

MINI-REVIEW

Autophagy in Tumorigenesis and Cancer Treatment

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Abstract

Autophagy is a self-digestion process, wrapping cytoplasmic proteins or organelles to form vesicles for degradation in lysosomes. The process plays an important role in the maintenance of intracellular homostasis. Here we overview articles on autophagy and cancer/tumors in Pubmed and found 327 articles. Autophagy exists in many tumors and is involved in cell malignant transformation and tumor cell growth. In early phases of tumorigenesis, autophagy clears the abnormally folded proteins and dysfunctional organelles such as mitochondria. Autophagy can also inhibit cell stress responses and prevent genetic damage. When a tumor develops, autophagy helps tumor cells survive nutritional deficiencies and hypoxic conditions. Studies of autophagy in the occurrence and progression of tumors should provide new therapeutic strategies for tumors.

Keywords: Autophagy - regulatory mechanism - signaling pathway - tumor - cancer treatment

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Introduction

In 1955, de Duve et al. (1955) first described the term “autophagy” to distinguish lysosomal degradation, or cellular “eating” (phagy) of self (auto), from the breakdown of extracellular material (heterophagy). Autophagy is a cytoplasmic, homeostatic process by which cells degrade their interior components, including targets that are too large for other degradative systems, in response to external and internal triggers (Mizushima et al., 2008). With the establishment of the model of autophagy in yeast and the development of gene technology, research on autophagy has been progressing rapidly over the last several decades. Autophagy is not only important to cell growth and differentiation and stress response to the environment but also plays a critical role in preventing some diseases such as cancer and neurodegenerative conditions as well as provides protection against infection of pathogenic microorganisms (White et al., 2011).

Type I programmed cell death (apoptosis) and necrosis are known and widely accepted as two types of cell death in mammals (Galluzzi et al., 2012). Type II programmed cell death (autophagy) is a cellular reuse of their own unnecessary or damaged organelles and macromolecular components, and generates energy and metabolites. Autophagy is a kind of adaptive response to sublethal stress (Hotchkiss et al., 2009) and it allows cells that are in a hungry status or lack of growth factor to survive temporarily. However the cells that cannot obtain nutrition over the long term will die eventually

(autophagy correlation cell death). Therefore autophagy has been identified as the third kind of mode of cell death (Levine et al., 2008). In recent years, the role of autophagy in cancer attracts more attention and likely to offer a new venue of developing novel treatment of cancer.

Definition and Three Kinds of Cell Autophagy

Autophagy was originally used to describe the adaptive response under the electron microscope, which exist in multiple stages of cell disruption. Single or double membrane structure of vacuoles fuse with lysosomes, then encircle and digest cytoplasmic components (including organelles) (Gozuacik et al., 2004; Klionsky, 2007). There are three major types of autophagy in eukaryotic cells-macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA)-and they are mechanistically different from each other (Massey et al., 2004; Klionsky, 2005) (Figure 1). Both macro- and microautophagy involve dynamic membrane rearrangement to engulf portions of the cytoplasm, and they have the capacity for the sequestration of large structures, such as entire organelles. Microautophagy involves the direct engulfment of cytoplasm at the lysosome surface by invagination, protrusion, and septation of the lysosome membrane. In contrast, during macroautophagy, portions of cytoplasm are sequestered into a de novo-formed double-membrane vesicle termed an autophagosome. Subsequently, the completed autophagosome fuses with the lysosome/vacuole and the inner single-membrane vesicle is released

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into the lumen. In either case, the membrane of the resulting autophagic body is lysed to allow the contents to be broken down, and the resulting macromolecules are transported back into the cytosol through membrane permeases for reuse. In contrast, CMA does not involve a similar type of membrane rearrangement; instead, it translocates unfolded, soluble proteins directly across the limiting membrane of the lysosome (Yang et al., 2009).

