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Review

The emerging role of oxidative stress in regulating autophagy: applications of cancer therapy

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Abstract: Emerging evidences show that autophagy, as a major cellular adaptive degradation mechanism, is involved in tumorigenesis, cell aging, inflammation and neurodegeneration. It has been reported that multiple stresses including nutrient deprivation, pathogen infection, oxidative stress, endoplasmic reticulum (ER) stress and metabolic stress can influence cellular autophagy, leading to distinct cell fate. Although numerous studies have been employed to elucidate the probable issues, the underlying mechanism of the initiation and maturation of autophagy remains unclear. Herein, we discuss the possible cause and effect relationship between oxidative stress and autophagy, as well as the potential molecular mechanisms that oxidative stress may mediate the role of autophagy in cancer therapy, therefore shed some light on new therapeutic strategies of cancer.

Key words: Autophagy; ROS (reactive oxygen species); Cancer therapy.

Introduction

Autophagy, known as a cellular "self-eating" incident, is a conserved process that enables cells to degrade damaged or unwanted cytoplasmic organelles and protein aggregated in the lysosome, thus play a critical role in the maintenance of cellular homeostasis (1-3). Basically, autophagy comprises three types that cells can utilize to deliver cytoplasmic materials which need to be degraded, including macroautophagy, microautophagy, and chaperone-mediated autophagy(CMA) (4). Beyond its function of self-cannibalism, autophagy is prominent in restoring resource since the products of autophagy such as nucleotides, amino acids and fatty acids can be circulated as cellular building block (5). Dysfunction of autophagy pathway might lead to multifarious diseases, from neurodegenerative disease, metabolic disease to cancer (6,7). Generally, stimuli-induced autophagy is an adaptive response which is thought to be cytoprotective (8). However, in neoplastic cells, autophagy is domesticated to cope with various stress and thus manages to favor tumorigenesis progression. In this scenario, autophagy can be a potential target for cancer therapy (9,10).

The regulation of oxidative stress is pivotal in both autophagy and tumorigenesis, since many signaling pathways involved in autophagy and tumorigenesis can be modulated by reactive oxygen species(ROS) through direct or indirect ways (11,12). ROS are characterized as oxygen-contained species with high reactive properties, including oxygen free radicals, such as hydroxyl free radicals ($HO^{\bullet}$), superoxide ($O^{2\bullet-}$) and non-radical molecules such as hydrogen peroxide (H_2O_2) (13,14). The excitation of ROS has been associated with endoplasmic reticulum (ER) stress, starvation, dysfunction of mitochondrial, and ROS is defined as byproducts of metabolic reactions in mitochondrial, ER, and peroxisomes (15-19). ROS have high reactive properties with cellular molecules, including DNA, lipids and proteins. Low to moderate levels of ROS can work as second messengers which could mediate the activation or expression of multiple signaling proteins such as mitogen-activated protein kinase (MAPK) (20), AMPK (21), Akt (22), extracellular signal-regulated kinase (ERK) (23,24), JNK (25), all of which are involved in cancer cell survival and proliferation. Excessive ROS are detrimental and could trigger cellular genetic damage or cell death, since high levels ROS may cause irreversible oxidative damage on biomacromolecules (26). Unraveling the regulation of cellular events at molecule levels by ROS may provide novel therapeutic basis for various diseases, such as cardiovascular diseases (27), diabetes (28), especially cancer (29). Here, we consider the versatile faces autophagy plays in cancer therapy as well as the emerging role of ROS in shaping the autophagy, thereon try to shed some lights on ways to develop novel strategies for cancer therapy.

An overview of autophagy

Macroautophagy, hereafter referred simply as autophagy, is known as the primary type of autophagy and is best studied (30). Autophagy is a multistep process and proved to include initiation, nucleation, elongation, closure, and mature degradation (31). The initiation of

