotes tumor growth.

V. AUTOPHAGY AND THE HALLMARKS OF CANCER

A. Autophagy Sustains Proliferation

One of the key characteristics of cancer cells is sustained proliferation.[148] Normal cells have precise controls of cell cycle progression to maintain proper cell growth and function. However, tumor cells obtain unlimited proliferating potential by bypassing cell cycle check points, due to mutations in genes such as *TP53* and *Retinoblastoma* (*Rb*).[148] Basal levels of autophagy in normal tissue maintain genome integrity and prevent tumorigenesis.[7,107] Autophagy deficiency by *Atg5* or *Becn1* deletion ($Atg5^{-/-}$ or $Becn1^{-/-}$) causes early death in mice.[112,137] Moreover, mice with mosaic deletion of *Atg5* or monoallelic deletion of *Becn1* show a high incidence of liver cancer.[112,119] In cancer cells, the PI3K/AKT pathway is often activated to promote cell proliferation through *PI3K*-activating mutations, increased expression of *AKT*, *EGFR* overexpression, *HER-2* amplification, or *PTEN* loss, followed by mTOR activation. Interestingly, mTORC1 is a major negative regulator of autophagy.[149–151]

BCL2 that is often overexpressed in cancer cells also inhibits autophagy through inhibitory binding to BECN1.[110,111] *TP53* is the most commonly mutated gene in human cancers and encodes the p53 protein. Activation of p53 via starvation or DNA damage activates autophagy, which may occur via inhibition of mTOR.[152,153] These findings suggest that autophagy suppresses cancer cell growth, which is consistent with its role as tumor suppressor.

However, as discussed previously, the role of autophagy in cancer is contextual. High levels of autophagy are also observed in RAS-BRAF-driven cancer cells, and autophagy is essential for these tumor cells to grow under both normal and starvation conditions.[144,145] Impaired autophagy in these tumors greatly inhibits tumor cell growth and tumor progression, revealing the role of autophagy in sustaining tumor cell proliferation. Taken together, these cases show that the complexity of tumors and the role of autophagy in regulating tumor cell proliferation are highly context-dependent.

B. Autophagy Promotes Epithelial–Mesenchymal Transition

Epithelial–mesenchymal transition (EMT), another hallmark of cancer, is the process by which epithelial cells lose their adhesive properties and become more migratory and invasive mesenchymal cells. Autophagy and EMT both play crucial roles in human cancer progression.[154,155] However, the interplay between autophagy and EMT remains unclear. Here, we focus on elucidating the intricate relationship between them.

Autophagy is an important mechanism by which cancer cells evade apoptosis and is a prerequisite of tumor metastasis.[156,159] Previous studies have revealed that autophagy is positively correlated to cancer cell EMT. Autophagy can activate hepatocellular carcinoma (HCC) cell EMT, which can subsequently promotes cell invasion.[160] Autophagy impairment through chloroquine (CQ) treatment or *Atg3* and *Atg7* silencing inhibits EMT in HCC cells.[160] Moreover, knockdown of *BECN-1*, a key autophagy activator, remarkably suppresses EMT in colon cancer cells.[161] Interestingly, ULK2, which phosphorylates the BECN-1 initiation complex, may also promote EMT in lung cancer cells.[162] Similarly, cisplatin treatment activates autophagy in nasopharyngeal carcinoma, and autophagy inhibition impairs EMT in this progression.[163]

Contrary to these findings, a number of studies have shown negative crosstalk between autophagy and EMT in cancer cells, which is likely due to the bipolar nature of autophagy. Several reports have shown that anticancer agents, such as the Aurora kinase inhibitors alisertib[164,165] and danusertib,[166,167] activate autophagy but supress EMT in cancer cells. In ovarian cancer, autophagy inhibition through *Atg7* knockdown promotes EMT via activation of the ROS/Heme Oxygenase-1 (ROS/HO-1) pathway.[168]

