Mini-review

p53-mediated autophagic regulation: A prospective strategy for cancer therapy

Juanjuan Tang a,1, Jiehui Di a,b,1, Huan Cao a, Jin Bai a, Junnian Zheng c,*

a Cancer Institute, Xuzhou Medical College, Xuzhou 221002, Jiangsu, China
b Department of Radiation Oncology and Lineberger Comprehensive Cancer Center, School of Medicine, the University of North Carolina at Chapel Hill, 101 Manning Drive, Chapel Hill, NC 27514, USA
c Jiangsu Center for the Collaboration and Innovation of Cancer Biotherapy, Cancer Institute, Xuzhou Medical College, 84 West Huai-hai Road, Xuzhou 221002, Jiangsu, China

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ABSTRACT

Autophagy is a major catabolic process that degrades and recycles cytosolic components in autophagosomes, which fuse with lysosomes. This process enables starving cells to sustain their energy requirements and metabolic states, thus facilitating their survival, especially in cancer pathogenesis. The regulation of autophagy is quite intricate. It involves a series of signaling cascades including p53, known as the best-characterized tumor suppressor protein. Recent reports have indicated that p53 plays dual roles in regulating autophagy depending on its subcellular localization. Nuclear p53 facilitates autophagy by transactivating its target genes, whereas cytoplasmic p53 mainly inhibits autophagy through extranuclear, transcription-independent mechanisms. The relationship between autophagy and neoplasia is complicated. It may be intrinsically associated with the functional status of p53, but this is not clearly elucidated. This review focuses on the role of p53 as a master regulator of autophagy. We conclude that the contextual role of autophagy in cancer, which could be switched by p53 status, is expected to be developed into a new anticancer therapeutic approach.

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Introduction

Macroautophagy (autophagy) is an evolutionarily conserved homeostatic process. This process is characterized by the formation of a double-membrane structure, which leads to the degradation of cytosolic components by delivering them into lysosomes or the vacuole (Fig. 1) [1,2]. When cells are subjected to stressful situation, including nutrient deprivation, invasion of pathogen microorganisms, and accumulation of damaged organelles, autophagy is activated. Autophagy activation is a protective mechanism through the lysosomal recycling of metabolites to the cytoplasm, where they are fed into catabolic breakdown or re-cycled in biochemical pathways, thereby maintaining cellular homeostasis and energy requirements [3,4]. The molecular basis of autophagy is intricate and depends on the activity of various autophagy-related genes (ATGs); these genes are key in understanding the autophagosome formation and autophagy regulation [5–7]. The network of stress signaling cascades, including the p53 signaling pathway that highlights important considerations for autophagy regulation, is even more complex. However, this network has not been clearly elucidated [8,9].

Autophagy is a multistep process, and is associated with several human diseases including cancer [10,11]. However, whether autophagy mediates the inhibition or acceleration of neoplasia has been a topic of debate [12,13]. Increasing evidence firmly demonstrates that autophagy functions as a suppressive factor to tumor initiation via eliminating damaged cells, preventing genome damage, limiting oxidative stress or other aspects of oncogene activation. Therefore, the important cell-cycle checkpoint that impedes tumorigenesis is alleviated. However, in established tumors, the cytoprotective effects of autophagy contribute to tumor progression because autophagy supplies metabolic substrates essential for cancer cell survival. This phenomenon enables tumor cells the capability to cope with endogenous stress (such as hypoxia, inflammation, and angiogenesis) and increase resistance against chemotherapy or radiotherapy [14–16]. Iacobuzio-Donahue and Herman

Abbreviations: ATGs, autophagy-related genes; mTOR, mammalian target of rapamycin; AMPK, AMP-responsive protein kinase; TSC, tuberous sclerosis complex; PTEN, phosphatase and tensin homolog deleted on chromosome 10; IGFBP3, insulin-like growth factor binding protein 3; DRAM, damage-regulated autophagy modulator; DAPK-1, death-associated protein kinase 1; MAP1B, microtubule-associated protein; ARF, alternate reading frame; HSP70, heat shock protein 70; VRK1, serine/threonine-protein kinase; JNK, c-Jun N-terminal kinase; TIGAR, TP53-induced glycolysis and apoptosis regulator; ROS, reactive oxygen species.