autophagy is associated with the formation of isolated membrane structure, which we called phagophore (autophagosome precursor). Although the original sources of isolation membrane are still disputable, the plasma membrane, outer membrane of mitochondria, ER membrane, Golgi complex are reported to be closely linked to the premier membrane nucleation of autophagy (32) (Fig. 1). The Unc51-like kinase 1 (ULK1) complex and class III PI3K(PI3KC3)/Vps34 complex is assigned to orchestrate the nucleation and assembly of the phagophore, ULK complex comprise ULK1/2 (orthologs of ATG1 in yeast), Atg13, Atg101 and FIP200 (FAK family kinase-interacting protein of 200 kDa) while class III PI3K complex consist of PI3K3/Vps34, p150/Vps15, and Beclin1(33). Once the ULK complex is activated, class III PI3K complex are phosphorylated and dissociated with microtubules, resulting in the approach of class III PI3K complex to ER (10) (Fig 2). And it is demonstrated that phosphatidylinositol-3-phosphate was generated to promote the nucleation of autophagosome when class III PI3K complex is activated (34). Beclin 1 is confirmed to enhance the activity of class III PI3K complex, and several apoptotic-associated proteins such as Bcl-2 and Bcl-XL are reported to bind with beclin 1 through BH3 domain and thus restrain autophagy (35,36), while UVRAG, the UV radiation resistance-associated gene protein, can activate the Beclin1-class III PI3K complex and enhance the tenor of autophagy (37) (Fig. 2).

Large number of autophagy-related (ATG) proteins are involved in the biogenesis, elongation, and sealing of the autophagosome, where two ubiquitin-like conjugation systems play critical roles in (38). The glycine residue of ATG12 is conjugated to the lysine residue of ATG5 through the ubiquitination-like system which contains ATG7, an E1-like enzymes (39), and ATG10, an E2-like enzymes (40). The complex of ATG5-ATG12 is further conjugated with dimeric ATG16 noncovalently (41). The proautophagic function of ATG5 can be regulated by calcium-dependent activation of the cysteine protease, known as calpain, which can cleave Atg5 at its Thr 193 and ultimately inhibit autophagy (42). The ATG12-ATG5-ATG16 complex function as a E3-like enzymes and promote lipid phosphatidylethanolamine (PE) integrating with the soluble microtubules-associated light chain-3 (LC3-I), a form which is cleaved by ATG4. LC3-I is obtained through Pre-LC3 cleavage by ATG4 and then undergoes ATG7 and ATG3 transition. The product is the substrate of ATG12-ATG5-ATG16

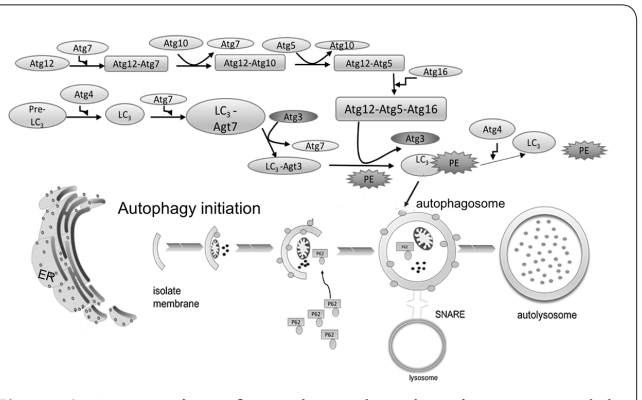

Figure 1. An overview of autophagy about how it appears and the proteins involved in autophagy formation.

(43,44). The lipidated LC3, which we called LC3-II, can conjugate with autophagosome membrane stably, and is widely used as a marker of the induction of autophagy (45). It has been evidenced that ATG16 plays a pivotal role in targeting the ATG12-ATG5-ATG16 complex to autophagosome membrane, however, has no E3-like enzymatic activity *in vitro* (46). Several adaptors are capable of recognizing and recruiting the cargoes needed to be degraded, such as sequestosome 1 (p62) and Neighbor of BRCA1 (NBR1). The p62 is widely established as a receptor which can bind with ubiquitinated proteins and transfer them to autophagosome through its ubiquitin-association (UBA) domain and LC3 interaction region (LIR) (47,48). As a matter of fact, although p62 and NBR1 have been demonstrated to participate the delivery of autophagic cargoes, the underlying mechanisms remain largely unknown. After maturation, completely sealed autophagosomes fuse with the lysosome and form an autolysosome, where the cargo sequestered in the autophagosome and the inner membrane of autophagosome can be degraded by the lysosomal hydrolases. Soluble NSF attachment protein receptors (SNAREs) and homotypic fusion, vacuole protein sorting (HOPS) are reported to be primary regulators during the fusion of autophagosome and lysosome (49). Subsequently, the products emerged in the lysosome can be transported to the cytosol and recycled as building block (3). Autophagy is further classified into two different types, including selective autophagy and non-selective autophagy. According to the substrates, selective autophagy can be divided into mitophagy (50), xenophagy (51), pexophagy (52). (Fig. 1).

