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Targeting cancer cells through autophagy for anticancer therapy

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Abstract

Autophagy is a cellular degradation process in which portions of the cell's cytoplasm and organelles are sequestered in a double-membrane bound vesicle called an autophagosome. Fusion of autophagosomes with lysosomes results in the formation of autolysosomes, where the proteins and organelles are degraded. This degradation pathway is induced under nutrient deprivation, metabolic stress or microenvironmental conditions to ensure energy balance, clearance of damaged proteins and adaptation to stress. Disruption of autophagy is involved in diverse human diseases including cancer. In particular, the regulation of autophagy in cancer cells is complex since it can enhance tumor cell survival in response to certain stresses, yet it can also act to suppress the initiation of tumor growth. Understanding the signaling pathways involved in the regulation of autophagy as well as the autophagy process itself represents new directions in the development of anticancer therapies. In this review, we discuss recent advances in our understanding the complexity of the autophagy process and the development of targeted therapies that modulate autophagy in cancer cells in the clinic.

Introduction

Autophagy is a self-digestive process that ensures lysosomal degradation of long-lived proteins and organelles to maintain cellular homeostasis. It is a conserved and dynamic process in which portions of the cytoplasm and organelles are sequestered in a double-membrane vesicle called an autophagosome [1]. The autophagosomes fuse with vesicles of the endocytic pathway to form amphisomes, which ultimately fuse with lysosomes, where the captured material is degraded. This multi-step pathway of autophagy can be modulated at several steps.

Initial steps include vesicle nucleation (isolation of the membrane), vesicle elongation and completion of the double-membrane vesicle. The autophagy-related genes (Atgs) play essential roles in the execution of autophagy. Although autophagy was initially discovered in yeast, about 30 Atg orthologs have been identified in mammals, including two ubiquitin-like conjugation systems—the Atg12–Atg5 and the Atg8 (LC-3)-PE (phosphatidylethanolamine) systems that are required for the elongation of the autophagosomal membrane [2,3•]. Autophagosomes then fuse with lysosomes, which

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acidify as they mature to become autolysosomes in a step called autophagic flux. However, the proteins and trafficking mechanisms involved in the autophagosomal maturation step are not completely understood. Although the fusion between autophagosomes with lysosomes could happen as a single step fusion to result in a fully degradative process, proteins involved in endocytic degradation have been identified to be required for autophagic maturation suggesting a convergence between these two degradation pathways [4].

Although autophagy was initially described as a protective mechanism for cells to survive and generate nutrients and energy, studies demonstrated that persistent stress can also promote autophagic, or programmed type II, cell death [5••,6]. Defective autophagy is implicated in different diseases including infections, neurodegeneration, aging, Crohn's disease, heart disease, and cancer [7]. In this review, we will focus on the role of autophagy in cancer, the signaling pathways known to activate or inhibit autophagy, and strategies to target cancer cells by autophagy for anticancer therapy.

Regulation of autophagy in cancer

Induction of autophagy that occurs in normal cells to generate nutrients and energy in response to starvation, metabolic stress or other stressful conditions is also observed in tumor cells where it promotes tumor cell survival in response to starvation, hypoxia, oxidative damage or other stress. Under these stresses, autophagy is able to protect dormant cells that have the ability to resume growth when conditions are more favorable [8]. In contrast to its protective role, inhibition of autophagy through specific gene inactivation can promote tumorigenesis (Figure 1) [9]. For example, Beclin 1, the human homolog of the autophagy-related gene Atg6/Vps30, has been found to be crucial for autophagy induction in mammalian cells. However, mutations or allelic loss of Beclin 1, is frequently found in breast, ovarian and prostate cancer [10,11]. Beclin 1 provided the first connection between cancer and autophagy [10]. Mice with a disrupted Beclin 1 gene had a higher incidence of lymphomas, lung and liver cancer suggesting that autophagy is a tumor suppressor pathway [12,13]. The activation of Beclin 1 inhibits tumor cell proliferation *in vitro* and tumor growth in nude mice. Mechanistically, Beclin 1 contains a Bcl-2 homolgy-3 (BH3) domain that mediates its interaction with Bcl-2 and other anti-apoptotic proteins under non-stress conditions. Bad and other BH3-proteins competitively inhibit the interaction between Bcl-2 and Beclin 1 in cells undergoing autophagy and provide a link between autophagy and apoptosis [14]. Beclin 1 has also been shown to form a complex with phosphatidylinositol 3-kinase (PI3K) class III (Vps34). The UV irradiation resistance associated gene (UVRAG) can also bind to beclin and forms a second PI3K complex, and is a positive regulator of autophagosome formation [15]. The Bax interacting factor 1 (BIF-1) has also been found in this complex and binds to UVRAG and has been proposed to be involved in causing membranes to curve [16]. Mutations of UVRAG or BIF-1 are found in certain tumors and result in decreased autophagy [17].