Autophagy-related Genes (ATG)

Due to the advantage of yeast as a powerful genetic system, researchers have identified 38 autophagy-related genes (ATG) that are specifically involved in autophagy (Huang et al., 2007; Geng et al., 2008; Klionsky, 2014). The autophagy process can be dissected into a series of steps: induction, vesicle nucleation, cargo recognition (for specific types of autophagy) and packaging, vesicle expansion and completion, ATG protein cycling, vesicle fusion with the lysosome/vacuole, vesicle breakdown and nutrient recycling. The ATG proteins can be categorized into different groups according to their functions at the various steps of the pathway. For example, the ATG1 kinase complex is involved in induction (although it also acts at later stages), ATG6 and ATG14 participate in vesicle nucleation, ATG11 and ATG19 are required for cargo recognition and packaging, the ATG8 and ATG12 ubiquitin-like conjugation systems are involved in vesicle formation, and ATG9, ATG23 and ATG27 participate in the 15-17 protein retrieval step (Ohsumi, 2006). Although the majority of the ATG proteins have probably been identified, their exact functions are largely unknown. Continued investigation of the molecular machinery in yeast will provide useful information that will be applicable for studying this process in other organisms. The process of autophagy in higher eukaryotes is essentially the same as that in yeast and mammalian orthologs of many of the yeast ATG genes have been identified. Many homologous ATG genes have been found in mammals. The naming of mammalian autophagy genes and yeast are similar, but there are individual differences, such as yeast ATG8 corresponding mammals LC3, yeast ATG6 corresponding Beclin 1 of mammals. Mammalian autophagy related genes are shown in Table 1 (Klionsky et al., 2003; Tanida et al., 2004).

The Involvement of ATGs and their Signaling Pathway in Tumorigenesis

Autophagy is highly regulated and under the control of a number of signaling pathways. The following is a summary of recent research on the regulation of autophagy.

PI3K-AKT-mTOR pathway

The PI3K-AKT-mTOR pathway (Figure 2) plays an important role in autophagy induction. Activated PI3K generates phosphatidylinositol-3,4,5-triphosphate, which recruits PDK1 and AKT serine/threonine kinase at the plasma membrane. This results in activation of AKT. AKT activates multiple downstream target, including the mTOR pathway. AKT in this pathway is flanked by two

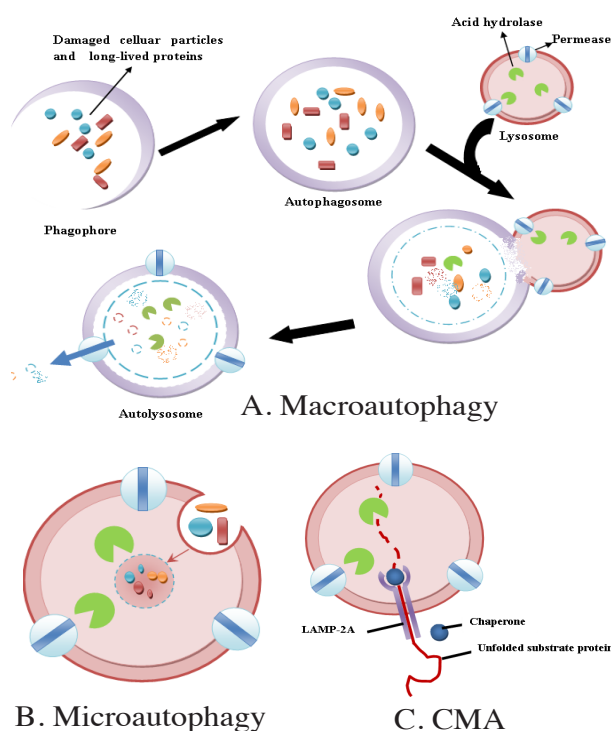


Figure 1. Three Main Types of Autophagy. The schematic depicts these processes in lower and higher eukaryotes. For example, the lysosome is much smaller than the fungal vacuole. Also, chaperone-mediated autophagy has only been characterized in higher eukaryotes, whereas microautophagy and macroautophagy are evolutionarily conserved. Macroautophagy is the best-characterized pathway out of the three and the hallmark of this process is the formation of a double-membrane vesicle that non-selectively sequesters cytoplasmic components and delivers them to the lysosome or vacuole for degradation and recycling of the cargo