The intersection between autophagy and cancer therapy

It is generally thought that autophagy has both positive and negative roles in cancer progression, in response to radiation and chemotherapy (53). Increasing studies have demonstrated that the role of autophagy in chemotherapy is primarily protective, which suggested that the promotion of established autophagy was an explanation of drug resistance. However, numerous studies showed that the opposite role of autophagy. That is, autophagy is cytotoxic rather than protective in some cases. What's more, on the basis of data from recent literatures, in addition to dual roles of autophagy mentioned above, there are two more that scientists concerned about: nonprotective autophagy and cytostatic autophagy, both of which are rarely reviewed.

Much evidences reveal that autophagy could act as a tumor suppressor through several mechanisms. First, autophagy is emerged as a cell-autonomous machinery to maintain the cellular homeostasis under conditions of various stresses including starvation, infection, metabolic stress, thus mitigating oncogenic protein aggregates, damaged organelles and ultimately preventing cells from tumorigenesis (54). Second, ROS are highly genotoxic since excessive ROS lead to gene instability and DNA damage. Beyond its function in clearance of damaged or unwanted macromolecules, autophagy also plays a important role in obliterating excessive ROS by eliminating damaged mitochondria and redox-active proteins (55). Autophagy defects leads to the accumulation of

damaged mitochondria which is an original source of ROS. Once ROS overwhelm the cellular NRF2 antioxidant system, that is, the activation of NRF2 is not sufficient enough to sweep away superabundant ROS, genome mutations may occur and tumorigenesis is on the way (56). NRF2 is constantly binding with kelch-like ECH-associated protein 1 (KEAP1, a negative regulator of NRF2) and degraded in normal conditions (57). However, in the presence of oxidative stress, KEAP1 is modified by ROS and dissociated from NRF2, the free NRF2 is then translocating to nucleus, binding with the antioxidant response element (ARE) and initiating the expression of numerous antioxidant proteins and phase II enzymes, such as HO-1, SOD1, CAT, NQO1, GST, GCS (58-60). Third, mounting evidence affirmed that autophagy can also mediate the activation of NRF2 by p62. In autophagy defective cells, p62 is abnormally accumulated (61). p62 can interact with KEAP1 through its KEAP1-interacting region (KIR), which results in the dissociation of NRF2 from KEAP1 and thus turning on the antioxidant system (62,63). In this scenery, KEAP1-NRF2 pathway is no longer tumor suppressive but may be a protumorigenic way which promote cell survival (54,64). Furthermore, the regulatory-associated protein of mTOR (RAPTOR) can also bind with p62, which leads to the activation of mTORC1 and thus contributing to cell growth and nutrient sensing. In deed, p62 plays significant role in the compartmentalization and activation of mTORC1(65). (Fig. 2) Moreover, sustained accumulation of p62 has been demonstrated to activate the pro-inflammatory NF-κB pathway by interactions with RIP1 and tumor necrosis factor receptor- associated factor 6 (TRAF6) through its ZZ domain, leading to a non-cell-autonomous mechanism of tumorigenesis (66-68).

The tumor suppressor role of autophagy was also strengthened by the finding that the death-effector domain-containing DNA-binding protein (DEDD) could domesticate autophagy by physically interacting with Beclin1-class III PI3K complex, leading to the autophagy-dependent degradation of Snail and Twist, thus attenuating epithelial-to-mesenchymal transition (EMT) in cancer cells (69). In addition, it has been proved that the Beclin1-class III PI3K complex could mediate the deubiquitination activity and stability of USP10 and USP13, both of which are deubiquitinating enzymes. Since USP10 regulates the deubiquitination of p53, this study provides a mechanism that how Beclin 1, as a tumor suppressor, affect the progression of tumorigenesis (70). This is consistent with observations that functional Beclin 1 inhibits the proliferation of various tumor, including lymphomas, hepato-cellular carcinomas, and lung carcinomas (6).