* Corresponding author. Tel.: +86 0516 85582513; fax: +86 0516 85582513.
E-mail address: jzengh@xzmc.edu.cn (J. Zheng).

1 These authors contributed equally to this work.

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p53, the best-characterized human tumor suppressor protein, is a critical component of the cellular reaction to diverse stresses, including genotoxic damage, oncogene activation, and hypoxia; hence, active p53 constitutes an anticancer barrier [18,19]. However, inactivation of p53 by mutation is determined in a high percentage of human tumors and is related to tumor metastasis and poor prognosis [20]. Under basic conditions, the intracellular levels of p53 are strictly controlled by MDM2-involved ubiquitination and proteasomal degradation. By contrast, p53 tends to be rapidly stabilized by reversible post-translational modifications under adverse situations. These modifications include acetylation, methylation, phosphorylation, and ubiquitination, which could integrate multiple stress signals and modulate its activity [21–23]. p53 is speculated to be a stress-responsive transcription factor because of its ability to transactivate multiple target genes in response to stress, thus exerting a series of prominent biological functions. Some examples of these biological functions include cell cycle arrest, apoptosis, senescence, metabolism, differentiation, blocking of angiogenesis, and autophagy modulation [24,25]. In addition, recent studies revealed a bidirectional role for p53 in regulating autophagy. Based on cellular localization, p53 can neither be a positive nor a negative regulator of autophagy [26,27]. At basal levels, p53 is recognized as an inhibitor of autophagy through protein–protein interactions in mitochondria [25]. In response to various forms of cellular stress, p53 levels are increased, and majority of p53 translocates to the nucleus, where it promotes autophagy by transactivating its target genes [26,28].

In this review, we summarize the function of p53 as a master regulator of autophagy. The function of p53 depends on its subcellular localization, as well as the relative contributions of transcriptional and transcription-independent mechanisms. Meanwhile, we also discuss the complex relationship between autophagy and neoplasia, and how this relationship relates to the functional status of p53. We propose the revolutionary strategy for cancer therapy.

**p53 as an autophagy inducer**

In the nucleus, stress-activated p53 is generally recognized as a pro-autophagic factor in a transcription-dependent manner [27]. Multiple p53 target genes stimulate autophagic flux, which often results in the downregulation of the central metabolic sensor mammalian target of rapamycin (mTOR); mTOR functions as a negative regulator of autophagy [29]. Several mechanisms have been proposed to explain how p53 downregulates mTOR signaling cascades and then facilitates autophagy. On one hand, p53 activates the AMP-responsive protein kinase (AMPK), a positive regulator of autophagy, through transcriptional regulation of Sestrins 1 and 2 [30,31]. Activated AMPK then promotes the phosphorylation of tuberous sclerosis complex (TSC) 1 and 2, which in turn shut down mTOR activity by inactivating mTORC1-interacting protein, Rheb [29,32]. On the other hand, p53 transactivates numerous genes, including the β1 and β2 subunits of AMPK, phosphatase and tensin homolog (PTEN), TSC2, and insulin-like growth factor binding protein 3 (IGFBP3). Each subunit is upregulated under stress conditions and then functionally antagonizes the autophagy-suppressive functions of mTOR in a p53-dependent fashion [32–34].

Damage-regulated autophagy modulator (DRAM), a p53 target gene encoding a lysosomal protein, is required for the ability of p53 to induce autophagy in response to different stresses [35,36]. DRAM can contribute to autophagosome accumulation by modulating autophagosome–lysosome fusion to generate autolysosomes [37,38]. A series of p53-inducible splice variants encoded by DRAM-1, including SV4 and SV5, could modulate autophagy. In contrast to ‘full-length’ DRAM-1 (SV1), both isoforms do not localize to lysosomes and endosomes, but instead exhibit partial localization in peroxisomes and autophagosomes, respectively, as well as in the endoplasmic reticulum (ER). These findings distinguish new autophagy regulators that highlight additional complexity in the control of autophagy downstream of p53 [39]. In addition, the p53 family member p73 is closely related to autophagy in DRAM-dependent or –independent manners. p73 can also transactivate DRAM, which is dispensable for the pro-autophagic signals of p73. p73 is reported to directly regulate autophagy genes, including Atg5 and 7 [40,41].