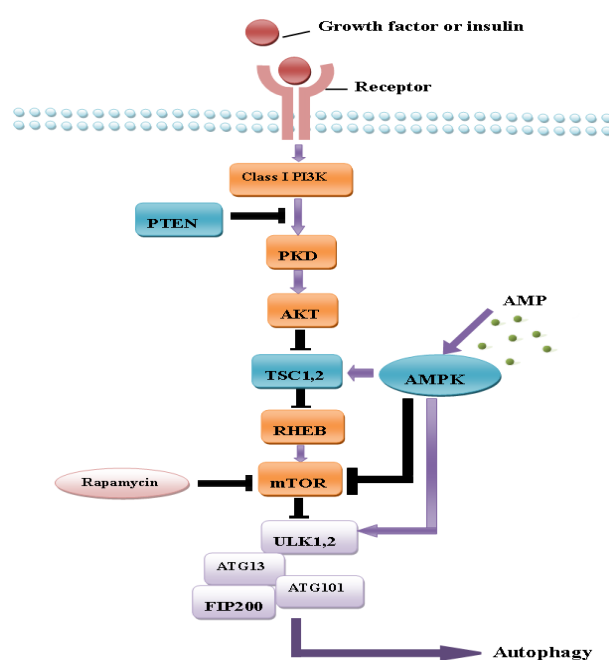


Figure 2. PI3K-AKT-mTOR Pathway: Proteins depicted in orange and blue ultimately inhibit and stimulate, respectively, the activity of the ATG1 kinase complex (the ULK1 and ULK2 complex in mammals) and subsequently, autophagy

Table 1. Mammalian Autophagy Related Genes

Yeast	Human	Mouse
ATG1	ULK1	
ATG3	hATG3/hAPG3	mATG3/mAPG3
ATG4	hATG4A/ HsATG4A/ HsAPG4A/autophagin-2 hATG4B/HsATG4B/ hAPG4B/autophagin-1 hATG4C/HsAUTL1/ autophagin-3 hAPG4D/autophagin-4	
ATG5	hATG5/hAPG5	
ATG6	BECLIN 1	
ATG7	hATG7/HsGSA7/hAPG7	mATG7/mAPG7
ATG8	LC3	
ATG10		mATG10/mAPG10
ATG12	hATG12/hAPG12	mATG12/mAPG12
ATG14	ATG14L	
ATG16		ATG16L/APG16L

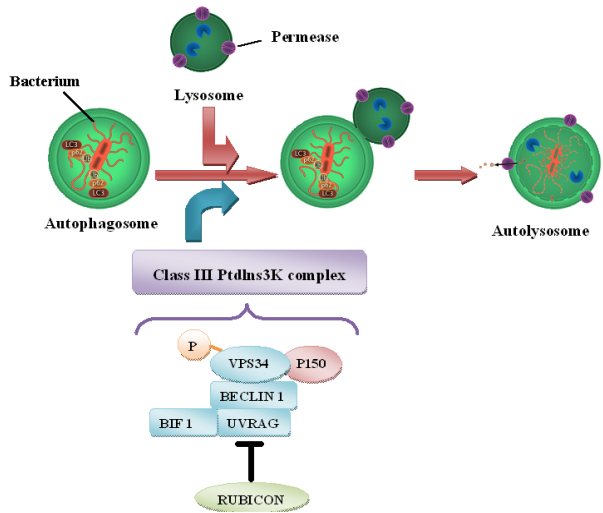


Figure 3. The Vps34 Complex in Autophagosome Formation and Maturation

tumor suppressors, PTEN and TSC1/TSC2 heterodimer. The PI3K-AKT-mTOR axis, a vital process for initiating the autophagy pathway, regulates several biological events including cell cycle and proliferation and is mutated in many human malignancies (Maiuri et al., 2009; Morselli et al., 2009). In tumorigenesis, growth signaling constitutively activates RTKs, which then activate Rheb and PI3K. Rheb is a small GTP-binding protein that activates mTOR in its GTP-bound form, whereas Rheb and PI3K converge to activate mTOR to stimulate cell growth and inhibit autophagy (Ghayad et al., 2010). Because most cancers can harbor activating mutations of master regulators, such as TSC1, TSC2, AKT, and ribosomal S6 kinase (RSK) (Inoki et al., 2009), many cancers exhibit enhanced activation of mTOR and inhibit autophagy. The PI3K-AKT-mTOR pathway is a frequently hyperactivated pathway in cancer and is important for tumor cell growth and survival. The development of targeted therapies against mTOR, a vital substrate along this pathway, led to the approval of allosteric inhibitors, including everolimus and temsirolimus, for the treatment of breast, renal, and

pancreatic cancers (Khan et al., 2013). For example, Chen et al. (2014) found that hypoxia-induced MIR155 could target multiple players in mTOR signaling, and enforced expression of MIR155 could increase autophagic activity in human nasopharyngeal cancer and cervical cancer cells. Furthermore, by downregulating mTOR signaling, MIR155 also attenuates cell proliferation and induces G(1)/S cell cycle arrest. The PI3K-AKT-mTOR pathway is a well established driver of cancer in humans, and therefore blocking different nodes of the pathway is a relevant treatment strategy for human malignancies.

