The role of interaction between autophagy and apoptosis in tumorigenesis (Review)

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Abstract. Autophagy is a highly conserved process that maintains cellular homeostasis during evolution. Autophagy can occur in the form of macroautophagy, microautophagy or molecular chaperone autophagy, among which macroautophagy is the most common. Apoptosis exists in all kinds of cell organisms, and is a kind of programmed cell death which is regulated by pro-apoptotic factors and anti-apoptotic signals. The main biological feature of apoptosis is the activation of caspase. Apoptosis is induced by a variety of cell signals, such as endoplasmic reticulum stress, induction of toxic substances, stimulation of pathogenic microorganisms and DNA damage. Inextricable links are found between autophagy and apoptosis. Studies have found that numerous of the autophagy molecules and autophagy signaling pathways involved in the process of autophagy are related to apoptosis. In addition to regulating autophagy, the autophagy signaling pathway also regulates apoptosis. The interaction between the two can achieve a dynamic balance to certain extent, which maintains the basic physiological functions of cells and reduces the damage to the body under stress. Disease occurs when the balance between autophagy and apoptosis is disrupted. Tumors form due to the ability of cells to avoid apoptosis. Autophagy is closely related to apoptosis, there must be a close connection between the three. In the present review, the mechanism between autophagy and apoptosis and the impact of their interaction on tumorigenesis shall be discussed.

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1. Introduction

Autophagy can remove and degrade damaged organelles and macromolecular substances, it participates in the basic transformation of cell components, so that nutrients can be recycled and cells can self-renew, thereby providing cells with nutrients and energy to maintain cell homeostasis (1-4). In recent years, numerous studies have shown that abnormality of autophagy is related to the occurrence of numerous kinds of tumors (4,5). Autophagy can promote cell survival by removing damaged organelles and macromolecules in cells and maintain cellular homeostasis. Nevertheless, autophagy can also promote cell death through its connection with apoptosis. There is a strong link between autophagy and apoptosis: Autophagy and apoptosis often interact with each other, autophagy can promote or inhibit apoptosis and apoptosis can also promote or inhibit autophagy (6-8). The disruption of the dynamic balance between autophagy and apoptosis may be one of the important reasons for tumorigenesis (9). However, the functions of autophagy and apoptosis in different types of tumors development are still up for debates. Since autophagy can influence both cell's death and survival, so it is very important to research. Under what circumstances autophagy can promote cell's death and under what circumstances autophagy can promote cell's survival. Only by truly grasping the relationship between autophagy and cell's fate, the study of autophagy can

start to develop effective drugs for autophagy-related tumor diseases. In the present review, the process of autophagy and the role of interaction between autophagy and apoptosis in tumorigenesis shall be described.

2. Molecular mechanisms of autophagy (Fig. 1)

Mammalian target of rapamycin (mTOR) is a central regulator of cell growth and proliferation (10). It consists of mTORC1 and mTORC2, among which mTORC1 is regulated by signaling factors such as cellular energy and amino acids (11). Under normal circumstances, autophagy is inhibited by mTOR. When cells are subjected to nutrient, oxidative and endoplasmic reticulum (ER) stress, the activity of mTOR C1 is inhibited and autophagy is initiated by phosphorylating unc-51-like kinase 1 (ULK1)-2 (ULK2) (12-15). The formation of a separation membrane (i.e., phagocytes) marks the beginning of autophagy. Under the action of autophagy-related proteins, the detached double-layered membrane at the ribose-free attachment zone of the rough ER will wrap the organelles or macromolecules in the cytoplasm that need to be degraded (16). Then the membrane elongates and self-encloses to form autophagosomes (17). The autophagosome and lysosome fuse to form autophagolysosome, and the relevant hydrolases in the lysosome decompose the encapsulated organelles or macromolecules into amino acids, fatty acids and free nucleotides, then release them back into the cytoplasm to realize the self-renewal of cell components (18).

Formation of autophagosomes. Formation of the initial phagocyte membrane relies on the class III phosphatidylinositol 3-kinase (PI3K) complex. VPS34 is the only class III [(PI3K) in mammals)], which binds to a coiled-coil protein encoded by beclin-1 to generate phosphatidylinositol 3-phosphate (PtdIns 3P) through phosphorylation at D-3 position of inositol ring (19,20). The autophagosome is formed in the cup-shaped chamber of PtdIns 3P, which is dynamically connected to the ER. When cells are under stress, this compartment and the ER membrane are rearranged under the action of autophagy-related proteins, thereby forming phagocytes (21-23). Beclin-1 is the mammalian homolog of the yeast autophagy-related protein Atg6, which is part of the Vps34 complex and plays an important regulatory role in the regulation of autophagy (24). The composition of autophagy-specific Vps34 complex is very complex, and its components include Vps34, Vps15, beclin-1 and Atg14L, UVRAG. In addition, VMP1, Ambra-1, Bif-1 and Rubicon have also been reported as components of the Vps34 complex (20,25,26). Each component of the VPS34 complex has broad regulatory roles in autophagy, with the Atg14L complex in autophagosome formation, the UVRAG complex in autophagosome maturation, and the Rubicon complex considered to inhibit autophagosome maturation (27-29). As a positive regulator of beclin-1, Ambra-1 plays an important role in the activation of beclin-1; while Dapper-1 promotes the formation of autophagosomes by enhancing the formation of beclin-1-Vps34-Atg14L complex (30), Bif-1 can regulate autophagosome maturation by interacting with UVRAG and beclin-1 (31).

AMPK is a well-known energy sensor which maintains cellular energy homeostasis when cells are in nutrient deprivation (32). AMPK consists of a catalytic α subunit and two regulatory β and γ subunits. Under energy stress, the AMP/ATP ratio increases, in which case the gamma subunit of AMPK binds directly to AMP (33). Afterwards, the AMPK complex undergoes morphological changes and allosteric activation, during which LKB1 leads to AMPK activation by promoting the phosphorylation of Thr172 in the AMPKα subunit and inhibiting its dephosphorylation (34,35). Activated AMPK can inhibit the activity of mTORC1, thereby activating the ULK complex. ULK1 induces autophagosome formation by phosphorylating beclin-1 and activating VPS34 lipid kinase (36-38). ULK can be directly activated by AMPK upon cell starvation (39,40). In addition, AMPK can directly regulate the VPS34 complex through phosphorylation. Activated AMPK can directly phosphorylate T163/s165 of VPS34 and s91/s94 of beclin-1 through ATG14L (41). Mammalian ULK1, 200-kDa focal adhesion kinase family interacting protein (FIP200) and autophagy-related protein Atg13 interact to form a stable complex ULK1-Atg13-FIP200 (42,43). This complex is localized to the phagosome during starvation and inhibits the dephosphorylation of mTOR-dependent sites, resulting in enhanced activity of ULK1 and interaction with the vertebrate-specific autophagy protein ATG101 (44), which plays an important regulatory role in autophagosome formation.

Maturation and elongation of autophagosomes. Beclin-1 binds to the UVRAG-targeted Class C Vps complex and recruits the mammalian homology of yeast Atg8, microtubule-associated protein-1 light chain kinase 3 (LC3), via the ATG5-ATG12/ATG16L multimeric complex, assisting in the maturation and elongation of autophagosomes. In addition, the formation and maturation of autophagosomes is also closely related to phosphatidylethanolamine (PE) conjugates (45,46). The location of the Atg16L complex on phagosome determines the location of LC3 binding reaction (47). ATG7 can activate LC3 and transmit it to ATG3 (48-50), and convert Pro-LC3 into its active cytoplasmic isomer LC3 I by enzymatically degrading a small segment of polypeptides from Atg4A-D and Atg4B in the Atg4 protein family. With the help of the ATG5/12 conjugate, glycine residues are left at C-terminus of LC3 I and binds to the polar head of PE, a component of the phospholipid bilayer, and converts to the autophagosome membrane type, LC3-II. The LC3-II/LC3I ratio is often considered the gold standard for macroautophagy. LC3-II wraps around the inner and outer surfaces of autophagosomes and, together with ATG5, acts as a discrete marker for autophagosomes and autophagosome precursors, respectively, until they fuse with lysosomes (51). Notably, ATG12 is also required to be activated by ATG7 to bind to an isopeptide bond on an internal lysine on ATG5.