Signaling pathways have also been identified in the regulation of autophagy. During energy deprivation, mammalian target of rapamycin (mTOR) activity is downregulated and can signal autophagy to adjust to the metabolic demand [18]. The signaling of mTOR is mediated by mTOR complex 1 (mTORC1)and complex 2 (mTORC2). By contrast,

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constitutive activation of PI3K observed in a significant number of cancers increases mTOR signaling, which increases protein synthesis, tumor cell proliferation and inhibits autophagy through mTORC1 and its target Unc-51-like kinase 1 (ULK1) and ATG13 [17,19]. In addition, tumor suppressor gene products upstream of mTOR signaling (phosphatase and tensin homolg deleted on chromosome ten PTEN, tuberous sclerosis complex TSC1 and TSC2) antagonize PI3K activation and promote autophagy by downregulation of mTOR.

The tumor suppressor gene p53 also plays a dual role in autophagy regulation. It is a positive regulator of autophagy in cells exposed to genotoxic stress in an AMP-activated protein kinase (AMPK) and TSC-dependent [20]. Moreover, nuclear p53 has been reported to increase autophagy through the transcriptional upregulation of DRAM (damage-regulated modulator of autophagy), a protein localized in lysosomes [21]. Interestingly, Kroemer and his colleagues report that cytoplasmic p53 inhibits autophagy in several tumor cells and that loss of p53 resulted in enhanced autophagy and survival in response to hypoxia and nutrient depletion [22•]. The mechanism by which p53 stimulates or inhibits autophagy is still under investigation, but these data suggest that p53 regulates autophagy depending on whether it is in the cytosol or the nucleus. Other signaling pathways have also been shown to regulate autophagy such as the death associated protein kinase (DAPk-1), which is silenced in many tumors by promoter hypermethylation. DAPk-1 has tumor and metastasis suppressor properties [23] and is activated by the accumulation of unfolded proteins (UPR) that induce ER stress and can activate autophagy by directly phosphorylating Beclin 1 [24,25].

The signaling pathways involved in the maturation of the autophagosome have been worked out in yeast and to a lesser extent in mammalian cells. The maturation of autophagosomes requires fusion with endosomes of a neutral pH, multivesicular bodies (MVB), and fusion with acidic endosomes and lysosomes that promote acidification and degradation of the cargo found in the autophagosomes. A great deal of progress has been made in understanding the maturation of autophagosomes. For example, UVRAG has been demonstrated to coordinate the maturation of autophagosomes and endocytic trafficking through its interaction with the class C vacuolar protein sorting (Vps) complex to stimulate Rab7-GTPase activity and the fusion of autophagosomes with late endosomes/lysosomes [26•]. This function of UVRAG is independent from the UVRAG–Beclin1 interaction that occurs at an early stage of the autophagosome formation. The coat protein complex I (COPI) that acts in early endocytosis as well as the endosomal sorting complex that is required for transport (ESCRT) have been shown to participate at the autophagosomal maturation step and support a stepwise fusion model that differs from the single step fusion of autophagosomes with lysosomes in yeast [27,28••]. Most importantly, the maturation of autophagosomes with lysosomes to form a functional autolysosomal is essential for protein and organelle degradation.