Cass III PI3K(Vps34 in yeast) complex signaling pathway

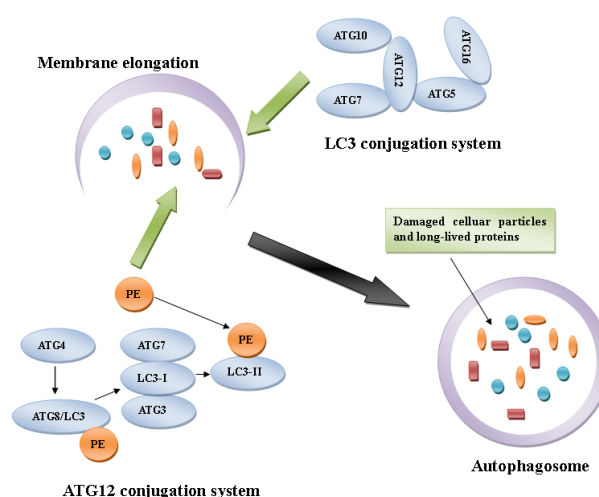
The Vps34 complex is essential for autophagosome formation and maturation. The Vps34 complex generates PtdIns3P, which may allow recruitment of certain ATG components to the phagophore. There are multiple Vps34 complexes, each of which contains the Vps34 lipid kinase, the Vps15 regulatory kinase (p150 in mammals) and ATG6 (BECLIN 1 in mammals). During phagophore formation, the Vps34 complex contains ATG14 (ATG14L in mammals), whereas during maturation into an autolysosome in mammals the complex includes UVRAG. Additional modulating proteins in mammalian cells include AMBRA1, BIF1, RUBICON and HMGB1 (Jaber et al., 2013) (Figure 3).

Emerging evidence suggests that submembers of Vps34 are involved in tumorigenesis. This is especially true for Beclin-1, a phylogenetically conserved protein that is essential for autophagy. In fact, the first association between autophagy and cancer was the landmark discovery of Beclin-1, which is also a haploinsufficient tumor suppressor (Mizushima et al., 2008). In 1999, Liang et al. (1999) used gene transfer techniques in human MCF7 breast carcinoma cells and found that the autophagy promoting activity of Beclin-1 in these cells was associated with inhibition of cellular proliferation. Furthermore, increasing studies show that the Beclin-1 locus (17q21) is frequently subjected to monoallelic deletions in human breast, ovarian, and prostate cancers as well as in brain tumors (Karantza-Wadsworth et al., 2007; DiPaola et al., 2008; Shen et al., 2008). Beclin-1 could be mediated to influence autophagy, tumor progression and chemoresistance. Wei et al. (2013) showed that active epidermal growth factor receptor (EGFR) bound Beclin-1 and led to multisite tyrosine phosphorylation, enhance binding to inhibitors and decrease Beclin-1 associated VPS34 kinase activity. In non-small-cell lung carcinoma tumor xenografts, the expression of a tyrosine phosphomimetic Beclin-1 mutant leads to reduced autophagy, enhanced tumor growth and dedifferentiation.

Further study demonstrated that Beclin-mediated tumor suppress involved a Beclin-1 domain. Through this domain, Beclin-1 directly interact with UVRAG and this interaction is purported to promote binding of Vps34 to Beclin-1. In addition, Bif-1, also known as SH3GLB1 or endophilin B1, was originally discovered as a Bax-binding protein, interacts with Beclin-1 via UVRAG and promotes Vps34 activation and autophagosome formation. *In vivo*, UVRAG has been reported to suppress cell proliferation and tumorigenesis, and monoallelic deletions or mutations

Both ATG12 conjugation and LC3 modification (ATG8 lipidation in yeast) have been reported to take part in the dynamic process of autophagosome formation (Figure 4); ATG12 conjugation is essential for the formation of preautophagosomes, and LC3 modification is necessary for the formation of autophagosomes (Sun et al., 2009). Recent studies suggest that several key regulators of autophagosome in these two conjugation systems, ATG12 and LC3 conjugations, especially those also associated with apoptosis, are correlated with tumorigenesis. For example, ATG5, playing a role in ATG12 conjugation in the procedure of autophagosome membrane elongation and completion, is reported to interact with Bcl-xL. Kang et al. (2009) reported that frameshift mutations of ATG5 in gastric and colorectal cancers may contribute to cancer development by dysregulating the autophagy process. Lee et al. (2009) recently demonstrated that cellular and viral FLICE-like inhibitor protein (FLIPs), which protect cells from apoptosis mediated by death receptors, limit the ATG3-mediated step of LC3 modification to regulate autophagosome biogenesis. Nevertheless, the precise mechanism linking autophagy-related conjugations and tumorigenesis is still unknown and requires further investigation.