Degradation of autophagosomes. After the maturation and elongation of autophagosomes, the selective autophagy adaptor protein p62/SQSTM1 can bind to LC3 through LC3 interacting region (LIR). P62 binds to ubiquitinated proteins at the C-terminus and to LC3-II at N-terminus. Therefore, p62 acts as a bridge between ubiquitinated proteins and LC3; p62 is degraded by autolysosomes after autophagosomes fuse with lysosomes to form autolysosomes (52,53). Simultaneous detection of LC3 and p62 can reflect the integrity of autophagic flux. The accumulation of p62 protein represents the impaired

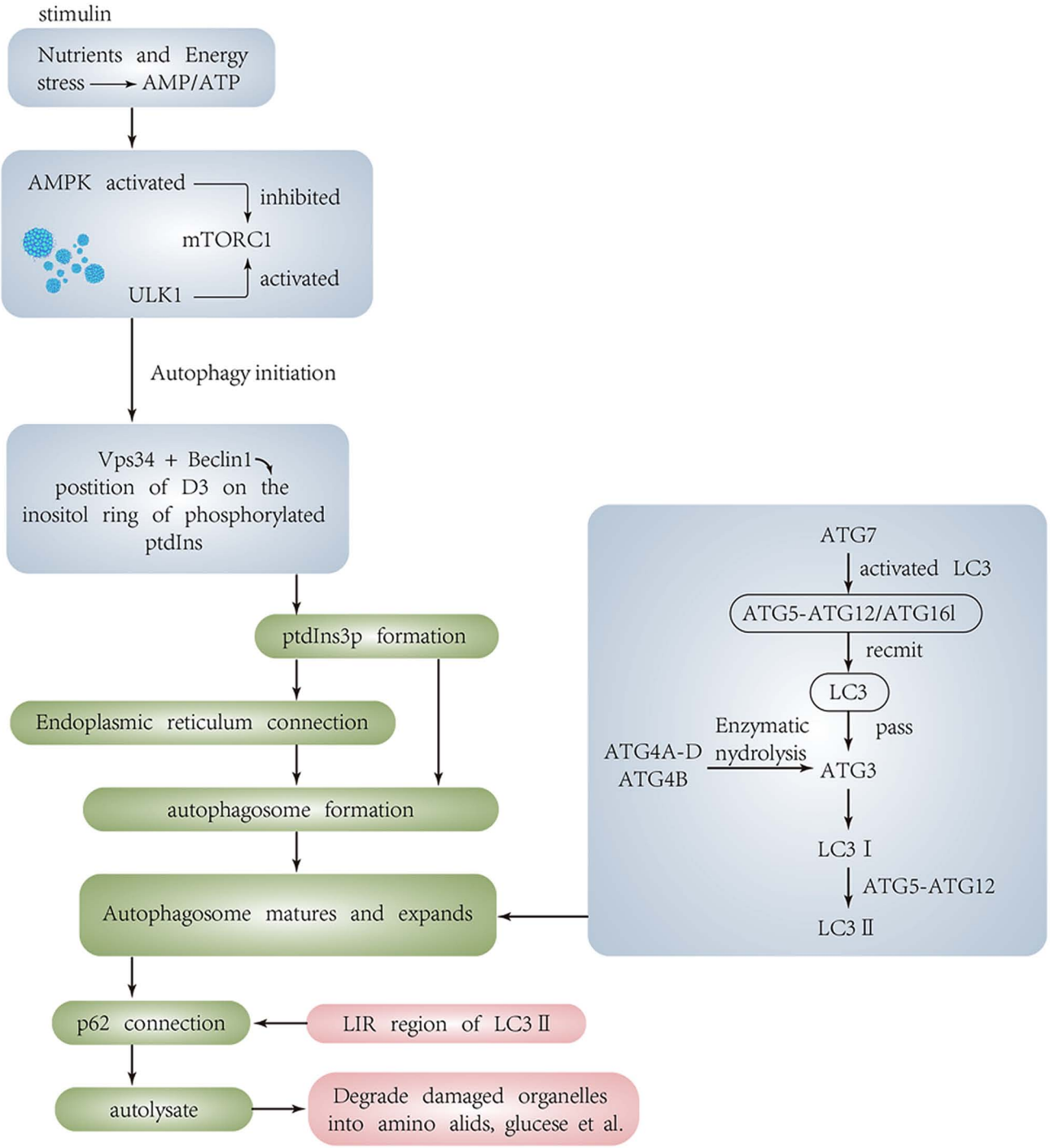

Figure 1. Complete autophagy process, Autophagy is activated under various triggers, After the formation of autophagosome, the maturation, extension and expansion of autophagosome, it finally fuses with lysosome to form autophagolysosome, performing lysis of damaged organelles or misfolded proteins to maintain cellular homeostasis and provide energy for cells.

degradation process of autophagosome, thus p62 is often regarded as a negative indicator of autophagy.

3. Mechanism of apoptosis

Death receptor (DR) pathway. The three main apoptotic pathways are DR pathway, mitochondrial damage pathway and ER stress initiation pathway. The extrinsic pathway is DR, which is mainly through the binding of Fas/FasL, tumor necrosis factor receptor 1 (TNFR1) and related death domain (TRADD), or TNF-related Apoptosis-inducing ligand receptor (TRAILR). The caspase protease caspase-8 is activated by dimerization following ligand/receptor binding. For example, FasL binds to its receptor Fas and induces Fas molecules to aggregate to form dimers. Through the binding of the death domain in the cytoplasm to the adaptor protein FADD, the FADD effector domain binds to caspase-8 to form a death signal complex DISC. When a large amount of DISC is generated, activated caspase-8 can bypass mitochondria and directly activate other proteins of the caspase family such as caspase-3, caspase-7,

caspase-6, thereby cleaving hundreds of different substrates, including cytoskeletal proteins, nuclear structural proteins, lipid metabolism and endonucleases. Cleavage-dependent activation or inactivation of specific proteins leads to changes in the morphological and biochemical characteristics of apoptosis, including phosphatidylserine exposure, plasma membrane blebbing, and DNA fragmentation, thereby inducing apoptosis (54,55).

Mitochondrial apoptosis pathway. Mitochondrial apoptosis pathway is mainly marked by mitochondrial outer membrane permeability (MOMP). When cells are induced by apoptotic signals such as DNA damage and cytokine extraction, the permeability of mitochondrial membrane is opened in an irreversible manner, releasing cytochrome c (Cyt c) from the mitochondrial intermembrane space; Cyt c and the adaptor protein APAF-1 binds to form a complex of apoptosomes and activates caspase-9. After caspase-9 is activated, caspase-3 and caspase-7 are cleaved and activated, thereby initiating caspase-level reaction and completing apoptosis. The aforementioned process is maintained by a delicate balance between BCL-2 protein family (56), which consists of anti-apoptotic proteins and pro-apoptotic proteins. Bcl-2 protein family is divided into three categories: i) Pro-apoptotic effector proteins (including BAX, BAK, Bik), which promote apoptosis and irreversibly change MOMP after being activated by pro-apoptotic signals; ii) Anti-apoptotic Bcl-2-like proteins (including Bcl-2, Bcl-xL and MCL-1) are mainly distributed in mitochondrial membrane and cytoplasm, bind and inhibit BH3 with pro-apoptotic activity protein and effector protein, block the occurrence of MOMP, thereby inhibiting cell death; iii) Pro-apoptotic BH3 pure proteins (including BID, BIM and PUMA). BID, located in the cytoplasm, is cleaved into truncated (t)BID by caspase-8, and tBID has strong pro-apoptotic activity, which can transmit apoptotic signals to mitochondria and induce the release of Cyt c. It promotes apoptosis by inhibiting anti-apoptotic Bcl-2 protein and directly activating effector proteins to signal MOMP activation (57). The exogenous and endogenous apoptotic pathways do not act on their own, but cross-talk each other through the activation and cleavage of pro-apoptotic protein BID mediated by caspase-8, produced BID cleavage product (58,59).