Autophagy as therapeutic target

The induction of apoptosis by anticancer agents is directed at eliminating cancer cells. However, defects in apoptosis are observed in many solid tumor cells and increase the resistance of tumor cells to chemotherapy, radiotherapy and molecularly targeted therapies. Previous studies have reported that the metabolic stress observed in human tumors leads

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cancer cells to acquire resistance to apoptosis and to stimulate autophagy to maintain energy demand and prevent necrosis [29]. Furthermore, chemotherapeutic agents have been reported to induce autophagy and autophagic cell death [8]. Although the mechanism underlying this form of cell death is unclear, accumulation of autophagosomes in response to chemotherapy or molecularly targeted therapeutics suggests that this type of cell death is associated with an inhibition of the maturation and degradation process. Autophagic cell death can also occur when protein and organelle turnover occurs beyond a crucial point needed for survival [8]. Thus, in the regulation of cancer, autophagy should be considered a new target for anticancer therapy.

The effectiveness of chemotherapeutics is diminished by the fact that they induce toxicity to both normal and cancer cells. To develop new therapeutics with a higher therapeutic index, targeted therapies have been investigated. Currently, signaling transduction pathways, tumor angiogenesis and malignant stem cells are considered prime targets for the development of new therapeutics. For example, CI-1040, PD0325901, AZD6244 are examples of mitogen-activated protein kinase (MEK) inhibitors targeting the Ras/Raf/MEK/Erk (extracellular signal-regulated kinase) signaling cascade that is involved in cell survival and proliferation of cancer cells [30].

Stabilization of hypoxia inducible factor (HIF) and the activation of its signaling pathways are also currently being investigated as new targeted therapies. Cell-based small molecule screening has identified agents such as topotecan, chetomin, and echinomycin to target HIF or HIF target genes and reduce tumorigenicity [31–33]. The role of HIF in inducing autophagy under hypoxic conditions is controversial. Clearly, in some tumor types, hypoxia-induced autophagy is independent of HIF-1 [34•]. The involvement of mTOR in autophagy has led to the use of temsirolimus and everolimus to inhibit HIF by targeting mTORC1, an mTOR effector. Several reports show that autophagy is induced by targeting mTORC1 using rapamycin and its derivatives temsirolimus and everolimus [35,36]. In a recent chemical screen, perhexiline, niclosamide, amiodarone, and rottlerin stimulate autophagosome formation by inhibiting mTORC1 [37]. Table 1 summarizes different agents that have been reported to have anticancer effects through autophagy in the monotherapy setting. Nonetheless, many of these agents have shown anticancer activity independent of autophagy regulation. Among these agents, imatinib (a Bcr-Abl tyrosine kinase inhibitor), which has been shown to be effective in chronic myelogenous leukemia (CML), can also modulate autophagy through the regulation of lysosomal components and can reduce the survival of multi-resistant Kaposi's sarcoma cells through autophagy [38,39].

Autophagy is also induced in cancer cells as an adaptive response and can lead to chemoresistance mechanisms and increased cell survival. Thus, the inhibition of autophagy combined with inducers of metabolic stress or chemotherapeutic agents could enhance effective anticancer therapy by inhibiting stress adaptation and increasing cell killing. Chloroquine (CQ) and hydroxychloroquine (HCQ), lysosomotropic agents that increase pH and inhibit autophagosomal maturation, have been shown to increase the anticancer activity of chemotherapeutic drugs and are being tested in clinical trials (http://clinicaltrials.gov) [8,40]. For example, administration of bortezomib with HCQ is in clinical trial in refractory multiple myeloma (NCT00568880). HCQ and ixabepilone have shown a therapeutic benefit

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in some breast cancers (NCT00765765), and the combination of HCQ, radiation and temozolomide are in clinical trials in patients with glioblastomas (NCT00486603) [41]. In CML, cell death is observed by the combined treatment of CQ and the histone deacetylase (HDAC) inhibitor suberoylanilide hydroxamic acid (SAHA) and is associated with an increase of cathepsin D [42]. Recently, 2-phenylethynesulfonamide, a small molecule targeting HSP70, has been shown to promote cell death that is associated with autophagy and inhibition of lysosomal function [43]. By contrast, the development of specific inhibitors of ULK or PI3K class III could also be effective in inhibiting the induction of autophagy and represent new targets for the future.