Three function of autophagy in cancer therapy

Cytotoxic function

Actually, the cause-and-effect association between autophagy and cytotoxic is not always an unequivocal argument. Since autophagy might initiate to protect cells in response to the stresses of cancer treatments at the very start, however, as the quantity of damaged proteins and organelles reached a certain level, autophagy may promote cell death to remove damaged cells. This kind of cell death, different from apoptosis (type I programmed cell death), is called autophagic cell death or type II programmed cell death (PCD) . Unlike apoptosis, during autophagic cell death, the activation of caspases is not involved and fragmentation of DNA can not be observed. Instead, increased number of autophagic vesicles, degradation of golgi apparatus, polyribosomes and endoplasmic reticulum can be characterized as hallmarks of autophagic cell death. Given that apoptosis signaling pathway is always inhibited in drug resistant cancer cells, autophagic cell death can be a promising target for cancer therapy. However, the underlying mechanism of autophagic cell death remains largely elusive. Another controversial issue is that autophagy contribute to cell death by itself or just promote lethal ways such as apoptosis or necrosis so as to execute cell death? In this regard, inhibition of autophagy could obviously lead to increased cell survival, however, it is hard to distinguish the cells die *with* autophagy from cells die *by* autophagy (71). Although autophagy can influence the fate of cell independently (act as protective autophagy or cytotoxic autophagy), the crosstalk between autophagy and apoptosis even make it more intricately (72). As we mentioned above, anti-apoptotic proteins such as Bcl-2 and Bcl-XL could bind with Beclin 1 and thus inhibit autophagy progression (Fig 2). It is worth mentioning that the well known tumor suppressor p53, can also exert influence on both autophagy and apoptosis via its subcellular localization. When present in the cytoplasm, p53 inhibits autophagy by decreasing the activity of ULK complex through interaction with FIP200, a important component of the ULK complex. Once the p53 translocated into the nucleus, pro-autophagic molecules such as AMPK (AMP-activated protein kinase) and DRAM1(damage-regulated autophagy modulator 1) can be transcriptionally unregulated by the combination of their promoter region and p53, thus induce autophagy (Fig 2). Moreover, p53 in nucleus could also enhance the expression of multiple pro-apoptotic gene and triggers cell death. Alternatively, to p53, some Ser/Thr kinases, including DAPK (death-associated protein kinase), JNK (JUN N-terminal kinase) have im-

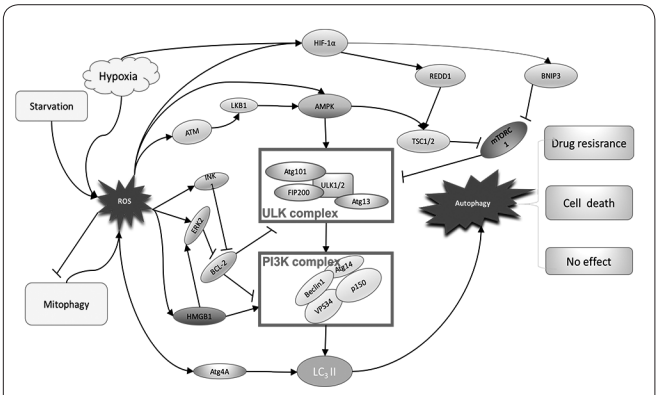

Figure 2. Signaling pathways about how ROS influences autophagy formation and the proteins participate in the process as a bridge. ROS could be induced by many endogenous or exogenous stimulations such as hypoxia, starvation and mitophagy. HIF1 α, ATM, AMPK, ERK2, ATG4 and HMGB1 are downstream factors activated after ROS induction. Those factors either initiate autophagy or participate in autophagy elongation through ULK complex or PI3K complex formation. Induction of autophagy could involve in drug resistance, cell death and any other cell processes.

plicated in regulating both of the apoptosis and autophagy. DAPK could phosphorylate Beclin 1 at its Thr119 and hence inhibit the interaction between Beclin 1 and Bcl-XL or Bcl-2. Concurrently, it has been reported that DAPK can also mediate the activity of protein kinase D (PKD), which activates VPS34, a critical component of class III PI3K complex. All theses result in the induction of autophagy. JNK can regulate both apoptosis and autophagy through the capacity to phosphorylate Bcl-2. The phosphorylation of Bcl-2 leads to the dissociation of Bcl-2 with Beclin 1 as well as the pro-apoptotic proteins (Fig 2). With the scope of elucidating the complicated crosstalk between autophagy and apoptosis in the context of cancer cells and hence excavating potential therapeutic targets, it will be crucial to unveil the underlying mechanism.