ER stress pathway. The ER stress pathway is a newly discovered apoptotic pathway in recent years, and ER stress is a very important trigger for the activation of autophagy. When ER is stimulated by hypoxia, starvation, infection and other factors, the homeostasis of ER is disrupted, resulting in the accumulation of unfolded or misfolded proteins, which induces ER stress. Sustained ER stress activates the ATF4/CHOP and IRE1/TRAF2/ASK/JNK pathways. Activation of both JNK and CHOP attenuates the function of anti-apoptotic protein Bcl-2, while enhancing the activity of pro-apoptotic proteins such as Bim, Bax and PUMA, leading to mitochondrial dysfunction and Cyt c release. ER stress activates IRE1 to recruit and activate necrotic tumor receptor-associated factor 2 (TRAF2), which further activates JNK and leads to apoptosis (60,61). CHOP can regulate the expression of Bcl-2, GADD34 and TRB3 (62). Firstly, CHOP downregulates Bcl-2 expression, but upregulates the pro-apoptotic gene Bim, and promotes the translocation of Bax to mitochondria to promote apoptosis (63). Secondly, CHOP can directly bind to the promoter of TRB3 gene and upregulate its expression (64), thereby inhibiting the activation of AKT and leading to apoptosis. Notably, TRB3 can regulate the expression of CHOP through a negative feedback mechanism. Overexpressed TRB3 inhibits the transcriptional induction of CHOP, whereas silencing TRB3 leads to the upregulation of CHOP under normal and stress conditions (64-66). During ER stress, p53 induces the activation of another BH3-only protein and promotes the expression of a regulator of apoptosis (PUMA). PUMA-deficient cells reduce ER stress-induced apoptosis. Activation of multiple apoptotic pathways during ER stress jointly induces apoptosis (67).

4. Inhibition and promotion of autophagy on apoptosis

Autophagy functions in both pro-survival and pro-death ways within the same cell. Autophagy can promote the survival of normal cells during nutrient starvation, when cells are in a state of stress, including oxidative, ER, nutrient and energy stress. Autophagy can maintain cell homeostasis by removing damaged organelles and can also provide nutrients for cell survival by degrading macromolecular substances in cells. Therefore, from this perspective, elevated levels of autophagy contribute to cell survival, and the lack of autophagy increases cell death susceptibility when cells are under stress (68,69). Another important mechanism by which autophagy inhibits apoptosis is that it can engulf damaged mitochondria. When mitochondria are damaged, various death signals will be released that cause the transmembrane potential within the mitochondria to dissipate, resulting in cell death. Autophagy can also reduce apoptosis by selectively reducing the abundance of pro-apoptotic proteins in cells. For example, autophagy can selectively remove active caspase-8. When the autophagy gene Atg7 is knocked out, the activity of caspase-8 is increased, indicating that autophagy deficiency can promote apoptosis (68).

Autophagy can promote apoptosis and induce cell death in cells with damaged apoptotic mechanisms, and excessive levels of autophagy also promote cell death. It was found that numerous components of autophagy are necessary for apoptotic factors to mediate cell death (69). In addition, numerous autophagy proteins can induce apoptosis. For example, Atg5 and Atg12 proteins can activate caspases through the mitochondrial pathway. When Atg5 and Atg12 are knocked out, the activity of caspases is significantly reduced (68-70). The increase in Atg12 mRNA expression promotes cell death (71,72); reducing the expression of Atg12 or other autophagy genes effectively inhibited cell death (73-76). Furthermore, autophagy can promote apoptosis by degrading anti-apoptotic and cell survival factors and depleting endogenous inhibitors of intracellular death pathways. For example, autophagy can degrade inhibitor of apoptosis proteins (IAPs) (77). When autophagy is activated, the accumulated autophagosomes can irreversibly open the mitochondrial membrane when they accumulate in the cell body, leading to apoptosis. Fap-1 is an inhibitor of Fas-mediated apoptosis, and its autophagic degradation sensitizes type I cells to Fas-induced apoptosis (78). In proliferating cell populations, different levels of autophagy within a single cell lead to different cell fates. Autophagy proteins, on the

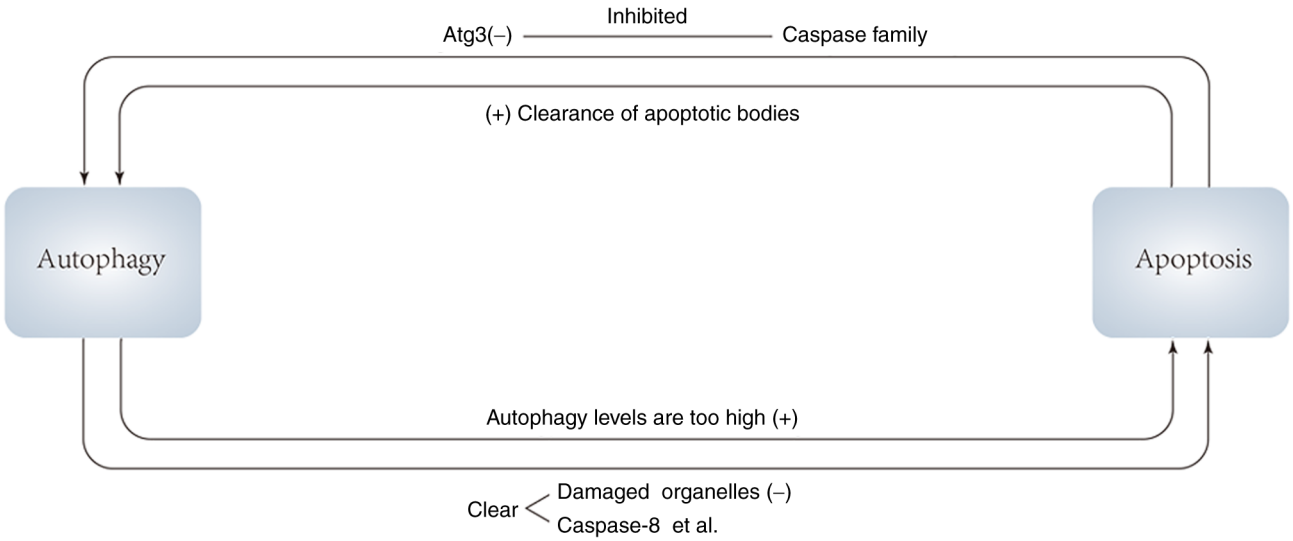

Figure 2. Relationship between autophagy and apoptosis is intricate. Autophagy and apoptosis can both inhibit and promote each other, which may be related to the different stages of cell.

other hand, promote cell death by providing scaffolds for cell death complexes and signaling molecules. In mouse embryonic fibroblasts treated with sphingosine kinase inhibitor (SKI), SKI promotes cell death by inhibiting sphingosine 1-phosphate (79). SKI induces the translocation of caspase-8 homologous complex and Fas-associated protein and death domain (FADD) to Atg5- and Atg16L-positive autophagosome membranes, which provides a scaffold for efficient formation of intracellular death induction signaling complex (iDISC) (54,79).

5. Promotion and inhibition of apoptosis on autophagy (Fig. 2)

Autophagy promotes or inhibits apoptosis, and in turn apoptotic signals and apoptotic products promote or inhibit autophagy. On the one hand, apoptosis can inhibit autophagy, and caspases, a key role in apoptosis, can digest several essential autophagy proteins, resulting in the inactivation of the autophagy program. For example, caspases can target Atg3 to cause its inactivation to inhibit the level of autophagy. In addition, the autophagy protein AMBRA1 can be irreversibly degraded under the combined action of caspases and calpains, and autophagy is thus inhibited (80,81).