Protein degradation occurs through autophagy in lysosomes but also within the proteasome for proteins that have been tagged with ubiquitin [44]. Whereas inhibition of proteosomal degradation can increase autophagy, downregulation of autophagy increases the formation of aggregates that accumulate polyubiquitinated proteins. Therefore, inhibition of both pathways could be interesting approaches to evaluate in regards to new therapeutics.

Autophagy for the treatment of renal cell carcinoma

Renal cell carcinoma (RCC) is the most lethal of the urological cancers. RCC is associated with metastatic disease and poor prognosis. Effective systemic therapies do not exist for the treatment of RCC since they are resistant to most cytotoxic chemotherapies. Targeted genetic approaches have been used to exploit the unique biology of RCC. Targeted therapeutics that have been shown to be effective in the treatment of RCC includes agents that inhibit angiogenesis (e.g. bevicuzamab, sorafenib, sunitinib) and agents that inhibit mTOR signaling (temsirolimus and everolimus) [45,46]. However, tumors eventually progress regardless of these therapies. The need for more effective cytotoxic agents to treat RCC has benefited from the concept of synthetic lethality. This new approach to selectively kill RCC cells is founded on the idea that two non-allelic and non-lethal mutations result in death when combined. On the basis of this approach, small molecule or RNA interference screens have been used to target the presence of an oncogene or the absence of a tumor suppressor gene in searching for synthetic lethality in mammalian cells. This concept has been taken into clinical trial in breast cancer, targeting tumor cells with a deficiency in the breast cancer 1 (BRCA1) or BRCA2 genes. The dysfunction of BRAC1 or BRAC2, which are important for homologous recombination, sensitizes breast cancer cells to killing by Poly-(ADP-ribose) polymerase (PARP) inhibitors, an enzyme involved in the base excision repair of DNA [47••].

Inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene arises in 75% of RCC and is an early event in the formation of renal cell cancer. Targeting the loss of VHL by synthetic lethality has promising implications in the development of new therapies for RCC. Accordingly, chromomycin A3 (ChA3), echinomycin and actinomycin D have been demonstrated to induce a genotype-selective toxicity for cells deficient in VHL [48]. These results demonstrated the feasibility to target the loss of VHL by synthetic lethality.

Recently, a chemical library of 64 000 compounds has been used to perform a fluorescence-based screen to identify small molecules that selectively induce toxicity in cells that lack a

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functional VHL gene. Among these compounds, STF-62247 was selectively toxic for the loss of VHL in multiple renal carcinoma cells and has been shown to inhibit the growth of tumors that lack VHL. Mechanistically, STF-62247 induces cell death in RCC deficient in VHL *in vitro* and *in vivo* through the chronic induction of autophagy. Silencing Atg5, Atg7, or Atg9 gene by siRNA increases cell survival in VHL-deficient cells, confirming that the induction of autophagy by STF-62247 in cells lacking functional VHL results in cell death [49••]. VHL-deficient cells exhibited higher acidification of mature autolysosomes in response to STF-62247, suggesting that cell death could be induced by disruption of autophagosomal maturation and autophagic protein degradation. These data support the concept that synthetic lethality is a powerful approach for the development of targeted therapies that modulate autophagy, and provides a new means to selectively kill tumor cells in a genotype specific manner.