Protective function

It is widely accepted that as tumor proceeding, cancer cells may face various stresses including nutrition starvation, oxidative stress and hypoxia due to the insufficient vascularization. Furthermore, when treated with chemotherapeutics or radiation which could effect cellular signaling pathways, autophagy can be promoted to maintain the homeostasis and finally lead to the drug resistance of cancer cells (73). In this case, inhibition of autophagy could increase the sensitivity of cancer cells to therapy and boost the curative effect of chemotherapy agents. Abundant literatures indicated that autophagy can be authentically inhibited both through the inhibitor of early stage and late stage of autophagic process. For instance, vinblastine, HCQ (Hydroxychloroquine) (74), CQ(Chloroquine), and baflomycin A1 (which target the late stage of autophagy), as well as 3-MA (3-Methyladenine), wortmannin (which target the early stage of autophagy) or the interfering of vital ATG proteins such as ATG5, ATG7, ATG12 can be employed to enhance the sensitivity of cancer cells to therapeutical strategies. Recent studies demonstrated that some tumors driven by the oncogenic mutant RAS and B-RAF could develop autophagy orientation process called "autophagy addiction", highly active autophagy appeared to be essential for promoting the transformation and homeostasis of tumor (75-77). A phase I study of combination treatment comprising HCQ and doxorubicin on dog with spontaneous non-Hodgkin's lymphoma was launched and indicated that HCQ could indeed inhibit autophagy and thus improve the therapeutic effect of doxorubicin. However, the uneven distribution among tumor tissue and blood make it difficult to evaluate the pharmacokinetic and pharmacodynamic endpoints (78). So we may need better autophagy inhibitors, especially with preeminent capacity of better bio-distribution and ability to target tumor tissues. Actually, one should also concern about the biological specificity of autophagy inhibitors when the autophagy inhibitor is used. It has been exhibited that CQ, a agent continually used to inhibit autophagy through elevating the lysosome PH and hence inhibit the fusion of autophagosome and lysosome, can also promote autophagy: as the accumulation of CQ contribute to the inhibition of mTOR1 and subsequently activate TFEB, a transcription factor which benefits the biogenesis of lysosomes (79).

Non-protective function

Increasing evidence demonstrated that autophagy also played a non-protective role in cancer therapy. Under this kind of situation, inhibition of autophagy induced by chemotherapy or ionizing radiation did not alter the sensitivity of cancer cells to treatment (80). This notion is experimentally supported by the study in breast tumor cells, ionizing radiation promoted autophagy in murine breast tumor cells and CQ was unable to sensitize tumor cells to radiation. Numerous reports have also been cited that the inhibition of autophagy was relatively ineffective in combination with cancer therapy (81).

Regulation of autophagy by oxidative stress

ROS are highly active oxygen contained species, including free radicals such as $O^{2\bullet-}$, $HO^{\bullet}$, and non-free radicals such as H_2O_2. ROS are produced through either the cellular oxidative phosphorylation or the activation of cellular redox associated enzymes including nitric oxide synthase, xanthine oxidase and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (82). Excessive ROS could lead to the oxidation of DNA, organelles, proteins as well as lipid and thus cause damage in cells (83). Cellular ROS state is a result of balance of the generation of ROS and intracellular antioxidant system. The antioxidant system is comprised by a series of antioxidant enzymes including superoxide dismutase (SOD), glutathione peroxidase, as well as catalase. Besides, NADPH, thioredoxin, and thioredoxin reductase form an additional antioxidant defense power, which is called the thioredoxin system. Together with peroxiredoxin (Prx), and sulfiredoxin (Srx), the thioredoxin system could facilitate the control of dithiol-disulfide exchanges among redox-sensitive proteins and thus modulate cellular redox signaling (84,85). In addition, some non-enzymatic molecules could also obliterate ROS, such as vitamin C/E, urate, NAC, and β-carotene. Anti-tumor treatments such as radiotherapy and chemotherapy could cause the accumulation of ROS (86). Researches related to ROS and autophagy have demonstrated that autophagy can be induced by ROS and antioxidants treatment could reverse the induction of autophagy (87,88). For instance, it is reported that ROS could induce neuronal autophagic cell death through withdrawal of nerve growth factor (89). Tumor necrosis factor α can also promote autophagy in a ROS-dependent manner (90). These observations, in conjunction with evidence that the oxidation of lipid in mitochondria mediated by ROS could also induce autophagy in yeast (91). However, the underlying mechanism remains largely unknown. It is commonly accepted that mitochondria is the main source of ROS, and oxidative stress would occur along with a variety of stresses such as nutrition starvation, endoplasmic reticulum stress (ER stress) and hypoxia. Upon drug treatment or chronic impairment, mitochondria is damaged and ROS can be highly produced by the dysfunctional mitochondria, thus autophagy which selectively targets mitochondria (mitophagy) is induced and the impaired mitochondria is removed. This presents a fine orchestration by which autophagy is utilized to eliminate excessive ROS and protect cell from oxidative damage.