p53, a typical tumor suppressor and its mutation could be observed in over 50% human tumor cells (Soussi et al., 2007). Mutant p53 gene can be detected in non-small cell lung cancer and cannot be found in normal lung tissues through immunohistochemistry SP method. The mutation of p53 may be an important molecular basis of lung cancer's occurrence and development (Zhang et al., 2014). p53 plays double-acting role in regulation of autophagy. In nucleus, genotoxic stress caused by DNA-damaging agents induces p53-dependent autophagy. Similarly, oncogenic activation, simulated by forced expression of ARF or p53, induces autophagy in human cancer cells. The mechanisms of p53-dependent induction of autophagy are still incompletely understood, but are thought to involve both transcription-independent functions (for example, AMPK activation), as well as transcription-dependent functions (for example, upregulation of mTOR inhibitors, PTEN and TSC1, or the p53-regulated autophagy and cell death gene, DRAM). In some cases, p53-induced autophagy may lead to cell death and this can be blocked by DRAM siRNA8. However, in cmyc-driven lymphomas, p53-mediated autophagy increases cell survival, as blockade of autophagosomal maturation enhances p53-mediated tumour regression and tumour-cell death. These seemingly disparate effects of p53-mediated autophagy on life and death decisions of the cell may be cell-type or stimulus-specific, and/or reflect the activation



The diagram illustrates the regulation of autophagy by P53. The P53 protein (red box) acts as a central hub, regulating various pathways. In the cytoplasm, P53 inhibits mTOR (light blue box) and promotes AMPK (light blue box). mTOR inhibits TSC1,2 (light blue box), which in turn inhibits AMPK. AMPK promotes P53. P53 also promotes DRAM (light blue box), which promotes Autophagy (purple box). P53 promotes PTEN (light blue box), which inhibits mTOR. P53 promotes DAPK-1 (light blue box), which promotes Autophagy. P53 promotes Bad, Bnip3, Puma, and Bax (light blue box), which inhibit Bcl-2, XL (light blue box). Bcl-2, XL inhibits Vps34 (light blue box), which promotes Autophagy. Bedin1 (light blue box) promotes Vps34. The Nucleus (light blue oval) contains P53 and PTEN. The Cytoplasm (light blue oval) contains the other components.

of a different constellation of p53 signals (Levine et al., 2008; O'Prey et al., 2009). However, p53 was able to inhibit autophagy in enucleated cells and cytoplasm, and the inhibition of p53 could induce autophagy. The mechanisms may be the mTOR pathway could not be activated efficiently after p53 is suppressed (Tasdemir et al., 2008). The Dual regulation of p53 in cell autophagy is shown in Figure 5 (D'Amelio et al., 2009; Maiuri et al., 2009; Sui et al., 2011; White et al., 2011).

The nuclear factor- κ B (NF- κ B) system is a critical signaling pathway induced to defend cells from cellular damage and environmental danger (Karin, 2006; Van Waas, 2007). NF- κ B activation mediates autophagy

repression through effects on mTOR complex in tumor necrosis factor- α (TNF- α)-treated Ewing sarcoma cells (Djavaheri-Mergny et al., 2006). In addition to its role in repressing autophagy, NF- κ B could activate autophagy that the NF- κ B family member p65/RelA (v-rel reticuloendotheliosis viral oncogene homolog A) up-regulated Beclin-1 mRNA and protein levels in different cellular systems (Copetti et al., 2009).

Reactive oxygen species (ROS), as some other signaling molecules, could regulate the activity of ATG4 and induce autophagy in starvation. Starvation stimulates formation of ROS, specifically H₂O₂. These oxidative conditions are essential for autophagy, as treatment with antioxidative agents abolished the formation of autophagosomes and the consequent degradation of proteins. The cysteine protease HsATG4 as a direct target for oxidation by H₂O₂, and specify a cysteine residue located near the HsATG4 catalytic site as a critical for this regulation. Expression of this regulatory mutant prevented the formation of autophagosomes in cells, thus providing a molecular mechanism for redox regulation of the autophagic process (Scherz-Shouval et al., 2007).

Retinoblastoma protein (RB), a key tumor suppressor and RB binding to E2 transcription factor (E2F) is required for autophagy induction and E2F1 antagonizes RB-induced autophagy, leading to apoptosis. Downregulation of E2F1 in cells results in high levels of autophagy. RB could induce autophagy by repressing E2F1 activity (Jiang et al., 2010).