Similarly, knockdown of *ATG5*, *ATG7*, or *BECN-1* in glioblastoma induces autophagy impairment, which leads to promotion of cancer cell by inducing EMT.[169] The direct interaction between CDH6 and GABARAP as well as BNIP3 and BNIP3L in thyroid cancer suppresses autophagy to promote EMT.[170] TWIST, the basic helix-loop-helix transcription factor, is the hallmark of EMT and plays crucial roles in cancer metastasis.[171,172] Recent studies have indicated that the degradation of TWIST underlies autophagy-inhibiting EMT in cancer cells. The death effector domain–containing DNA-binding protein (DEDD) directly interacts with PI3KC3/BECN-1 to induce autophagy-mediated lysosomal degradation of SNAIL and TWIST,[173] which consequentially inhibit EMT. Finally, autophagy impairment stabilizes TWIST1 to promote EMT.[174]

Recent studies indicate that p62 and TGF-β mediate crosstalk between autophagy and EMT. Earlier studies revealed that p62, an autophagy adaptor protein, may bind to EMT regulators to affect EMT progression. For example, p62 sustains a level of HDAC6 to promote EMT in prostate cancer.[175] p62 also interacts with TWIST to promote EMT by inhibiting its degradation.[174] Similarly, p62 increases EMT in cancer cells by stabilizing SMAD4 and TWIST,[176]and it has been shown to increase the transcriptional activity of NF-κB to promote EMT by enhancing the nuclear translocation of p65.[177]

TGF-β signaling is the most important regulator of EMT in human cancers.[178,179] It has been shown that TGF-β plays a crucial role in crosstalk between EMT and autophagy by

promoting autophagy in cancers. TGF-β treatment induces autophagy in hepatocellular carcinoma (HCC)[160,180] by inducing autophagy regulators such as BECN-1, ATG5, and ATG7.[180] Interestingly, autophagy impairment by CQ or *ATG5* knockdown suppresses TGF-β2–induced EMT.[181] Additionally, TGF-β2 activates autophagy via the SMAD and JNK pathways in glioma cell lines.[182] Autophagy inhibition blocks TGF-β2–induced EMT by influencing mitochondrial trafficking and membrane potential.

C. Role of Autophagy in Tissue Invasion and Metastasis

Tumor cells have the capability for local invasion and distant metastasis. The cascade of tumor invasion and metastasis can be divided into a series of steps: local invasion, intravasation into nearby blood and lymphatic vessels, transit of cancer cells through the circulatory system, extravasation, formation of small nodules of cancer cells, and finally outgrowth of micrometastatic lesions into macroscopic tumors. This process requires the translocation of cancer cells to new microenvironments, in which metastatic tumor cells must overcome numerous challenges to survive. These include altered nutrient supply, immune surveillance, and T-cell–mediated killing mechanisms.[183,184] Given the key role of autophagy as an adaptive response to stress, its involvement in the different stages of the metastatic cascade has been postulated.[159] Indeed, autophagic flux has been found to be upregulated by the different environmental stressors that promote invasion and metastasis of cancer cells, such as hypoxia and nutrient deprivation.[185] In addition, recent studies have identified an association between increased punctate staining for LC3B and metastasis of various cancers, including human breast cancer, melanoma, and HCC.[186–188]

Autophagy can either promote or impede cell invasion and metastasis. At the initial steps of metastasis, autophagy promotes the survival of tumor cells from hypoxia and metabolic stress by reducing tumor cell necrosis. Consequently, autophagy reduces the infiltration of macrophages at the primary tumor site, which is required for the initiation of metastasis.[189,190] During detachment from the extracellular matrix, autophagy is induced in tumor cells to overcome anoikis, a type of cell death signal triggered by the absence of anchorage to the extracellular matrix.[191,192] A connection between autophagy, EMT, and invasion has also been seen in HCC and lung cancer cells, where autophagy is critical for EMT and invasion of tumor cells.[160,162]