Inhibition of ATG4 induces autophagy

Another issue when one focus on the crosstalk between ROS and autophagy must be that how redox signaling influence the autophagy pathway. So far, four types of mammalian homologues of ATG4 have been published, and therein, HsAtg4A and HsAtg4B, shows different preference in cleaving mammalian Atg8s: HsAtg4A mainly cleaves the GATE-16, while HsAtg4B is prone to cleave all three homologues of Atg8, including GATE-16, GABARAP, and LC3 (92). Scherz-Shouval et al. have reported that the cysteine protease, HsAtg4, which is involved both in the formation of autophagosome as described above and delipidation of LC3-II, is a direct target of ROS (93). Since the priming step of autophagy is not affected in short-time starvation, it can be concluded that the delipidation activity is virtually the target of redox signaling. Once the Cys 81, an amino acid residue located near the catalytic site of HsAtg4, was oxidized to sulfenic acid by H_2O_2, the delipidation activity of HsAtg4 was inhibited. Mutation of Cys 81 to serine dramatically decreased the redox sensitivity of HsAtg4A and the formation of GATE-16–labeled autophagosomes was impaired. Although the disulfide bridge was not reported in this study, the author put it forward that there may exist a disulfide bridge between the regulatory cysteine residue (Cys81 of HsAtg4A or Cys78 of HsAtg4B) and catalytic cysteine residues ((Cys77 of HsAtg4A or Cys74 of HsAtg4B). As such, this work provides a molecular mechanism that how redox signaling influences the autophagic process. Along this line, ATG proteins with conserved cysteine may carry the potential to be regulated by ROS and thus alter the autophagic process. What's more, it is worth mentioning that p62, a receptor of autophagy, contains a ZZ (zinc-finger motif) which is rich in cysteine residues, and this metal binding domain may be necessary for the redox regulation although no evidence yet has been published.

Activation of AMPK is linked to autophagy

AMPK is a pivotal regulator of cellular metabolism, particularly the energy metabolic process. AMPK has been supported to be a classic regulator of autophagy by modulating the phosphorylation of ULK and mTOR complex (94) (Fig 2). Recently, it has been confirmed that the activity of AMPK could be mediated by ROS through the glutathionylation of Cys299, Cys304 as well as its β-subunits, and this is consequent on higher kinase activity of AMPK. Hypoxia could also activate AMPK via the formation of mitochondria ROS and this process is independent from the ratio of AMP/ATP (95). On the other hand, autophagy can be enhanced by DNA damage caused by oxidative stress. As DNA damage could activate p53 and subsequently repress mTORC1 (96). Ataxia telangiectasia mutated (ATM) is a serine/threonine kinase which participates the DNA damage response and mediate the repair of DNA via stimulating and increasing the amount of p53 (97). ATM is also reported to be activated by ROS in the absence of DNA double-strand breaks (DSBs) and the Mre11-Rad50-Nbs1 (MRN) DNA repair complex (98). ATM can be oxidized to a disulfide-cross-linked dimer, the mutation of cysteine involved in the formation of disulfide bond could block the activation of ATM by ROS (99). Activated ATM could further activate AMPK and tuberous sclerosis complex 2, a suppressor of mTORC1, and finally leading to the induction of autophagy (Fig 2). Studies focused on the mechanism by which ROS mediates autophagy and thus influences the progression of cancer therapy is a relatively a new field which may provide novel insights into understanding and development of therapeutic strategies based on the crosstalk between ROS and autophagy.