In the process of mammalian embryonic development, autophagy neither delays nor promotes apoptosis, but the clearance of apoptotic bodies requires autophagy, thus apoptosis promotes autophagy in a sense (82). From this, it is hypothesized that in mammals, if impaired autophagy cannot effectively remove apoptotic corpses, the accumulation of apoptotic bodies may induce gene changes, or there may be a negative feedback mechanism in apoptosis. When apoptotic bodies accumulate, they will negatively feed back to the pro-apoptotic signaling pathway and the anti-apoptotic signaling pathway, resulting in the inhibition of the pro-apoptotic signaling pathway and the activation of the anti-apoptotic signaling pathway, thereby reducing apoptosis (80). When autophagy is defective, apoptotic bodies cannot be removed by autophagy, and their accumulation induces cell mutation. On the other hand, the accumulation of apoptotic bodies inhibits apoptosis, so that cells that should be apoptotic continue to survive, leading to tumorigenesis over time. A recent study identified that under aggressive tumorigenic conditions associated with metabolic stress, autophagy prevents genomic destabilization, thereby suppressing tumorigenesis (82). The aforementioned study also verifies our conjecture to certain extent.

There are intricate connections between autophagy and apoptosis. Numerous autophagy and apoptosis factors can directly interact with each other through specific domains to affect the expression of each other. The relationship between them cannot be simply judged. It may be different due to different environments or stimulatory signals, so maintaining autophagy and apoptosis in a relatively stable state is of great significance for maintaining the physiological functions of cells. When the balance between autophagy and apoptosis is disturbed, it will lead to diseases like neurodegenerative diseases or cancer. Next, the possible mechanism of the imbalance between autophagy and apoptosis in pathogenesis of cancer will be explored.

6. Effects of autophagy and apoptosis on tumorigenesis

Cancer cells can proliferate due to their ability to avoid apoptosis or death. This is why inducing apoptosis in cancer has been identified as a target of cancer therapy, as numerous cancer patients have been found to have mutations in apoptosis-related genes (83,84). The inhibition of pro-apoptotic genes and the activation of anti-apoptotic genes are considered to be closely related to the occurrence of cancer. Numerous studies have found that excessive apoptosis may also have oncogenic functions (54,85,86), and that higher levels of apoptosis may be associated with poor prognosis in cancer patients (87). It has also been revealed that the abnormal level of autophagy is also one of the important mechanisms leading to cancer. Beclin-1 has been identified to be a tumor suppressor that inhibits

tumorigenesis. Beclin-1 can inhibit tumorigenesis, and its expression level is reduced in human breast cancer. These findings suggested that reduced expression of autophagy proteins may contribute to the development and progression of breast cancer and other human malignancies (88). Autophagy can not only prevent tumorigenesis by removing abnormal cells, but also reduces the oncogenic mutation of cells by removing abnormally large amounts of DNA-damaging reactive oxygen species released from damaged mitochondria by removing damaged mitochondria (89). However, after the occurrence of tumors, autophagy can provide nutritional support for tumor cells by degrading macromolecular substances and damaged organelles, and promote the survival of tumor cells. When the expression level of autophagy in tumor cells is elevated, tumor cells antagonize anticancer drugs due to autophagy. The balance is the key to maintaining the biological function of cells. When this balance is disrupted, the apoptosis of cells is abnormal and cell homeostasis is disrupted, which in turn promotes tumorigenesis.

Effects of p53-related autophagy on tumorigenesis. P53 is considered a BH3-only protein that acts both as a direct activator of Bax and as a de-repressor. Under pro-apoptotic conditions, p53 co-immunoprecipitates with Bcl2, Bcl-XL and Bak (90). p53 suppresses oncogenic potential by mediating irreversible cell cycle arrest or triggering apoptotic cell death. Under the induction of various apoptotic stimuli, p53 moves to the mitochondria, and after reaching the mitochondria, p53 induces MOMP, thereby triggering the release of pro-apoptotic factors in the mitochondrial intermembrane space (91,92). Due to its pro-apoptotic effect, p53 is considered an important tumor suppressor gene, as ~half of human types of cancer have p53-inactivating mutations. Most of the remaining malignancies are caused by the inhibition of the pro-apoptotic function of p53 by increasing its inhibitors, decreasing its activators, or inactivating its downstream targets (93). A recent study found that p53 has a significant inhibitory effect on autophagy, and the loss of autophagy makes cells sensitive to TRAIL through up-regulation of PUMA (p53 upregulated modulator of apoptosis). Autophagy counteracts the lethal effect of MOMP by removing damaged and permeable mitochondria. The inhibition of autophagy by p53 reduced this effect and further promoted cell death via the MOMP pathway. Previous studies have found that the inhibition of autophagy is mediated by p53 in the cytoplasm rather than the nucleus, and physiological inducers of autophagy (such as nutrient depletion) must destroy the p53 pool in the cytoplasm to induce autophagy. Thus, inhibition of ubiquitin E3 ligaseMdm2 targeting p53 disruption can inhibit starvation, rapamycin, lithium or ER stress-induced autophagy (94). Another study demonstrated that p53 in the cytoplasm can inhibit the expression of AMPK and activate the activity of mTOR, thereby inhibiting autophagy. However, how these effects are achieved remains a puzzle. Certain studies are contradictory to the aforementioned research conclusions, considering that p53 can prevent the occurrence of tumors by inhibiting mTOR and increasing autophagy and promoting apoptosis (9,94).

A previous study also found the close relation between Atg7 and apoptosis that p53 and Atg7 exist in a single complex (9). Abnormal expression of Atg7 is closely related to the occurrence of rectal cancer. Cells lacking Atg7 impair p53-mediated cell cycle arrest. When cells are under nutrient stress, endogenous Atg7 exists in the promoter region of p21 together with p53, and cells lacking Atg7 cannot properly induce the expression of p21 (95). The p53 tetramer domain mediates the interaction with Atg7, and Atg7 promotes p53 tetramer formation. Atg7 and p53 can directly bind to each other, and this binding is facilitated when cells are under nutrient stress. In the case of Atg7 deficiency, the pro-apoptotic activity of p53 induced by metabolic stress also changes, and the enhancement of the pro-apoptotic activity of p53 can also regulate autophagy through Atg7. Summing up, the correlation between the two maintains the balance between autophagy and apoptosis, which plays an important role in tumor suppression (9,95).

DNA mis-match repair (MMR) is one of several DNA repair processes critical for maintaining genome stability (96). MMR is an important tumor suppressor mechanism, and MMR deficiency contributes to the development of human rectal cancer and solid tumors (96,97). As a response to DNA damaging agents such as 6-thioguanine (6-TG) and 5-fluorouracil (5-FU), MMR plays an important role in cell cycle arrest, autophagy and apoptosis. 6-TG induces an MMR-dependent autophagic response, and autophagic flux in cells is upregulated after 6-TG induction. MMR initiates 6-TG-induced autophagy in a p53- and mTOR-dependent manner (98-100). A recent study revealed that adenovirus E1B 19 kilodalton interacting protein (BNIP3) was also required for induction of autophagy after DNA MMR treatment of 6-TG and 5-FU. BNIP3 is a Bcl-2 homeodomain protein of the Bcl-2 protein family, which can cause autophagy, apoptosis and necrosis depending on the type and nature of cell stimuli (101). A previous study found that BNIP3 plays an important role in mediating 6-TG- and 5-FU-induced autophagy (102). Reactive oxygen species are considered to be key triggers for the activation of autophagy, which are abundantly produced during BNIP3-mediated apoptosis. After being driven by reactive oxygen species signaling, mTOR activity is inhibited and autophagy is initiated. Notably, the mTOR-S6K1 axis regulates BNIP3 protein translation (S6K1 is one of the mTOR downstream effectors) and plays an active role in regulating 6-TG-induced autophagy. During apoptosis, overexpression of BNIP3 induces apoptosis. Upon initiation by inducible MMR treatment with 6-TG and 5-FU, p53 was activated and acted as a transcription factor to upregulate BNIP3 transcription. Inhibition of p53 expression impairs BNIP3 upregulation. It is hypothesized that the role of BNIP3 in apoptosis may be related to the interaction of P53. Furthermore, BNIP3 is localized to the mitochondrial outer membrane through its transmembrane domain, which leads to the loss of mitochondrial membrane potential and the opening of the mitochondrial permeability transition pore, promoting apoptosis (103,104). The mechanism by which BNIP3 and MMR inhibit tumorigenesis may be related to the regulation of autophagy and apoptosis.