Upon successful extravasation, autophagy is proposed to facilitate tumor cell dormancy by promoting quiescence, a process that is also necessary for the maintenance of cancer stem cells.[193] Indeed, autophagy has been shown to be induced by the tumor suppressor gene aplasia Ras homolog member I (*ARHI*) to increase tumor cell dormancy.[194] The dormancy of tumor cells has also been suggested to result in resistance to genotoxic therapies that primarily target proliferating cells.[195] If autophagy is truly required for dormancy, the combination of genotoxic therapy with autophagy inhibition comes into focus as a therapeutic option to eliminate dormant tumor cells and thereby limit metastatic disease.

The studies previously described suggest that autophagy prevents initiation of invasion and metastasis by preventing tumor necrosis and inflammation. However, once the tumor cells have entered a new microenvironment, autophagy helps them survive and maintain dormancy until they successfully establish distant colonies. Therefore, autophagy may be

regulated differently at the various stages of metastasis in a way that has significance for the use of autophagy modulators in cancer therapy.

D. Autophagy Reprograms Tumor Metabolism

It has been established that tumor cells have to change their metabolic pathways to meet the heightened metabolic requirements necessary for tumor survival and unconstrained proliferation.[196] To accomplish these goals, tumor cells have been shown to use various sources of energy. Indeed, some tumors employ increased aerobic glycolysis rather than oxidative phosphorylation to generate the biosynthetic intermediates required for proliferation (termed the Warburg effect).[197] This is an acquired property of tumors caused by the impaired mitochondrial metabolism that also helps tumor cell survival in hypoxic microenvironments caused by dysfunctional vasculature. In the absence of pyruvate, other substrates are required to undergo the tricarboxylic acid (TCA) cycle for ATP synthesis, and autophagy can provide these substrates by recycling intracellular macromolecules.[198] Autophagy can lead to the degradation of various substrates, thereby providing metabolites for numerous metabolic pathways.[199] For instance, autophagy can provide sugars and nucleosides for glycolysis by degrading carbohydrates and DNA, respectively. It can also provide metabolites for the TCA cycle by degrading proteins and lipids. Therefore, autophagy plays an important role in reprogramming metabolic pathways to promote tumor cell survival.

In addition to cancer metabolism, autophagy also functions in the metabolic crosstalk between tumor cells and other stromal components, such as pancreatic stellate cells.[200] Autophagy is required for stellate cells to secrete metabolic substrates, such as the nonessential amino acid alanine, to support pancreatic cancer mitochondrial metabolism.[201]

E. Implications of Autophagy in Cancer Stem Cells

Cancer stem cells (CSCs) are defined as a small subset of cancer cells within a tumor that can self-renew and generate heterogeneous lineages of cancer cells that make up the tumor.[202,203] CSCs are intrinsically resistant to conventional chemotherapy and radiation treatment, and are postulated to contribute to treatment failure and tumor recurrence.[204] Therefore, targeting CSCs represents a useful strategy to improve the effectiveness of therapeutic interventions.

The involvement of autophagy in the physiology of CSCs is complicated and is not yet fully elucidated. Accumulating evidence suggests that autophagy plays critical roles in the maintenance and function of various normal stem cells. Given the similarities between normal stem cells and CSCs, it is expected that autophagy may be crucial in the maintenance and function of CSCs. The expression of the CSC marker CD133 is positively correlated with the expression of autophagy-related proteins ATG5, ATG12, and LC3. Autophagy induction markedly enhances the radiation resistance of $CD133^+$ glioma stem cells (GSCs).[205] In $CD44^+/CD24^{-/low}$ breast CSCs (BCSCs), ATG4 regulates BCSC populations by promoting their self-renewal *in vitro* and tumor growth *in vivo*.[206,207] Along similar lines, CQ-mediated autophagy inhibition depleted the $CD44^{+/}CD24^{-/low}$ BCSC population in triple-negative breast cancer in both preclinical and clinical settings.[208] Moreover, inhibition

of autophagy by *ATG4B* knockdown altered GSC phenotypes. Inhibition of ATG4B using a specific antagonist, NSC185058, sensitized GSCs to gamma-irradiation and reduced their capability to form glioma tumor spheres. These findings illustrate that autophagy is a crucial regulator of GSCs.[143] A better understanding of the molecular mechanisms governing autophagic responses in various CSCs may prove critical for the development of novel antineoplastic therapy aiming at tumor eradication.