Inhibition of Beclin1 complex binding with Bcl-2 is essential for autophagy initiation

As mentioned above, the function to initiate autophagy of Beclin1 can be suppressed by Bcl-2 family members, such as Bcl-XL and Bcl-2. JNK could negatively regulate Bcl-2 through phosphorylation. Intriguingly, JNK is deciphered to be activated by ROS and contribute to induction of autophagy. Concurrently, high-mobility group box 1 protein (HMGB1), not only a chromatin binding factor but also a cytokine, has been reported to regulate cellular autophagic process under a ROS-dependent mechanism (100,101). HMGB1 translocates to the cytosol from nucleus after being oxidized by ROS and subsequently conjugates with Beclin1, by which protects Beclin1 from association with Bcl-XL and Bcl-2, and result in the initiation of autophagy (Fig 2). The Cys23 and Cys45 residues of HMGB1 are required to form the disulfide bond which is involved in the conjugation of HMGB1 and Beclin1 (102).

Autophagy is result of ROS and mitophagy

As the main site of ROS production, mitochondria could also regulate cellular autophagy (103). However, when the impairment of mitochondria occurs, ROS can be rapidly accumulated and promote the self-removal of damaged mitochondria, which called mitophagy (104). Mitophagy is a negative feedback process by which autophagy is induced to eliminate excessive ROS thus protect cell from severe damage. Two major mechanisms of mitophagy are reported (105). The first one is NIX/Bnip3L (Bcl-2/adenovirus E1B 19-kDa-interacting protein 3, long form) dependent. NIX/Bnip3L is capable of recognizing GABARAP (the autophagosome sited GABA receptor-associated protein), and then excites the remove of mitochondria. The second one is based on the Parkin and PTEN-induced putative kinase 1 (PINK1). Parkin is a E3 ligase which links with Parkinson's disease while PINK1 is a Ser/Thr kinase which could also sense the mitochondrial transmembrane potential. Parkin could be recruited by PINK1 and ubiquitylate outer mitochondria proteins such as VDAC1 (voltage dependent anion channel 1) (106). The ubiquitylated proteins can be subsequently recognized by p62 and degradated via the lysosome-dependent mitophagy or proteasome. (Fig. 2).

Therapeutical strategy based on autophagy by targeting ROS

We have discussed the functions of autophagy in cancer cells above as it could be protective or cytotoxic. Actually, there exits multiple drugs which targeting ROS and killing tumor cells as a result of influence autophagy. Temozolomide is a chemotherapy drug which

is used to treat certain types of brain tumors called glioblastoma multiforme or anaplastic astrocytoma. Previous studies have shown that temozolomide could activate AMPK, thus inhibit mTOR complex 1 (mTORC1) signaling and promote the degradation of Bcl-2 (107). Furthermore, temozolomide could increase the production of ROS and induce autophagy rather than apoptosis at a clinically achievable dose (100μM). Strikingly, when 3-MA, a phosphatidylinositol 3-phosphate kinase inhibitor was added, the anti-tumor effect of temozolomide was reduced. In contrast, when bafilomycin A1, a specific inhibitor of vacuolar type H^+-ATPase which prevents autophagy at a late stage by inhibiting fusion between autophagosomes and lysosomes was used (108), apoptosis was activated. This experiment showed the complexity of autophagy in cancer therapy. Inhibiting the early stage of autophagy may retard the anti-tumor properties while inhibiting the late stage of autophagy may hold the potential to enhance the anti-tumor properties. These observations suggested that, we must admit that autophagy is a multi-steps process and influence different stages of autophagy may lead to inequable consequences. Tamoxifen is a medication which is mainly used to prevent breast cancer. Tamoxifen has been reported to directly target the mitochondria (109,110). We found it could induce cellular nitric oxide (NO) and up-regulate ROS hence results in cancer cell death through a caspase-independent, autophagy-related manner (111,112). As published, treatment with tamoxifen led to the accumulation of autophagic vacuoles and an increase in the expression of Beclin-1. Paclitaxel is a widely used chemotherapeutic drug for several type of cancers. It has been demonstrated that paclitaxel could induce cell death via interfere cellular microtubules during cell division. Moreover, some studies have shown that paclitaxel could induce autophagy in various cancer cells. Paclitaxel-induced autophagy was mediated by ROS generation and up-regulation of Beclin-1. Otherwise, when we suppressed the autophagy by autophagy inhibitors chloroquine (CQ) or shRNA against the autophagic gene beclin 1, Paclitaxel-mediated cell death was further strengthened (113,114), suggesting that combination therapy strategy of paclitaxel with autophagy inhibitors could be much more effective in cancer therapy. In summary, ROS and ROS-induced autophagy remain largely unknown and still need further investigation to improve cancer therapeutical strategies. In addition, cancer therapies using ROS inhibitors or inducers can also influence therapeutic effect which have been validated in experiment. Furthermore, these cancer therapy strategy has been tested in clinical trials.