Two ubiquitin-specific peptidases, USP10 and USP13, were found to regulate the deubiquitination of beclin-1 in the Vps34 complex. Decreased expression of USP10 significantly reduced the levels of ubiquitinated beclin-1. Similarly, the removal of beclin-1 or Vps34 also significantly reduces the levels of USP10 and USP13. As a deubiquitinating enzyme of

p53, USP10 and USP13 can regulate p53 levels through p53 ubiquitination and degradation (105). The abnormal expression of USP10 is closely related to the occurrence of breast cancer. A recent study found that the lack of USP13 and USP10 also reduces the expression level of p53. Decreased expression of beclin-1 leads to a decrease in the expression level of p53 by increasing its ubiquitination. In addition to beclin-1, inhibition of the expression of Vps34 complexes such as Vps34, p150, UVRAG and Atg14L leads to a decrease in the level of p53 (106). Vps34 complexes may regulate the cellular level of p53 through deubiquitinating enzymes such as USP10 and USP13, in which beclin-1 may be the target of the interaction of Vps34 complex with USP10 and USP13. While the removal of other Vps34 complex components (such as Vps34, p150, UVRAG and Atg14L) may result in decreased p53 levels due to the codependent regulation of stability of the core components of the Vps34 complex, beclin-1 deubiquitination may be sufficient to control levels of the entire complex (45).

DRAM is a lysosomal protein that regulates autophagy. A previous study found that DRAM is significantly downregulated in certain epithelial malignancies, and the p53/DRAM axis plays a very important role in the treatment of breast cancer (107). The mechanism by which DRAM causes tumorigenesis may be related to the ability of DRAM to regulate autophagy and apoptosis. DRAM is induced by DNA damage and is a direct target of p53. Even in the presence of inhibitors of protein synthesis, DRAM-induced RNA damage does not require the synthesis of intermediate proteins and can therefore be considered a major target of p53. DRAM knockdown reduces p53-mediated apoptosis, indicating that DRAM is directly involved in p53-mediated apoptosis. p53 has been shown to regulate autophagy (108), and p53 induces autophagy in a DRAM-dependent manner, indicating that DRAM plays an important regulatory role in autophagosomes. DRAM is a regulator of p53-induced autophagy, and DRAM-dependent induction of autophagy is required and critical for p53-mediated apoptosis. Therefore, the decreased expression of DRAM leads to the decrease of autophagy and apoptosis levels, which may be an important mechanism of tumorigenesis.

Effect of beclin-1-related autophagy and apoptosis on tumorigenesis. Beclin-1, the mammalian homolog of yeast ATG6, is a mammalian tumor suppressor (109,110). The *beclin-1* gene is monoallelic, deleted in up to 75% of ovarian, 50% of breast and 40% of prostate cancers (111). Reduced expression of beclin-1 is also observed in other types of cancer such as human brain tumors and cervical cancers (112,113). Beclin-1 acts as an important confluence of autophagy and apoptosis through its interaction with the apoptotic protein family Bcl-2 (114). It was found that Bcl-2 interacts with the BH3 domain of beclin-1, UVRAG interacts with the CCD of beclin-1, and class III PtdIns 3-kinase interacts with the ECD and CCD of beclin-1. Beclin-1 acts as a platform or scaffold for the formation of complexes during autophagy, and is also a bridge for the interaction between autophagy and apoptosis. Previous studies have shown that synthetic peptides containing the BH3 domain of beclin-1 induce apoptosis (73,109-115), beclin-1 function can be regulated by other BH3-only proteins, such as Bad. In addition to its pro-apoptotic effects, Bad induces autophagy by competitively disrupting the interaction between beclin-1 and Bcl-2/Bcl-X. The interaction between Bcl-2 and beclin-1 is greatly reduced after starvation, suggesting that the segregation of Bcl-2 and beclin-1 is of great importance for the activation of autophagy, which contributes to the protection of cells upon starvation (73,115). Since autophagy and apoptosis are interconnected, and their relationship may vary in specific contexts, beclin-1 may play a regulatory role in apoptosis and other related cellular events. In a mouse model, it was found that beclin-1 is not required for apoptotic cell death, but for the generation of signals that allow phagocytes to clear apoptotic corpses (116). However, in another study, there was a different opinion, that the autophagy genes ATG7 and beclin-1 are required for apoptosis (117). Therefore, the regulatory mechanism of beclin-1 in autophagy and apoptosis still needs to be further explored.

JNK is an important pro-apoptotic component; a recent study found that the activation of JNK signaling plays an important role in inhibiting the occurrence of lung cancer (118). It has been revealed that JNK can reduce the mutual inhibition of beclin-1 and Bcl-2 pro-apoptotic family members by phosphorylating Bcl-2 in the flexible loop between its BH4 and BH3 domains, thus inducing autophagy and apoptosis. Besides, reactive oxygen species can inhibit DNA repair and promote cell cycle arrest by activating JNK signaling, thereby promoting the occurrence of autophagy and apoptosis.

DAP kinase (DAPK), a death-associated protein kinase with important pro-apoptotic effect (89,119), is an important tumor suppressor. Recent studies found that the activation of DAPK has a very important inhibitory effect on thyroid cancer and small cell lung cancer (120,121). DAPK can activate protein phosphatase 2A (PP2A), a form of cell death caused by shedding of adherent cells from their substrates, to promote cell death in the presence of dysregulated ceramide-induced apoptosis. Meanwhile, DAPK is also an autophagy stimulator and is involved in the regulation of autophagy and apoptosis. DAPK phosphorylates beclin-1 within its BH3 domain (Thr119), which prevents beclin-1 from binding to its inhibitor Bcl-2/Bcl-x, thereby promoting its autophagic activity (122). In addition, DAPK can activate protein kinase D (PKD), and PKD activates VPS34 through phosphorylation and degradation (123), which promotes the occurrence of autophagy. As the binding between beclin-1 and the pro-apoptotic protein family BCL-2 is inhibited, not only the level of autophagy but also the level of apoptosis is increased, thereby inhibiting tumorigenesis.

S100A8/A9 are two members of the S100 calcium-binding protein family, and their abnormal expression is related to the occurrence of various cancers. S100A8/A9 can effectively inhibit the occurrence of head and neck squamous cell carcinoma (124). Its complex can promote the apoptosis of various cells, and S100A8/A9 is also closely related to the occurrence of autophagy (125). S100A8/A9 was revealed to activate caspase-9, caspase-3 and caspase-7, leading to cleavage of poly (ADP-ribose) polymerase-1 in cells, thereby promoting apoptosis. The mechanism of S100A8/A9-induced apoptosis may also be related to BNIP3 and reactive oxygen species. BNIP3 has a single BH3 domain and a C-terminal trans-membrane (TM) domain. As can be observed from the previous description, BNIP3 is an atypical pro-apoptotic Bcl2 family member with strong pro-apoptotic activity. Transient-transfected BNIP3

showed mitochondrial damage and mitochondrial autophagy, accompanied by the opening of mitochondrial permeability transition pore and increased production of reactive oxygen species, leading to mitochondrial dysfunction, which in turn results in cell apoptosis (126,127). A very important process in BNIP3-induced apoptosis is that BNIP3 needs to be integrated into the mitochondrial outer membrane to induce cell death. A rapid decrease in mitochondrial membrane potential was identified when cells were treated with S100A8/A 9, triggering the pro-apoptotic mechanism of Bak and promoting the translocation of BNIP3 to mitochondria. The association of BNIP3 with mitochondria is enhanced after S100A8/A9-induced apoptosis (104,128). The damage of mitochondria is accompanied by the release of a large amount of reactive oxygen species, which is an important signal for the activation of autophagy. In the meantime, it was found that after S100A8/A9 treatment, the number of autophagosomes and apoptotic bodies increased significantly; the formation of LC3-II protein, Atg12-Atg5 and the expression level of beclin-1 were both increased under transmission electron microscope. This indicated that S100A8/A9 can promote both apoptosis and autophagy. In S100A8/A9-treated cells, LC3-II co-localized with mitochondria and lysosomes, and the increased autophagy induced by S100A8/A9 may be related to the induction of mitochondrial damage (125).