Another mechanism whereby p53 induces autophagy emerges with the discovery of death-associated protein kinase 1 (DAPK-1), which is a well-established tumor suppressor protein and is also upregulated by activated p53 [42]. Several mechanisms have been clarified to explain how DAPK-1 controls autophagy. First, DAPK-1 can favor autophagy induction by binding to, and thereby suppressing, the microtubule-associated protein MAP1B, which is an anti-autophagic factor via interacting with LC3 [43]. Second, the phosphorylation of the BH3 domain of Beclin1, an essential autophagy modulator, by DAPK-1 will finally result in the release of
Beclin1 from Bcl-2/Bcl-xL-mediated sequestration [44,45]. Release of Beclin1 occurs by suppressing the transcription of Bcl-2 and Bcl-xL [46] or by upregulating the expression of Bax, Bad, Bnip3, and p53 upregulated modulator of apoptosis (PUMA). These BH3-containing proteins of the Bcl-2 family are speculated to induce autophagy [47,48]. In addition, DAPK-1 sustains the activation of the alternate reading frame (ARF, a well-described p53/Mdm2-dependent tumor suppressor) [49]. Subsequently, DAPK-1 promotes the stabilization of p53 through binding and inhibiting the E3 ubiquitin ligase for p53 (MDM2), thereby stimulating autophagy [50].

p53 can also induce autophagy via transactivation of the ARF tumor suppressor. This suppressor is involved in the induction of autophagy besides maintaining p53 stability [51,52]. ARF exists in two isoforms, namely, smARF and full-length ARF. These isoforms also exert proautophagic functions in a p53-independent mechanism [53]. However, whether the principal molecule involved is full-length ARF or smARF remains unknown. Reef et al. reported that the smARF variant of this protein preferentially traffics to mitochondria [54], where it may interact with the mitochondrial protein p32 [55,56]. They also found that smARF is the only form of ARF that can induce autophagy, because full length (nucleolar) ARF fails to induce autophagy unless ARF is expressed at non-physiological levels, at which time ARF leaves the nuclear compartments [54,57]. Abida and Gu [53] showed that full-length ARF, in contrast to smARF, induces autophagy in both p53-dependent and -independent manners, which depended on the cellular context. Significantly, Pimkina et al. [58] showed that mitochondrial ARF disrupts Beclin 1/Bcl-xL complex formation, releasing Beclin-1 to induce autophagy. This finding provides a basis for ARF-induced autophagy. Furthermore, the cytosolic heat shock protein (HSP70) possesses a critical role in ARF-mediated autophagy and promotes ARF translocation to mitochondria because of the proautophagic function [59]. However, the precise mechanisms of regulating ARF trafficking to mitochondria remain unresolved. In view of the conflicting views and the uncertain roles of ARF or smARF in autophagy, researchers proceeded to map a region located in the highly conserved 5′ end of CDKN2A exon 2, which was required for autophagy induction by human and murine ARF. They eventually concluded that full-length ARF can induce autophagy (non-selective macroautophagy), whereas smARF enhances selective autophagy of mitochondria (mitophagy). This finding is consistent with the preferential localization of smARF to mitochondria that drives its mitophagy function. However, the observation that silencing Tp53 can induce autophagy in an ARF-dependent manner while ARF is considered as a positive regulator of p53 seems contradictory (see “p53 as an Autophagy Suppressor” section) [60]. Grenier et al. [61] recently showed that smARF is localized to mitochondria, where it induces its depolarization and triggers mitophagy in a Parkin/PINK1-dependent manner. In summary, the functions of ARF in autophagy induction are rather elusive, which may involve multiple potential pathways, including p53-dependent and -independent mechanisms. Therefore, the end-result of ARF-mediated autophagy is also controversial. These conflicting data are unclear and need further exploration.