Conclusion

Autophagy, primitively thought to be a protective cellular event which remove damaged or unwanted organelles and proteins through a well-arrangement signaling cascade under various stresses (7). Recently, it is gradually recognized that autophagy has more than one face in response to cancer therapy such as chemotherapy and radiotherapy (115). In detail, autophagy is reported to act at least three roles in cancer progression :1) Protective autophagy, which copes with the stress induced by cancer therapies and thus protect cancer cells from death. In this situation, autophagy inhibitors, such as CQ, HCQ, 3-MA could be conducted to enhance the curative effect. Prior to the application of autophagy inhibitors, the activity and specificity should be estimated or the combination strategies may do not make sense (116). 2) Cytotoxic autophagy, which enhance the curative effect of cancer therapies. 3) Non-protective autophagy, which exerts rare influence on cancer therapies either inhibited or promoted by chemical agents (117,118). However, it is difficult to assess the role of autophagy in clinical therapy and observation. When it comes along with oxidative stress, which would regulate both of the autophagy and cancer progression, one can bring forward novel notion for cancer therapy (11,119,120). Since numerous cancer treatments could induce the formation of ROS and thus promote autophagy, ROS scavengers such as NAC, vitamin C/E, and urate can be employed to inhibit the protective autophagy, which would shed lights on new fashioned therapeutic strategies. Furthermore, autophagy is demonstrated to be induced to obliterate excessive ROS, by which cancer cells can survive from the fatal stress, suggesting that one can add ROS inducers to sensitize cancer cells to excessive ROS through overwhelming the capacity of ROS-elimination via autophagy and innate cellular antioxidant system. Nevertheless, the mechanism underlying the regulation of autophagy by ROS still remains largely unknown. Thus, more studies with an eye to unveil the mask of the crosstalk between autophagy and ROS will favor exploring effective drug-combination strategies in cancer therapy.

Upper is generation of LC3-II, which is important in autophagy processing. First of all, LC3 is cleaved and activated by Atg4, then presented in UBL system; In this UBL system, LC3 is catalyzed into LC3-II and functions in phagophore formation by E1. E2. E3 enzyme. On the other hand, p62 protein acts as a cargo to carry targets into phagophore. In the first place of autophagy, isolate membrane is sourced from ER or Golgi which is not clear now. Second, LC3-II facilitates membrane promotion and p62 protein acts as a cargo to carry targets proteins into phagophore. Finally, autophagosome and lysosome fuses into autolysosome while things in autophagosome could be degraded into small molecules for duty-cycle operation.

Box1 Other types of autophagy

Chaperone-mediated autophagy (CMA)

During Chaperone-mediated autophagy (CMA), cytosolic proteins with specific pentapeptide motif (KFERQ) are recognized by chaperones (e.g. heat-shock cognate protein 70) and translocated to lysosome surface (121). Then the substrate proteins are delivered into lysosomes via lysosome-associated membrane protein type 2A, known as LAMP2A (122), a lysosome single span membrane protein (123). CMA is a quite unique kind of autophagy since its substrates are selective and are directly delivered to lysosome lumen without the formation of double-membrane-bounded vesicles. CMA can be active in many tissues, such as brain and liver (124).

Microautophagy

Microautophagy is another type of autophagy which

also involved in nutrient recycling under stress conditions (125). It is generally a non-selective process mediated directly by lysosomes engulfment and the cellular constituents are trapped into lysosomal lumen for degradation through random membrane invagination. According to the species of its substrate cargo, microautophagy can be divided into micromitophagy, micropexophagy (126).

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