Roles of Autophagy in Tumorigenesis

Autophagy is a lysosomal degradation pathway that acts as a dynamic regulator of tumorigenesis. Specifically, autophagy has been shown to impede early cancer development while facilitating advanced tumor progression (Kenific et al., 2014).

The “pro death” function of autophagy could inhibit the formation and development of tumor. In the process of the formation of tumor cells, lack of autophagy may cause energy imbalance and the quality control deviation of proteins and organelles, which can lead to cell damage caused by metabolic stress. Stimulating the DNA damage response and genome unstable expression is main performance, and these could promote tumor occurrence and development. In recent years, a number of specific genes about autophagy were found missing in human malignant tumor (Levine, 2007; Shi et al., 2013). Activated genes in malignant tumor such as PI3K and AKT can prevent autophagy (Ahn et al., 2007; Maiuri et al., 2009). In mouse models, the inactivation of specific genes about autophagy such as Beclin1, ATG5 can lead to an increased incidence of cancer, and up regulate these genes can inhibit tumor formation (Yorimitsu et al., 2005; Rosenfeldt et al., 2011).

The “pro survival” function of autophagy could promote tumor cells survival in stress. Tumor cells induced autophagy and produces response to metabolic stress. Multiple tumor suppressor genes in human malignant tumors such as p53 and PTEN often mutate, which start the occurrence of autophagy. In addition,

autophagy is confined to the metabolic stress areas in solid tumors (Degenhardt et al., 2006), and autophagy defects in these areas reduce the survival rate of tumor cells, which is associated with the increase of cell death and inflammation (White et al., 2010). Recent studies have uncovered several tumor-promoting functions for autophagy; these include the maintenance of multiple metabolic pathways critical for aggressive tumor growth and the promotion of tumor cell survival downstream of the unfolded protein response. Furthermore, autophagy supports anoikis resistance and cancer cell invasion. At the same time, because autophagy cargo receptors, which are essential for selective autophagy, lie upstream of diverse cancer-promoting signaling pathways, they may profoundly influence how alterations in autophagy affect tumor development (Kenific et al., 2014).

The dual function of autophagy make it complicated on tumor treatment. The “pro death” function can kill tumor cells spontaneously, or to help radiation and chemotherapy kill tumor cells. The “pro survival” function could help the tumor cell survival in nutrition deficiency environment and resist ionizing radiation and chemotherapy. Therefore, this contradiction may lead to more intense debate about the relationship between autophagy and cancer: whether autophagy is good or bad for tumor.

Autophagy as a Tumor-suppressing Mechanism

Deficiencies in autophagy lead to the accumulation of damaged macromolecules and organelles (particularly mitochondria), subsequently inducing oxidative stress, DNA damage and chromatin instability. Thus, autophagic defects are ultimately associated with the accumulation of oncogenic mutations and increased tumor susceptibility. Some of the most important evidence for the role of autophagy in tumor suppression comes from studies on the Bcl-2-interacting protein, Beclin1 (BECN1, also called ATG6), and much study showed that allelic loss of beclin1 promotes mammary tumorigenesis and activation of the DNA damage response in tumors *in vivo* (Karantza-Wadsworth et al., 2007). Furthermore, autophagy has been shown to reduce intratumoral necrosis and local inflammation (Degenhardt et al., 2006). Collectively, these results support the contention that autophagy plays a tumor-suppressing role in cancer, and suggest that reduced autophagic activity may constitute a hallmark of cancer (Hanahan et al., 2011).

At present, autophagy molecular mechanism of inhibiting tumor is not completely understood. More and more evidences suggest that autophagy antitumor effect may be associated with its potential “pro death” and “pro survival” function. The lack of monoallelic Beclin1 or biallelic ATG5 may lead to epithelial tumors, but it will not reduce cell death (Yorimitsu et al., 2005; Rosenfeldt et al., 2009).

Research suggests (Du et al., 2010) that tumor cells cannot die through apoptosis in the condition of metabolic stress; however, autophagy can prevent cell death at this time. Local inflammation may increase once cell necrosis happen, which will increase tumor growth. ATG genes’

missing may increase genomic instability in metabolic stress condition, which leads to proto-oncogene activation and tumor process promotion (Rufini et al., 2011).