Several molecular cascades promote autophagy (at least in part) through p53 stabilization, including proteasomal inhibition (directly resulting in p53 accumulation) [62]. However, the downregulation of the p53-stabilizer VRK1 by p53 in response to DNA damage is mediated by the autophagic pathway, and the downregulation of VRK1 protein levels requires DRAM expression [63]. A proautophagic role is also attributed to c-Jun N-terminal kinase (JNK). p53 partially contributes to JNK activation, which eventually regulates autophagy via two distinct mechanisms. On one hand, JNK activation phosphorylates Bcl-2 in its non-structural N-terminal loop, releasing beclin-1 from the Bcl-2-Beclin-1 complex [64,65]. On the other hand, JNK facilitates DRAM upregulation [66,67], both of which conclude with an increased autophagy level. Moreover, JNK, in turn, regulates the activity of p53 by promoting phosphorylation and mediates several autophagic gene expressions, including beclin1, Atg5, Atg7, and p62, which may constitute an amplification loop in the context of autophagy regulation [67,68]. JNK pathway activation can promote the expression of sestrin 2, sequentially resulting in AMPK-dependent inhibition of mTOR signaling, which is a novel player in autophagy induction [69]. Notably, Chikh et al. [70] were the first to identify iASPP (encoded by PPP1R13L), an evolutionarily conserved p53 inhibitor, as a novel autophagy inhibitor in keratinocytes. They identified iASPP through interfering with the formation of the Atg5–Atg12–Atg16L1 complex, thus preventing autophagosome maturation. However, the effect of iASPP on downregulating autophagy accompanied with p53 inhibition remains unclear; therefore, further studies are required.

**p53 as an autophagy suppressor**

Not all p53-derivable genes have proautophagic factors. Bensaad et al. [71] reported another target gene of p53, TP53-induced glycolysis and apoptosis regulator (TIGAR). This target gene contributes to the regulation of metabolic pathways or oxidative stress [72]. It also contributes to the anti-autophagic function of cytoplasmic p53. TIGAR expression is characterized by suppressing autophagy by lowering fructose-2,6-bisphosphate levels in cells; this expression leads to glycolysis inhibition and overall decline in intracellular reactive oxygen species (ROS) levels, rather than via the mTOR pathway in response to nutrient starvation or metabolic stress [73].

In contrast to the transcription-dependent mechanisms of p53, multiple experimental settings about the important role of cytoplasmic p53 also exist; p53 inhibits basal autophagy independent of its transcriptional role, especially in unstressed cells [74,75]. Accordingly, in human, mouse, and nematode cells, when p53 is subjected to gene knockout, RNA interference or pharmacological inhibition, p53 exhibits an increased level of basal autophagy that may converge on the classical autophagy pathway based on the AMPK-dependent inhibition of mTOR. This phenomenon is particularly observed in the G1 phase and, in a lesser degree, in the S phase of the cell cycle, suggesting cell cycle-dependent regulation of autophagy by p53 [74,76]. The inhibitory effect for p53 on autophagy may also involve the resultant upregulation of ARF. Pimkina et al. [58,60] first reported that silencing p53 in mouse embryo fibroblasts is sufficient to upregulate ARF and then induce autophagy. Furthermore, various autophagic triggers, including nutrient withdrawal and mTOR inhibition by rapamycin, facilitate Mdm2-dependent proteasomal degradation of p53. This proteasomal degradation is required for autophagy induction exposed to ER stress and other agents. Retransfection of HCT116 p53−/− colon carcinoma cells with wild-type p53 reduces baseline levels of autophagy [74]. All of these results indicate that cytoplasmic p53 functions as an inhibitor of autophagy, even in the absence of DNA damage or other p33-activating conditions.

