1. Introduction

Autophagy is a self-eating pathway that converts the damaged cellular components to new cell components. This process is characterized by formation of double membrane autophagosomes. Digestion and regeneration of unwanted damaged cellular components occurred by overexpression of the autophagic genes that enables the cells to create vacuoles in which cellular damaged organelles are degraded after fusion of these vacuoles with lysosomes. The digested materials are recycled to provide nutrients for the cell (Shao et al., 2018). Autophagy is an important mechanism for cell survival, in particular when cells are under stress conditions such as oxidative stress and starvation (Seda et al., 2018; Zhong et al., 2018). However, autophagy also participates in the etiopathogenesis of many important human diseases, such as cancer, and metabolic disorders (Dianshan et al., 2018). Autophagy abnormalities in various diseases have been reported, including neurodegenerative diseases, lysosomal storage diseases, infections, metabolic diseases, ischemia / reperfusion and cancer (Schneider and Cuervo, 2014).

2. Mechanism of autophagy

After autophagy induction, double-membrane autophagosomes are formed in the cytoplasm to degrade damaged cytoplasmic components (Yoshihiko, 2018). This degradation is mainly controlled by GTPases where guanosine diphosphate (GDP) and guanosine triphosphate (GTP) act as autophagy stimulator and inhibitor, respectively (Yong et al., 2018). Apg protein conjugation system (including Apg5, Apg7, and Apg12) is involved in this degradation (Ashok et al., 2018; Elizabeth and Daniel, 2018; Noboru, 2018). The fusion between autophagosomes and lysosome causes the inner membrane of the autophagosome to release the autophagic body into the lysosome lumen. The autophagous body is decomposed due to the degrading nature of the lysosome (Levent et al., 2018) and its components (Yoshihiko, 2018). This degradation is mainly controlled by the ligase-like Atg7 protein E1 (Lee et al., 2012). Phosphatidylethanolamine (PE), a lipid molecule considered to anchorAtg8/LC3-II to membranes, is a crucial element of the LC3-modifying system; Atg8/LC3-I (mammalian MAP / LC3 proteins) is linked to PE in a series of biochemical reactions assisted by Atg7 and transformed into Atg8/LC3-II, leading to the autophagic vacuoles formation (Behrends et al., 2010).

3. Types of autophagy

There are three types of autophagy: microautophagy, autophagy mediated by chaperone (CMA) and macroautophagy. In microautophagy, the binding between the membranes of cellular lysosome and autophagic vacuole occurred for damaged cytosolic components engulfment, in addition, microautophagic vacuoles play an active role in the organelle size maintenance (Mijaljica and Devenish, 2011; Nicole et al., 2018). In chaperone-mediated autophagy, which composed of chaperon complex proteins consisting of HSC70 (HSP70 family heat shock cognate) that play a great role in directing of proteins containing the targeting and recognition motif and its co-chaperones to lysosomes, the selective breakdown of a variety of specific soluble and damaged proteins are allowed in lysosomes. The target of chaperone-mediated autophagy is proteins oxidized and misfolded elimination, and it contributes to the response of starvation (Kaushik and Cuervo, 2012).

The Macro-autophagy is most common and great cellular autophagic pathway. In this pathway, autophagosomes or autophagic vesicles are synthesized in the cytosol and composed of double membrane autophagosomes. Double membrane autophagosomes are formed in the cytoplasm to degrade damaged cytoplasmic components. After autophagy induction, double-membrane autophagosomes are formed in the cytoplasm to degrade damaged cytoplasmic components (Yoshihiko, 2018). This degradation is mainly controlled by GTPases where guanosine diphosphate (GDP) and guanosine triphosphate (GTP) act as autophagy stimulator and inhibitor, respectively (Yong et al., 2018).