The pro-apoptotic kinase Mst1 is a serine-threonine kinase with strong pro-apoptotic activity. Studies have found that the expression of Mst1 in cancer tissues of patients with cervical and lung cancer is significantly lower than that in adjacent tissues, which may be related to the pro-apoptotic activity of Mst1. Mst1 is a component of the Hippo signaling pathway, and previous studies have found that the Hippo pathway is a tumor inhibiting signaling pathway (129), which indicates the importance of Mst1 in inhibiting tumors. With the in-depth study of Mst1, it was found that Mst1 can inhibit autophagy by promoting the interaction between beclin-1 and Bcl-2. Mst1 phosphorylates the Thr108 residue in the BH3 domain of beclin-1, and phosphorylated beclin-1 co-locates with ER marker motifs, but not with mitochondrial or Golgi markers, suggesting that Mst1 phosphorylates ER beclin-1 (130). The interaction between beclin-1 and Bcl-2 and Bcl-xL is enhanced upon phosphorylation by Mst1, which disrupts the interaction between beclin-1 and Vps34, while attenuating the binding of Atg14L to beclin-1. Phosphorylation of Mst1 directly inhibits the formation of the beclin-1-VPS34 complex, leading to the formation of beclin-1 homologous dimer and thus inhibiting autophagosome formation. When Bcl-2 and Bcl-xL were downregulated, the inhibition of autophagy by Mst1 was abolished, indicating that the inhibitory effect of Mst1 on autophagy occurs mainly by enhancing the mutual binding between beclin-1 and Bcl-2. MST1-induced Bcl-2 and Bcl-xL are sequestered by beclin-1, which activates Bax, thereby stimulating apoptosis and inhibiting tumorigenesis. The ability of Mst1 to regulate autophagy and apoptosis may help suppress tumorigenesis and progression by eliminating adaptive mechanisms for tumor cells to survive in hypoxic environments and promoting cell death (129,130).

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase whose upregulation has been implicated in the development of cancers (131). Studies have found that EGFR is an important target for the treatment of non-small cell lung, breast and gastroesophageal cancer (132). Active EGFR blocks autophagy and active EGFR inhibits autophagy by activating the PI3K/AKT/mTOR signaling pathway and inhibiting beclin-1 (133). Active EGFR could co-immunoprecipitate with amino acids 1-135 of beclin-1 but not with amino acids 1-115, suggesting that amino acids 115-135 containing the BH3 domain contribute to the interaction between beclin-1 and EGFR. Furthermore, EGFR can bind to the amino acid 244-377 domain of beclin-1 (i.e., the evolutionarily-conserved domain ECD), thus beclin-1 has at least two domains of BH3 and ECD that can bind to EGFR (132). As aforementioned, Bcl-2 interacts with the BH3 domain of beclin-1, and the ECD domain of beclin-1 can bind to the autophagy inhibitor Rubicon. Notably, study demonstrated that active EGFR also helps with the initiation of autophagy while inhibiting it (131,132). Inactive EGFR promotes the separation of the Rubicon-beclin-1 complex through its interaction with Rubicon, thus initiating autophagy. There is an ECD region between EGFR, Rubicon and beclin-1, and the three can be combined with each other. Therefore, the binding of EGFR and Rubicon may also be through the ECD region. Active EGFR selectively binds to the BH3 domain of beclin-1 through the BH3 region, resulting in the inability of beclin-1 to bind to the BH3 domain of Bcl-2 through the BH3 domain. Bcl-2 is separated from beclin-1, and the release of Bcl-2 leads to increased anti-apoptotic ability, which in turn leads to tumorigenesis (131). However, inactive EGFR selectively binds to the ECD domain of Rubicon through the ECD region, resulting in the release of beclin-1 and thus promoting autophagy. When cells are not stimulated by external stimuli, EGFR activity is inhibited and the binding of the ECD domain of EGFR is active, and the BH3 domain is inhibited. At this time, autophagy proceeds normally and tumorigenesis is inhibited. When cells are stimulated by external stimuli, EGFR activity increases so that the binding of the ECD domain is inhibited while the BH3 domain is activated, thereby inhibiting autophagy and stimulating tumorigenesis (131,133).

Inhibition of autophagy is considered to be an important mechanism of tumorigenesis, but autophagy can instead promote cancer cell survival when cells are under metabolic stress (134). Lysosome-associated trans-membrane 4B (LAPTM4B) is a 4-transmembrane protein localized in late endosomes and lysosomes (135). Studies have found that abnormal elevation of LAPTM4B is closely related to liver cancer. Moreover, elevated LAPTM4B has also been observed in breast, lung, ovarian and colon cancers (132), suggesting that abnormal expression of LAPTM4B stimulates normal cell mutation, and LAPTM4B also promotes cancer cell proliferation, migration and invasion (136,137). LAPTM4B is important to EGFR-mediated cell survival. It is suggested that LAPTM4B promotes cancer cell proliferation by upregulating PI3K/AKT signaling (136), and promotes active EGFR signaling by blocking EGF-stimulated EGFR intraluminal sorting and lysosomal degradation (132). Serum starvation increases EGFR endosomal accumulation and enhances the correlation between LAPTM4B and EGFR, whereas EGF stimulation reduces the interaction between the two, suggesting that LAPTM4B preferentially interacts with inactive EGFR and that EGFR-dependent autophagy initiation may be associated with LAPTM4B-mediated endosome localization of EGFR.

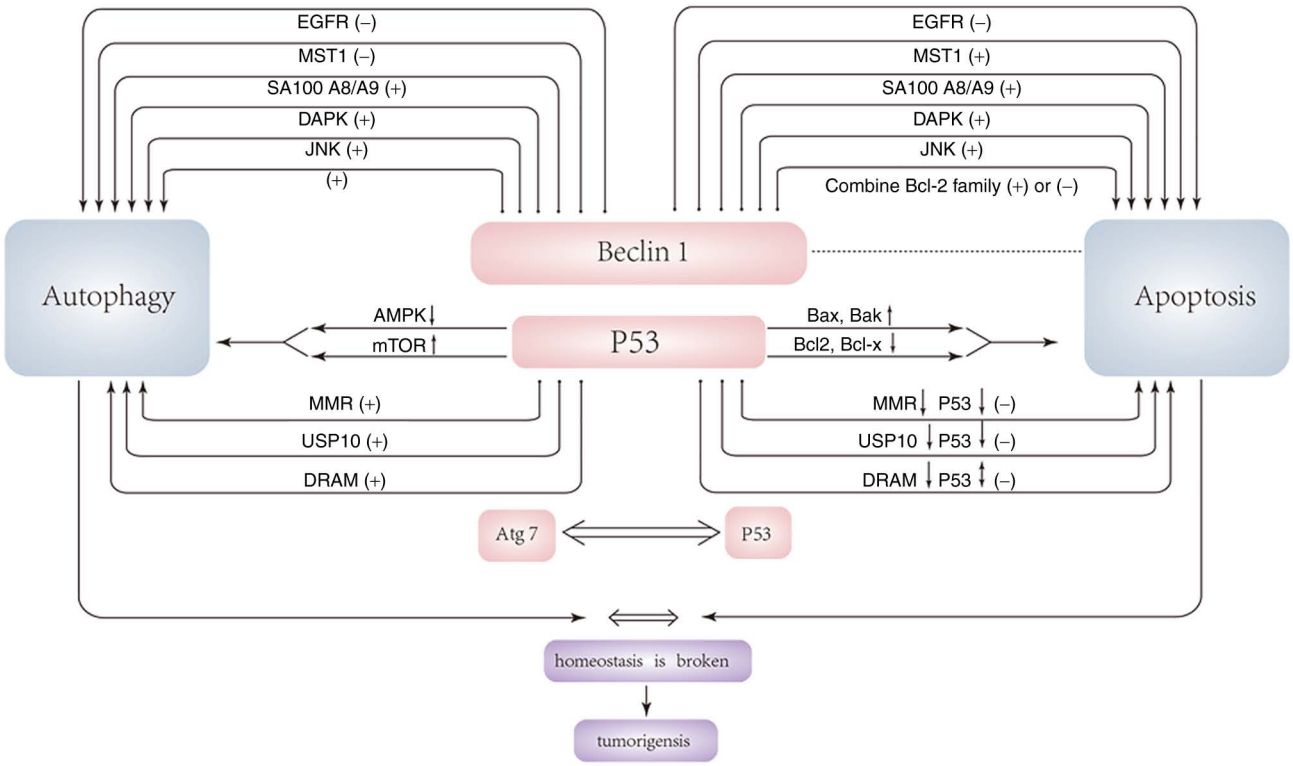

Figure 3. Interaction between autophagy and apoptosis is regulated by a variety of molecules. When the expression of these molecules is abnormal, the balance between autophagy and apoptosis is disrupted, thus tumors may be induced.