In normal cells, it is not clear whether autophagy can make gene expression stable and plays an important role in inhibiting tumor. Another possibility is that autophagy plays a direct role in negative growth. Research shows that enhancing Beclin1 expression does not lead to increased cell death, and can also slow tumor cell line proliferation, reduce the cell cycle regulatory proteins E and phosphorylation of Rb (Koneri et al., 2007). Beclin1, on the other hand, mammary gland epithelial cells and spleen lymphocytes in mice were greatly expanded when monoallelic Beclin1 missing (Qu et al., 2003).

Also studies have shown that although autophagy has “pro survival” effect, autophagy can avoid inappropriate cell differentiation when tumor cells in metabolic stress. In Beclin1 +/- mice, mammary epithelial cells which are in dormant state at usual times can proliferate spontaneously. This suggests that autophagy can coordinate the relationship between environmental signal and the cells enter or maintain in G0. Although it is not clear whether cell survival/death is associated with the tumor inhibition effect of autophagy, but this phenomenon is a very important entry point to tumor treatment in the future. Recently, some scholars questioned the effect of sensitizing tumor cells to cytotoxic therapy by blocking autophagy. One study attributes that the effect of regulating the autophagy depends on the tumor intrinsic properties and the nature of the combination cytotoxic drugs. Thus, although regulating autophagy may affect tumor growth, metastasis and treatment resistance, the unique attributes of tumor and the cytotoxic drugs we choose may decide the result of treatment (Yang et al., 2011).

In fact, in mice lymphoma induced by c-Myc, chloroquine can reduce autophagosomes degradation and enhance p53 or DNA alkylating agent' function of inducing tumor cell death and regression. That means autophagy serves as a potential “pro survival” and antitumor effect in cancer chemotherapy. Chloroquine is effective to both tumor cells and host immune system (Apetoh et al., 2007), so we cannot deduce that its anti-tumor effect is only mediated by inhibiting autophagy. We need more *in vivo* test to compare the advantages of blocking tumor cell survival pathway and the disadvantages of blocking tumor suppressor pathway.

The Role of Autophagy in Cancer Treatment

For all eukaryotes, autophagy specific gene can promote the survival of normal cells in times of nutrient scarcity. Autophagy also could improve the survival ability of tumor cells which is facing lack of oxygen or metabolic stress because of poor blood supply. In some huge tumor, abnormal vascular system will eventually lead to low oxygen, low pH and nutritional deficiency in the center of the tumor cells, and these metabolic stress area is where autophagy occurs (Karantzis-Wadsworth et al., 2007). Therefore, tumor cells could rely on autophagy to survive under the condition of lack of energy and nutrition, and is likely to degrade damaged mitochondria and other

organelles through lysosome. Thus, it can inhibit the activation of tumor suppressor gene or buffer treatment stress to promote the survival of tumor cells. This means we can block autophagy in tumor treatment; on the contrary, the lack of autophagy will lead to cell death, chronic inflammation and genomic instability, which makes tumor easy to happen, so reducing cell damage by autophagy is a new tumor suppressor mechanism (Maiuri et al., 2009). Recent years studies showed that chloroquine as an autophagy inhibitor did not only inhibit autophagy but also inhibit the function of lysosome, so it may be beneficial for tumor therapy (Rosenfeldt et al., 2009). However, excessive autophagy or autophagy happens in cells lack of apoptosis mechanism, could also cause cell death (Ahn et al., 2007). We cannot easily get an conclusion that tumor cells can be killed through turning on or off the autophagy pathway.

In addition, the residual or metastatic tumor cell could survive against metabolic stress through autophagy, and it may be a key mechanism of tumor recurrence (Aguirre-Ghiso, 2006). Thus, inhibition of autophagy has great significance in tumor cells intolerance low metabolic status and improving prognosis.

Now autophagy has been recognized as an important regulator of cancer development and progression and a key factor in determining tumor cell sensitivity to anti-cancer therapy. Numerous conventional and experimental anti-tumor strategies, including combination therapies with autophagy regulators, have shown that targeting autophagy is a beneficial approach to cancer therapy (Li et al., 2011).