After autophagy induction, double-membrane autophagosomes are formed in the cytoplasm to degrade damaged cytoplasmic components (Yoshihiko, 2018). This degradation is mainly controlled by GTPases where guanosine diphosphate (GDP) and guanosine triphosphate (GTP) act as autophagy stimulator and inhibitor, respectively (Yong et al., 2018). Apg protein conjugation system (including Apg5, Apg7, and Apg12) is involved in this degradation (Ashok et al., 2018; Elizabeth and Daniel, 2018; Noboru, 2018). The fusion between autophagosomes and lysosome causes the inner membrane of the autophagosome to release the autophagic body into the lysosome lumen. The autophagous body is decomposed due to the degrading nature of the lysosome (Levent et al., 2018) and its components (Yoshihiko, 2018). This degradation is mainly controlled by the ligase-like Atg7 protein E1 (Lee et al., 2012). Phosphatidylethanolamine (PE), a lipid molecule considered to anchorAtg8/LC3-II to membranes, is a crucial element of the LC3-modifying system; Atg8/LC3-I (mammalian MAP / LC3 proteins) is linked to PE in a series of biochemical reactions assisted by Atg7 and transformed into Atg8/LC3-II, leading to the autophagic vacuoles formation (Behrends et al., 2010).

The microtubule-associated light protein chain 3 (LC3), a mammalian Atg8 yeast homologue, is located in autolysosomes and autophagosomes. LC3-II is linked to the degree of autophagosome formation, and provide the initial molecular marker for the autophagic activity detection (Beatriz et al., 2018). The Beclin-1 (yeast Atg6 mammalian homologue) plays a central role in the formation of autophagous vacuoles (Chen and Klionsky, 2011). Atg12 is conjugated immediately after its synthesis to Atg5 in the first ubiquitin-like system, and this process is primarily regulated by the ligase-likeAgt protein E1 (Lee et al., 2012). The Atg12/Atg5 complex then leads to larger protein complexes formation, which are further transported to the membrane, which is necessary for autophagic vesicles formation (Beatriz et al., 2018). Phosphatidylyethanolamine (PE), a lipid molecule considered to anchorAtg8/LC3-II to membranes, is a crucial element of the LC3-modifying system; Atg8/LC3-I (mammalian MAP / LC3 proteins) is linked to PE in a series of biochemical reactions assisted by Atg7 and transformed into Atg8/LC3-II, leading to the autophagic vacuoles formation (Behrends et al., 2010).

Abstract

Autophagy is a survival process in which a cell preserves its components in case of nutrient deprivation by recycling its digested contents and cannibalizing itself. It is characterized by formation of double membrane autophagosomes and it has a role in cancer treatment by many mechanisms. Interestingly, autophagy has a significant effect in the treatment of many diseases by different mechanisms. Autophagy has been included as a treatment mechanism of various diseases, such as degenerative diseases of the muscle and nervous system. Abundant autophagic vacuoles were formed inside the damaged cells in many of these degenerative disorders. Autophagy can help both living cells and cancer cells to survive so some antitumor agents targeted autophagy in cancer cells. In this review, we illustrated the definition of autophagy, autophagic pathways, therapeutic implications of autophagy in cancer, the relationship between autophagy and cell death, inflammation, and necrosis.
membrane structures “isolation membranes” for macromolecules engulfment and degradation. Autophagosomal outer membrane fuses to membranes of lysosome leads to the transfer of autophagic macromolecules into the lysosome lumen and autolysosome formation. Inside autolysosomes, the hydrolysis of the autophagic macromolecules into their building blocks by hydrolases enzymes occur to allow recycling them back to cytosol. The transition to mitochondrial permeability conversion pore to an open state leads to mitochondrial degradation by macroautophagy and thereafter necrosis and apoptosis (Didad et al., 2018; Sabateshan et al., 2018). Then, macroautophagy protects oxidative damage cells that results from mitochondrial integrity loss without apoptosis triggering (Dawson and Cho, 2000). Mitochondria has been detected in autophagosomes in the yeast (Xueyan et al., 2018) to provide additional evidence for macroautophagic mitochondrial degradation.