F. Autophagy and Cancer Cell Resistance to Therapy

Most anticancer therapies, including radiation therapy, chemotherapy, and targeted therapies, invoke autophagy in tumor cells[209–211] which predominantly functions as a cytoprotective mechanism against therapy-induced stress responses.[212,213] Preclinical data from immunodeficient host animal models indicate that pharmacological suppression of autophagy with inhibitors such as 3-methyladenine, CQ, or hydroxychloroquine (HCQ) can augment cytotoxicity in combination with various anticancer treatments. These treatments include conventional chemotherapeutics (e.g., cisplatin,[214] 5-fluorouracil,[215] temozolomide,[216] and epirubicin[217]), radiation therapy,[218,219] targeted agents (e.g., gefitinib[22]), and antiangiogenic agents (e.g., bevacizumab[221]). Moreover, genetic silencing of autophagy regulatory genes, such as *ATG5*, *ATG7*, *BECN-1*, and *LC3*, leads to an enhanced sensitivity of tumor cells to chemotherapy,[214] ionizing radiation,[222] and antiangiogenic therapy.[142,223] The mechanism of autophagy-mediated cancer therapy resistance includes removal of genotoxic ROS,[224,225] blockade of apoptosis,[226,227] and maintenance of the CSC pool.[204,228] Such preclinical evidence supports the idea of targeting autophagy as a promising therapeutic strategy to overcome cancer drug resistance. Multiple ongoing clinical trials are deciphering the combination effect of CQ or HCQ with various therapies.[213,229]

Autophagy is also involved in the induction of robust antitumor immune responses, which play a pivotal role in eliminating tumor cells after cytotoxic chemotherapies.[230] Like tumor cells, the immune system derives benefits from the cytoprotective effects of autophagy, and therapy-induced autophagy in tumor cells can cause immunogenic cell death, leading to efficient recognition by the immune system.[231,232] Thus, autophagy-targeted therapy may generate undesirable effects that weaken the host immune system against malignant cells upon treatment. This assertion is evidenced by studies of immunocompetent hosts showing that defective autophagy can limit (rather than increase) the sensitivity of tumors to therapies that activate anticancer immune responses.[222,223] Currently, available clinical data on CQ or HCQ combinational therapy is disappointing, indicating that the immune-promoting function of autophagy seems to dominate over its tumor cytoprotective effect in response of anticancer therapy.[223] Future efforts should be dedicated to confirming the function of autophagy activation in malignant cells upon multiple anticancer regimens in the presence of a functional immune system.

VI. TARGETING AUTOPHAGY FOR CANCER THERAPEUTICS

Cytoprotective autophagy is an important response to treatment with chemotherapeutic agents and radiation.[234] In most cases, autophagy supports the survival of cancer cells in anticancer therapy; however, under certain conditions it fosters cell death.[235] In any case,

strategies aimed at the modulation of autophagy bear the potential to improve the efficacy of chemotherapy and radiation therapy. The optimal strategy seems to depend on tumor type, stage, genetic context, and specific treatment.[236] Additionally, autophagy manipulation might sensitize resistant cancer types to the cytotoxic effects of treatment. Furthermore, a combination of autophagy modulators and conventional treatments may sensitize cancer cells to cancer therapies.[237]