Upon serum starvation, LAPTM4B senses EGFR inactivation on endosomes and selectively complexes with inactive EGFR, and recruit the Sec5 exocyst subcomplex (137). This EGFR complex binds to the autophagy inhibitor Rubicon, causing it to dissociate from beclin-1, releasing the Rubicon-free beclin-1 complex to initiate autophagy. Under nutrient-rich conditions, activated EGFR inhibits autophagy through agonist-stimulated EGFR signaling. Under metabolic stress conditions, inactivated EGFR promotes the survival of cancer cells under starvation by activating autophagy (138-140). Therefore, inactivated EGFR may have dual roles in tumorigenesis, that is, to promote autophagy to inhibit tumorigenesis when tumorigenesis has not yet occurred, while its autophagy activation promotes tumor cell survival when tumorigenesis occur (Fig. 3).

7. Effects of other types of autophagy and apoptosis on tumorigenesis

Glycolysis is a major determinant of mitotic survival. PFKFB3 is a key regulator of the glycolytic kinase phosphofructokinase-1 (PFK1), is often overexpressed in cancer cells leading to the Warburg effect, a metabolic shift from oxidative stress to rapid glucose extraction, glycolysis and lactate export. This is characteristic of numerous tumor cells (141,142). A recent study found that the high expression of PFKFB3 is closely related to the incidence and poor prognosis of nasopharyngeal carcinoma (143). PFKFB3 is known to be regulated by AMPK and p38 MAPK in a phosphorylation-dependent manner in cancer. AMPK-dependent phosphorylation of PFKFB3 may help enhance glycolysis during mitosis to promote cell survival. AMPK is a major homeostatic regulator of cellular ATP levels, and its activity is enhanced during mitosis (144), and an increase in the AMP/ATP ratio during mitotic arrest may contribute to AMPK activation (145). Mitotic cells may be more sensitive to AMPK due to the absence of the nuclear envelope. AMPK activation can significantly increase glucose uptake and glycolysis, and can promote more energy-efficient oxidative metabolism by upregulating mitochondrial biogenesis and oxidase expression (146). Activation of AMPK and subsequent glycolysis switches observed in mitotic cells increase the possibility of energy-dependent pathway survival in mitosis. In the context of mitochondrial dysfunction, AMPK triggers glycolysis and further promotes autophagy during mitotic delay. From this perspective, activation of AMPK and autophagy appears to contribute to tumor cell survival, but there is ample evidence that AMPK activation inhibits the development of numerous cancers and tumors (147). AMPK activity is necessary and sufficient for activation of pro-apoptotic proteins (such as Bim or Bmf) and for cell death. Studies have found that autophagy can regulate cell survival during mitosis. Since Raptor is a member and active regulator of mTORC1 that inhibits autophagy, knockdown of Raptor resulted in early mitotic death, whereas downregulation of Ulk1, Vps34, or beclin-1 prevented cell death during mitosis.

Atg5 plays a very important role in autophagy. In addition to promoting autophagy, studies have also found that it has important pro-apoptotic properties. A previous study found loss of Atg5 associated with melanoma development and poorer overall survival (148). The Atg5-Atg12 complex triggers autophagic cell death through the interaction of Atg5 with FADD, which has been shown to have a critical role

in interferon-γ-induced cell death. Atg5 is also a substrate for calpain, and the truncated form of Atg5 is generated by calpain-dependent cleavage at the Thr 193 position, a pro-apoptotic molecule that translocates to mitochondria. The pro-apoptotic activity of the truncated form of Atg5 can be attributed to inactivation of Bcl-x binding, as the truncated calpain-cleavage form of Atg5 can not only induce apoptosis but also sensitize tumor cells to anticancer drug treatment (149). In addition, studies have found that other autophagy proteins also have pro-apoptotic functions after being cleaved by caspases. For example, the autophagy protein beclin-1 is cleaved by caspases to generate a pro-apoptotic BH3 domain, and BH3 localizes to mitochondria in cells, leading to increased mitochondrial permeability and promoting the release of Cyt c. Similarly, ATG4D acquired pro-apoptotic ability after being cleaved by caspase 3. The aforementioned increase in the expression level of autophagy proteins not only promotes autophagy, but also produces apoptotic protein precursors for apoptosis, which can accelerate apoptosis upon activation of caspases (17).

Abnormalities of the PI3K-AKT signaling axis. Abnormal activation of PI3K-AKT signaling axis is closely related to the occurrence of breast cancer (150), and it was found that PI3K/AKT signaling, a signaling pathway that inhibits apoptosis, also inhibits autophagy. AKT inhibits autophagy in a PI3K-dependent manner, AKT phosphorylates Bcl-1-related agonist of death, apoptosis signal-regulating kinase 1 (ASK1 also known as MAP3K5), human caspase 9, and E3 ubiquitin ligase MDML, thereby inhibiting apoptosis. AKT also inhibits apoptosis by promoting the degradation of TKB, thereby activating NF-kB and inhibiting apoptosis by transcribing anti-apoptotic genes. It was previously revealed that the inhibition of autophagy by Akt can be mediated not only by activating mTOR (151), but active Akt can also inhibit autophagy through an mTOR-independent mechanism. Studies also found that beclin-1 is phosphorylated by Akt at residues 295 (and possibly 234) in an mTOR-independent manner. Beclin-1 interacts with 14-3-3 protein via phosphorylation sites S234 and S295, and this interaction is negatively regulated by starvation and Akt inhibition. Active Akt promotes the interaction of beclin-1 with vimentin via the 14-3-3 protein (151,152). And the mechanism through which active Akt regulates the interaction of beclin-1 with 14-3-3 vimentin is through the intermediate filament to inhibit autophagy and Akt-mediated transformation. Expression of beclin-1 mutants resistant to Akt-mediated phosphorylation increases autophagy and inhibits Akt-driven tumorigenesis. Akt signaling, intermediate filaments, and 14-3-3 proteins may be involved in autophagy inhibition and tumorigenesis mechanisms through regulation of the beclin-1 complex (152). AKT1 inhibits autophagy in fibroblasts, reduces co-immunoprecipitation of class III PI3K Vps34 with beclin-1 and reduces beclin-1-associated lipid kinase activity, which all suggest that the inhibition of autophagy may be a mechanism of tumorigenesis. The interaction between oncogenic factors and autophagy may be a key factor regulating carcinogenesis (152,153).

A previous study found that knockout of the Bif-1 gene in mice promotes tumorigenesis, and the expression of Bif-1 is reduced in gastric cancer. The mechanism of the inhibition of Bif-1 gene expression to promote tumorigenesis may be related to the interaction of Bif-1 in autophagy and apoptosis. It was previously described that Bif-1 is an important regulator involved in autophagy: Bif-1 contains a C-terminal SH3 domain that forms a complex with beclin-1, thereby participating in the formation of autophagosomes (154); during starvation, Bif-1 forms a complex with beclin-1 via UVRAG to enhance PI3KC3 lipid kinase activity and induce autophagosome formation. Bif-1 plays a key role in vesicle formation for coat protein I (COPI)-mediated retrograde transport from the trans-Golgi network to the ER, whereas beclin-1 has been shown to be localized to the Golgi (155-158), thus Bif-1 may act as a bridge in the formation of autophagy. In addition to being an important regulator of autophagy, A previous study found that Bif-1 plays a very important role in caspase-independent cell death, that is, when the activity of Bif-1 is inhibited and the expression of autophagy decreases, it also promotes activation of caspase-3. Initiation of autophagy inhibits apoptosis while activating non-caspase cell death pathways. During apoptosis induced by endogenous death stimuli, Bif-1 localizes to mitochondria and regulates the activation of pro-apoptotic Bax and Bak proteins (159). The activation of Bif-1 plays a very important role in both autophagy and apoptosis, thus the loss of Bif-1 can induce tumorigenesis.