Conclusion

Discovery of new therapeutic compounds for clinical management of tumors has been possible owing to a better understanding of the genetics, biology, and molecular biology of cancer cells. Autophagy has received a great deal of attention as it plays a role in cancer. However, whether to inhibit autophagy or induce autophagy to kill tumor cells appears to depend on tumor genotype and the therapeutic agents that are used. Radiation, tamoxifen, rapamycin, imatinib, arsenic trioxide, and their combined therapies have all been identified to induce autophagic cell death in some tumor types. Small molecules that induce autophagic cell death selectively in VHL-deficient RCC demonstrate the possibility of targeted therapy using synthetic lethality that could serve as a paradigm for other solid tumors.

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cells under conditions of hypoxia and nutrient depletion. Inhibition of p53 led to autophagy in enucleated cells, and cytoplasmic, not nuclear, p53 was able to repress the enhanced autophagy of $p53^{-/-}$ cells. Inhibition of p53 degradation prevented the activation of autophagy in several cell lines, in response to several distinct stimuli. These results link autophagy to the cancer-associated dysregulation of p53. [PubMed: 18454141]

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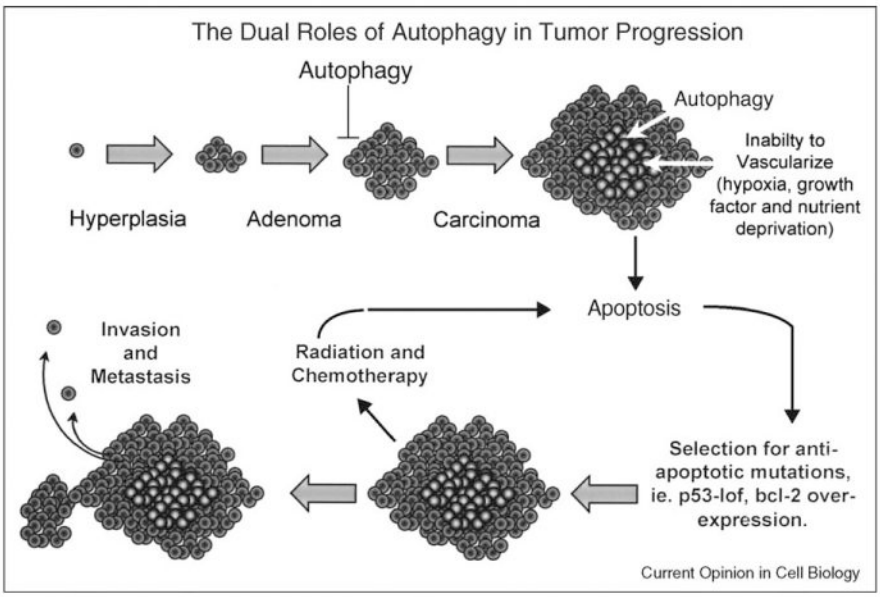

Figure 1.

Autophagy can act as a tumor suppressor and inhibit the progression of cells from adenoma to carcinoma. In tumors that are already established autophagy can protect cells from stress-inducing microenvironmental conditions such as low oxygen and nutrient deprivation [9].

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Table 1
Chemotherapeutic agents that induce autophagy

Drugs	Target identified	Reference
Autophagosome formation		
Imatinib	Bcr-Abl	[38]
Temsirolimus	mTORC1	[35]
Everolimus	mTORC1	[36]
Perhexiline	mTORC1	[37]
Niclosamide	mTORC1	[37]
Amiodarone	mTORC1	[37]
Rottlerin	mTORC1	[37]
Curcumin	mTORC1	[50]
Sorafenib	VEGF	[51]
Resveratrol	?	[52]
EB1089 (vitamin D)	CamKK	[53]
Arsenic trioxide	BNIP3	[54]
AICAR	AMPK	[55]
Metformin	AMPK	[56]
SAHA	HDAC	[42]
Perifosine	Akt	[57]
GSK69O693	Akt	[57]
Triciribine	Akt	[57]
Autophagosome maturation		
SB202190	p38	[58]
PES	HSP70	[43]
STF-62247	?	[49••]