Sensitization of tumor cells to therapies is one of the most researched topics in the autophagy field. There is mounting preclinical evidence that targeting autophagy can enhance the beneficial effects of many cancer therapies. In many cancer types, inhibition of the nucleation step of autophagosome formation with type III PI3K inhibitors [e.g., 3-methyladenine (3-MA) or LY294002] enhances the efficacy of chemotherapy or radiation. For example, inhibition of autophagy using 3-MA enhanced cytotoxicity of radiotherapy in human esophageal squamous carcinoma cells.[238] Similarly, treatment of 3-MA enhanced the efficacy of the Gli inhibitor GANT-61 and increased apoptotic cell death.[239] Many preclinical studies indicate that lysosomotropic agents (e.g., CQ and HCQ) prevent lysosome acidification and block autolysosome formation, thereby augmenting the effect of chemotherapies and radiotherapy on various types of cancers.[237,240] For example, in non-small-cell lung cancer, bevacizumab in combination with CQ increases the efficacy of cancer treatment.[241] However, it should be noted that CQ and HCQ are not specific autophagy inhibitors and they may impact biological processes other than autophagy. These may include lysosomal membrane permeabilization, normalization of tumor vasculature, and subsequent activation of the mitochondrial pathway of apoptosis.[242,243] Also, CQ is reported to eliminate CSCs through autophagy-independent pathways, including the deregulation of Janus kinase 2 (JAK2)[208] and the inhibition of CXCR4 and Hedgehog signaling.[244] An important limitation of HCQ is its potency, as high doses (up to 1,200 mg daily) generate only modest autophagy inhibition *in vivo*.[237] Moreover, HCQ fails to block autophagy flux in tumor environments due to a decrease in drug uptake by cells. Therefore, more potent and selective autophagy inhibitors are urgently needed.

A specific ATG4B inhibitor, NSC185058, has been developed and shown to effectively inhibit ATG4B activity and autophagy without affecting the activities of mTOR and PI3K.[245] ATG4B is a cysteine protease that is essential for LC3 lipidation and recycling.[246] Inhibition of autophagy with NSC185058 had a negative impact on the development of Saos-2 osteosarcoma tumors *in vivo*.[245] Additionally, NSC185058 in combination with radiotherapy markedly slows tumor growth and provides survival benefits in mice with intracranial glioblastoma xenografts.[143] ATG4 proteases are emerging as potential pharmaceutical targets for the treatment of aggressive cancers, such as osteosarcoma and glioblastoma.

While significant progress has been made with the discovery of autophagy inhibitors in the last decade, we must keep in mind that many of these pharmacologic agents do not exclusively target the autophagy pathways. Therefore, the development of more potent and specific drugs targeting autophagy at the preclinical stage (e.g., ATG4B inhibitors) is highly warranted. This can help maximize the potential for autophagy manipulation in treating cancers.

VII. CONCLUSIONS

A plethora of evidence indicates the importance of autophagy in tumor development and progression, with both tumor-suppressive and tumor-promoting roles. Whether autophagy modulation should be attempted in tumor therapy remains controversial. Nevertheless, various research groups are focusing on therapeutically targeting autophagy in cancer. Furthermore, many current clinical trials are using CQ and HCQ for autophagy inhibition in combination with other therapies for cancer treatment. However, existing drugs, such as CQ, HCQ, and 3-MA can mediate multiple effects. Thus, it is not entirely clear that autophagy inhibition per se is solely responsible for observed therapeutic benefits.[247] It is therefore important to develop more potent and selective autophagy inhibitors to improve our understanding of autophagy and expand our therapeutic options for multiple diseases.

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ABBREVIATIONS:

ATG	autophagy-related protein
mTORC1	mammalian target of rapamycin complex 1
ULK1	unc-51-like autophagy-activating kinase 1
TFEB	transcription factor EB
UBL	ubiquitin-like protein
EMT	epithelial-mesenchymal transition
CSC	cancer stem cell
CQ	chloroquine

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