It was recently revealed that long non-coding RNAs (lncRNAs) can regulate a variety of cellular processes, which play important biological functions. A recent study found that lncRNAs NBR2 can inhibit the occurrence of liver cancer (160). Previously, it was shown that the downregulation of lncRNAs NBR2 expression is related to the occurrence of various tumors (161). Deficiency of NBR2 can lead to unexamined cell cycling under energy stress conditions and promote cell proliferation, thereby promoting tumorigenesis (162). The reason why NBR2 inhibits tumor may be related to the fact that NBR2 can promote autophagy. A study found that NBR2 can directly bind to the α subunit of AMPK, thus NBR2 may promote AMPK kinase activity through the interaction with the AMPK kinase domain as all three splicing isoforms in the NBR2 gene can induce AMPK activation. During glucose starvation, the binding of NBR2 to AMPK is significantly enhanced, and the binding can directly promote the activation of AMPK (161). NBR2 deficiency leads to decreased AMPK activity, rendering AMPK unable to be activated under energy stress conditions, resulting in enhanced mTORC1 activity, thereby suppressing autophagy levels. When autophagy is inhibited, damaged organelles and macromolecular substances cannot be removed by autophagy, and harmful substances such as reactive oxygen species produced by these substances will induce gene mutations, thereby inducing tumorigenesis (160-162).

Impaired autophagy can lead to the accumulation of p62, and p62 overexpression can stimulate the production of reactive oxygen species and enhance genomic instability, thereby promoting tumorigenesis. It was recently revealed that autophagy defects in apoptosis-impaired tumor cells lead to increased p62 accumulation, which is necessary for tumor inducers to induce tumorigenesis *in vitro* and *in vivo* (163). The oncogenic potential of p62-deficient cells is reduced, thus the elimination of p62 by autophagy can inhibit the tumorigenesis (164,165). P62 is a protein with multiple domains involved

in the activation of transcription factor NF-κB (163). The domains of P62 include LIR, TRAF6 binding (TB) domain, PB1 domain, ubiquitin-associated domain (UBA) and ZZ-type zinc finger domain. P62 interacts with LC3 through the LIR signaling domain to allow itself to be cleared by autophagy, and binds through the TB domain to TRAF6, a lysine 63 (K63) E3 ubiquitin ligase involved in NF-κB activation (166). After p62 binds to TRAF6, it activates TRAF6 by promoting its oligomerization, and then induces K63 polyubiquitination of TRAF6, which leads to the activation of NF-κB (167,168). The UBA domain of p62 helps to improve the efficiency of p62 catalyzing TRAF6. In addition, p62 can also induce the activation of NF-κB signaling pathway through other pathways. For example, p62 can interact with APKC signaling molecules through the PB1 domain, which is related to interleukin-1 (IL-1), RANK ligand (RANKL) or nerve growth factor (NGF) activation of cells to stimulate the downstream transcription factor NF-κB signaling pathway. Activation of the NF-κB signaling pathway leads to the abnormal expression of a series of tumor-related genes and inhibits the apoptosis of tumor cells. Impaired autophagy leads to accumulation of P62 to activate the NF-κB signaling pathway, thereby inhibiting apoptosis-inducing tumor (163,168).

In conclusion, autophagy and apoptosis interact with each other, either promoting or inhibiting. The mechanism of their link in tumorigenesis is still being explored. Certain scholars consider that autophagy can reduce tumorigenesis by promoting apoptosis (17,109-113,141-143,148,149): When autophagy is inhibited, cell apoptosis decreases, resulting in abnormal cell growth and tumorigenesis. Other scholars consider that autophagy and apoptosis are mutually inhibitory (68-70,73-76): Numerous cellular molecules often promote apoptosis by inhibiting autophagy, thereby reducing tumorigenesis. Nevertheless, more scholars tend to consider that autophagy plays a double-edged sword role in tumors: On the one hand, autophagy inhibits tumorigenesis by promoting apoptosis. On the other hand, autophagy provides energy and material support for the growth of tumor cells through its own catabolic ability after tumorigenesis. Not only that, but elevated levels of autophagy also lead cancer cells to develop resistance to antitumor drugs. Besides, there is no doubt that autophagy is of great importance in pathogenesis. It would be interesting to investigate how to regulate the relationship between autophagy and apoptosis, thereby inhibiting tumorigenesis. As aforementioned, it was found that numerous protein molecules related to tumor pathogenesis affect tumorigenesis by regulating autophagy and apoptosis, most of which are through autophagy protein beclin-1, apoptosis protein family Bcl-2 or interaction between the two. The key link is the BH3 domain, which is also the direct link between the two. The interaction between P53 in the apoptosis family and Atg5, Atg7 and beclin-1 in autophagy protein family is also an important connection point for regulating the interaction between autophagy, apoptosis and tumorigenesis. Therefore, the link between P53 and autophagy, beclin-1 and Bcl-2 may serve as one of the targets for the treatment of cancer in the future. It is hypothesized that the dual role of autophagy in tumors can be attributed to the different expression levels of autophagy before and after tumorigenesis. When the tumor does not occur and the expression of autophagy is reduced, necrotic cells and unfolded or misfolded proteins cannot be cleared by autophagy. The accumulation of these harmful substances in the human body leads to gene mutation, which leads to a decrease in the expression of apoptosis-related molecules, which leads to impaired apoptosis and induces tumorigenesis. After apoptosis is impaired, the interaction between autophagy proteins and apoptotic proteins is weakened, and the level of autophagy increases. At this time, autophagy provides conditions for cancer cells to survive under hypoxic conditions. Therefore, there may be a possibility that the expression level of autophagy varies greatly before tumorigenesis, during precancerous lesions and different tumor stages. In the future, it may be able to design an experiment to detect the levels of autophagy and apoptosis in cells with different pathological morphologies in tumor patients, which may provide us with a greater understanding of the role of autophagy in tumor pathogenesis. Only by improved understanding of the expression levels of autophagy in different stages of tumors, new treatment and tumor prevention solutions for autophagy can be developped. Perhaps one day in the future, autophagy can become an important target for the treatment of tumors. It is known that the fragment of autophagy protein cleaved by caspases has a pro-apoptotic effect. From this perspective, autophagy promotes apoptosis while apoptosis inhibits autophagy. Therefore, the interesting question is, since autophagy is inhibited by apoptosis, that is, the apoptosis promoted by autophagy in turn inhibits itself, how does autophagy proceed? Is there a negative feedback mechanism between autophagy and apoptosis? Autophagy proteins are cleaved by apoptosis, and autophagy is inhibited, which in turn stimulates the activation of autophagy to generate more autophagic signals to promote the synthesis of autophagic proteins. Then, the question is what are the stimulatory signals in this negative feedback mechanism of autophagy. Is it as it was hypothesized before? Autophagy is required to remove apoptotic bodies, and the autophagy pathway is thereby activated, resulting in the production of autophagic proteins. On the one hand, autophagy proteins play the function of autophagy to remove abnormal cells and harmful substances in the body, thereby maintaining cell survival. On the other hand, autophagy proteins are cleaved by caspases and play a pro-apoptotic function. This mechanism keeps autophagy and apoptosis in a dynamic balance to maintain cell life and death. This mechanism enables cells in the human body to survive and die normally, thereby preventing the occurrence of cancer. When cells are stimulated by external stimuli, this mechanism can keep the survival and death of cells at a normal level, so as to reduce the damage caused by external stimulation to human body. However, when the intensity of external stimulation exceeds this regulatory mechanism of cells, it leads to tumorigenesis. The interaction between autophagy and apoptosis is a very delicate process. Only by studying this mechanism more thoroughly, a greater chance of success in future research on anticancer drugs can be achieved.

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HX wrote the manuscript. QD took charge of the examination and modification of manuscript. SW, BW and XH participated in the induction of literature and part of the examination and modification of manuscript. RS and ML participated in the literature searching and the examination of manuscript. XL revised the manuscript. All authors listed have made a substantial, direct and intellectual contribution to the work and approved the final version of the manuscript.

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Competing interests

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