4. Autophagy and cancer

Autophagy has multiple roles in both cancer therapy and carcinogenesis (Liu and Ryan, 2012). The tumorigenesis initiation may be inhibited by autophagy by preventing the damage of cellular cytoplasm, genomic instability and subsequent inflammation and functional loss of certain genes of autophagy may predispose the cellular biological system to cancer. Autophagy also causes cell senescence that can stop the progression of cancer. In contrast, autophagy may also be a protective pathway through the preservation of cancer cell survival. The treatment of renal cell carcinoma promised new agents, such as mTOR inhibitors that induce autophagy (Anbalagan et al., 2012). Preclinical models and early phase autophagy clinical studies are underway to study inhibition of autophagy in the restoration of chemosensitivity and enhanced tumor cells (Yang et al. 2011). Indeed, targeted cancer autophagy manipulation will provide new therapeutic avenues for drug development and optimum therapeutic strategies for cancer treatment in patients (Lee et al., 2012).

4.1. Autophagy and apoptosis of cancer cells

A complex interplay between cell survival and/or death, including necrosis, apoptosis and autophagy, can regulate tumor metastasis and carcinogenesis afterwards. In addition, tumor vascular insufficiency can lead to glucose/oxygen depletion and participation in increasing the production of reactive oxygen species, extracellular acidosis in the micro-environment of the tumor which may eventually lead to autophagy, involving depletion of glucose and/or deprivation as important autophagy trigger (Petiot et al., 2000).

Beclin, a key player in the autophagy signal transduction pathway, acts as a tumor suppressor gene (Sanaz et al., 2018). Beclin1 can be a critical molecular switch between autophagy and apoptosis via caspase-9, thus regulating tumorigenesis (Wang et al., 2007). Beclin 1 can bind to Bcl-2 which is an antiapoptotic protein for prevention of mitochondrial cytosome c release which depends on Bax. Reduced levels of the Beclin 1 protein were correlated with breast tumor development or progression. Beclin1 regulates anti-tumor activity and Beclin1 overexpression in cells may enhance paclitaxel-induced apoptotic cell death (Sun et al., 2010). Autophagy and apoptosis may have differential contributions to carboplatin-induced cancer cells death; overexpression of Beclin1 in cells may enhance apoptosis signaling. However, Autophagy prevents cisplatin-induced apoptosis in cancer cells suggesting that autophagy inhibition may improve cisplatin chemotherapy (Xu et al., 2012). In addition, recent study by our group proved that trehalose which is a natural disaccharide and safe treatment with low toxicity as we proved also can induce the antitumor potential of chemotherapeutic drug methotrexate against mice bearing Ehrlich ascites carcinoma (EAC) through induction of apoptosis and oxidative stress, and inhibition of autophagy in EAC cells (El-Magd et al., 2017).

Autophagy is specifically associated with the programmed cell death of type II (nonapoptotic) (Bursch et al., 2000). However, it has been indicated that early stages of autophagy may play a role in the programmed cell death of type I apoptotic. It has been shown that human apoptosis-specific protein is homologous to the APG5 gene product. In fact, oncogenic transformations, such as the activation of the PI3K / Akt pathway through the activation of PI3 K mutations, AKT amplifications or loss of phosphatase and tensin homolog(PTEN), are correlated with reduced autophagy through mTOR activation in different cases (Sinha and Levin, 2008). In the malignant necrotic core / cancerous cells, hypoxia and vascular insufficiency of microenvironment of the tumor contributes to drug resistance and progression of cancer (Fels et al., 2008). It has been suggested that the cell death mode was cell type-dependent as colorectal carcinoma cells DLD1 showed enhanced apoptosis while carcinoma cells activated autophagy, blocked apoptosis and eventually led to necrosis; autophagic genetic or pharmacological ablation was associated with increased apoptosis levels.