Autophagy plays a complicated role in tumorigenesis and treatment responsiveness. It can be tumor-suppressing during the early stages of tumorigenesis, as reduced autophagy is found in tumor cells and may be associated with malignant transformation. In this case, induction of autophagy would seem to be beneficial for cancer prevention. In established tumors, however, autophagy can be tumor-promoting, and cancer cells can use enhanced autophagy to survive under metabolic and therapeutic stress. The pharmacological and/or genetic inhibition of autophagy was recently shown to sensitize cancer cells to the lethal effects of various cancer therapies, including chemotherapy, radiotherapy and targeted therapies, suggesting that suppression of the autophagic pathway may represent a valuable sensitizing strategy for cancer treatments. In contrast, excessive stimulation of autophagy may also provide a therapeutic strategy for treating resistant cancer cells having high apoptotic thresholds. In order for us to develop successful autophagy-modulating strategies against cancer, we need to better understand how the roles of autophagy differ depending on the tumor stage, cell type and/or genetic factors, and we need to determine how specific pathways of autophagy are activated or inhibited by the various anti-cancer therapies.

In short, autophagy play an complex role in tumor biology for its two sides of effects on tumor cells. As a new theory in tumor treatment field, with the further research of the mechanism and function of autophagy, exploring tumor treatment strategy on the level of autophagy has broad prospects.

Plant Natural Drugs Play Anti-cancer Effects Through Autophagy

Natural compounds derived from plant sources are well characterized as possessing a wide variety of remarkable anti-tumour properties, such as modulating apoptosis and autophagy. Here are some anti-tumor natural compounds, and recent studies showed that their anti-tumor effects may be associated with autophagy.

Resveratrol, a natural phytoalexin present in grapes, nuts, and red wine, has antineoplastic activities (Opipari et al., 2004), and it is notable that Resveratrol can inhibit initiation and growth of tumours in a wide range of cancer models. Research proves that resveratrol could induce autophagy through death-associated protein kinase 1 (DAPK1) in human dermal fibroblasts under normal culture conditions (Choi et al., 2013); also, resveratrol could protect H₂O₂-treated H9c2 cells by upregulating autophagy via the p38 MAPK pathway (Lv et al., 2012). Curcumin, derived from turmeric, has been shown to demonstrate activity in a wide range of biological functions, particularly against cancer (Pal et al., 2005). Moreover, curcumin has been reported to regulate autophagy, resulting in inhibition of several types of cancer cell proliferation. Curcumin can significantly decrease the expression of PI3K, phosphorylated Akt and rapamycin (mTOR) at protein levels, respectively. It suggests that curcumin induces autophagy by downregulating PI3K/Akt/mTOR signaling pathway (Wang et al., 2014). Cucurbitacin, isolated from the root of *Hemsleya amabilis*, is another anti-tumor natural compound. Cells treatment with cucurbitacin I up-regulated Beclin 1 and triggered autophagosome formation and accumulation as well as conversion of LC3-I to LC3-II. Activation of the AMP-activated protein kinase/mammalian target of rapamycin/p70S6K pathway, but not the PI3K/AKT pathway, occurred in autophagy induced by cucurbitacin I, which was accompanied by decreased hypoxia-inducible factor 1 α (Yuan et al., 2014). Cucurbitacin family, such as cucurbitacin IIa, cucurbitacin B, cucurbitacin E have some analogous effects (Zhu et al., 2012; He et al., 2013).

There are many other natural compounds from plants, like Matrine, palmitic acid, lycopene, capsaicin, deguelin and quercetin have been found to induce cancer cell death by regulation of autophagy (Choi et al., 2010; Wang et al., 2013; Yang et al., 2013; Chen et al., 2014; Chen et al., 2014; Tu et al., 2014). With the accumulating exploration of molecular mechanisms of plant natural compound activity, they have been widely used as candidate anti-tumour agents; more importantly, some have been further applied to preclinical and clinical cancer therapies.

Conclusions

In summary, autophagy is a ubiquitous process in eukaryotic cells that results in the breakdown of cytoplasm within the lysosome in response to stress conditions, which allows the cell to adapt to environmental and/or developmental changes. Increasing evidence indicates that autophagy is associated with a number of pathological process, including cancer. We have already found several

key autophagic mediators (eg, Beclin1, UVRAG, Class III and I PI3K, mTOR, and p53) that play important roles in autophagic signaling networks in cancer. However, Cancer is a complex, multi-step human disease that is closely related to the Janus of autophagy. Currently, much work should be done to determine the molecular mechanisms of autophagy in cancer, to define how the crucial modulators of autophagy in cancer impacts cancer initiation and progression, and to elucidate why targeting autophagic signaling pathways is promising for cancer therapeutics. The present research shows that appropriate modification of autophagy, that is, suppression of cell-protective autophagy or enhancement of cell-killing autophagy, can augment cytotoxicity caused by anti-cancer therapy. Hence, modulating autophagy will open new areas for cancer therapy.

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