The coordinated regulation of Akt (protein kinase B) and the ribosomal protein S6 kinase (p70S6 kinase) also showed an interesting connection between autophagy and apoptosis. The activity of P70S6 kinase is controlled by mTor by phosphoinositide-dependent protein kinase-1, PDK1 (Pullen et al., 1998). PDK1 is a multifunctional effector which can control different kinases. (Vanhaesebroeck and Alessi, 2000). Phosphorylation by mTor P70S6 kinase, or presumably PDK1, can prevent autophagy. The activity of class I phosphatidylinositol 3-kinase (PI 3-kinase) enables Akt to be recruited by its pleckstrin homology domain. Phosphorylation PDK1 activates Akt and prevents apoptosis (Hemmings, 1997). Thus, apoptosis and autophagy may be blocked by class I PI3-dependent PDK1 products. It has been shown that certain of the same signals that induce apoptosis may trigger autophagy (Suh et al., 2018). Autophagy can cause cell death even when apoptosis inhibitors are present when it is activated. Previous findings support the idea that autophagy is the second mechanism of cell death programming. In fact, programmed cell death related to autophagy may have evolved before apoptosis (Jiyao et al., 2018).

4.2. Autophagy inhibits inflammation in tumor

Inflammation can contribute to tumor development and proliferation. Chronic inflammation is in fact a common future for the development of early cancer. Also, autophagy has been suggested that different mechanisms can modulate these inflammatory reactions, as autophagy-deficient tumors show an increased necrosis and inflammation. Autophagy activation in tumor cells has been reported to be able to inhibit necrotic cell death. In contrast to apoptotic cell death, necrosis-dying cells stimulate a strong inflammatory response in vivo (Kono and Rock, 2008). Impairment of both autophagy and apoptosis has been reported to promote in vitro and in vivo necrotic cell death associated with an inflammatory response and an increased tumor growth (Degenhardt et al., 2006). Autophagy has been suggested to participate in the regulation of cell death caused by necrosis and therefore in subsequent inflammation.
4.3. Autophagy prevents genomic instability and oxidative stress in cancer cells

The involvement of autophagy in oxidative stress management and maintenance of genomic integrity seems to be linked to its antitumorigenic activity. Autophagy has been shown to reduce the damage of DNA, chromosomal instability and aneuploidy that can explain its antitumorigenic activity (Mathew et al., 2007). It has been suggested in previous studies that the ubiquitin and LC3-binding p62 protein can play a decisive role. Indeed, the inability of autophagy-deficient cells to degrade p62 causes this protein to accumulate abnormally, which promotes tumorigenesis (Mathew et al., 2009). It has been shown in our recent studies that trehalose acts as an anticancer novel treatment by modulating oxidative stress with decreasing the autophagic activities and increasing the apoptotic activities of cancer cells (Eldeen et al., 2018; El-Magd et al., 2018).

Summary

Autophagy is a self-eating pathway that converts the damaged cellular components to new cell components and this process is characterized by the double membrane autophagosomes formation. Autophagy can help both living cells and cancer cells to survive and prevent apoptosis. Cautions should be taken when using autophagy inhibitor to target cancer cells as this may negatively affect health cells.

References


Dianshan Ke, Xiaomin Fu, Ying Xue, Haojie Wu, et al., 2018. IL-17A regulates the autophagic activity of osteoclast precursors through RANKL-JNK1 signaling during osteoclastogenesis in vitro. Biochemical and Biophysical Research Communications., 497 (3):890-896.


Nasr Eldeen et al., 2019, AJMS 2 (2):27-29, DOI:10.5455/ajms.19

Nasr Eldeen et al., 2018, AJMS 2 (2):27-29, DOI:10.5455/ajms.19

Nasr Eldeen et al., 2019, AJMS 2 (2):27-29, DOI:10.5455/ajms.19