Intriguingly, p53 mutants also play an effective role in inhibiting autophagy when transfected into p53−/− cells through its preferential localization to the cytoplasm, rather than in the nucleus [77]. The autophagy-repressing role of p53 is independent of the existence of nuclear compartment. This role is reserved by p53 mutants despite the fact that most of them have lost their transactivating activities because of point mutations or short deletions impairing the DNA-binding domain. Therefore, p53 mutants fail to interact with DNA or Bcl-2 family member [74,77]. Accordingly, when only the cytoplasmic localization signal remains, the nuclear localization sequence is deleted; mutant forms of p53 inhibit autophagy to a great extent, which is associated with its nuclear-to-cytosolic redistribution [77]. These results first demonstrate that the cytoplasmic (and not the nuclear) pool of p53 can be an
efficient autophagy inhibitor via protein–protein interaction, which is also retained by mutant p53 [78]. These results also indicate that the two biological activities of autophagy inhibition and proapoptotic mechanism by cytoplasmic p53 are distinct depending on the structure [77]. The specific mechanisms involved in the cytosolic p53 should be further investigated, particularly the tumor-derived mutant forms of p53.

In addition, the functions of p53 (including autophagy correlated and -uncorrelated) can be affected by other transcription factors, such as FOXO3A. This transcription factor can weaken the transcriptionsal activity of p53 and accelerate its nuclear export machinery, accumulating in the cytoplasm and negatively regulating autophagy [79]. Morselli et al. [80] suggested a potential mechanism by which cytoplasmic p53 suppresses autophagy, that is, by directly interacting with the mammalian ortholog of yeast Atg17 (RB1CC1/FIP200). This mechanism interferes with the initiation of the autophagic flux by inactivating Atg1 (ULK1) and affects its redistribution to nascent phagophores.

Most studies focus on the cytoplasmic form of p53 and its roles in autophagy inhibition. However, a newly published report has shown that the cytoplasmic accumulation of p53 exerts its stimulatory role of autophagy dependent on the PIASy-mediated Tip60 sumoylation, which involves transcription-associated p53 modifications that is independent of PUMA. The new report proposed that PIASy binding to p53 and PIASy-activated tip60 result in K386 sumoylation and K120 acetylation of p53, respectively. These modifications are not only related to p53 transcription function but also facilitate cytoplasmic translocation of p53 and activation of PUMA-independent autophagy. Consistently, they found that mutation of K120 or K386 of p53 impairs its cytoplasmic accumulation by p53 immunofluorescence and biochemical fractionation. Moreover, suppressing nuclear export signals of endogenous p53 results in impaired autophagy flux. Given these findings, they speculated that K120-acetylated and K386-sumoylated p53 reaches the nuclear pore complex, where it is desumoylated prior to nuclear export, and K120-acetylated p53 probably targets mitochondria to induce autophagy [81].

**Conclusions and future directions in cancer therapy**

This review mainly focuses on the dual role of p53 in autophagy regulation, which is associated with its intracellular distribution, as well as its transcriptional and transcription-independent mechanisms (Fig. 2). In general, nuclear p53 enhances autophagy by interacting with its target genes in a transcriptional manner, whereas cytoplasmic p53 shuts down autophagy mainly through extranuclear, transcription-independent mechanisms, although p53-mediated transactivation of TIGAR suppresses autophagy. However, a contradictory report exists. Cytoplasmic p53 was proven to induce PUMA-independent autophagy, which is reasoned to be correlated with K120 acetylation and K386 sumoylation of p53. Moreover, K120-acetylated p53 probably targets mitochondria to induce autophagy [81]. Scherz-Shouval and Weidberg observed aberrant autophagosome accumulation in HCT116 p53−/− cancer cells, but not in HCT116 p53+/+ cells, when both are exposed to prolonged starvation. This observation indicates that p53 can modulate autophagic flux to an affordable rate and ensure autophagic homeostasis. Thus, the authors proposed that p53 is neither a positive nor negative moderator of autophagy; p53 functions as a rheostat that sustainably maintains better autophagic homeostasis, consequently increasing cell fitness and better long-term survival [82].

Following genotoxic stress or oncogene activation, p53 can activate various genes to regulate significantly in apoptotic and autophagic responses, which are complex and partially overlapping mechanisms [83]. Activation of these genes is differentially controlled by stress level and depends on cell content. For example,
one of the p53 target genes, TIGAR, reduces both autophagy and apoptosis by suppressing ROS, although TIGAR can indirectly influence ROS levels through a decreased rate of the glycolytic pathway, which in some cells can be proapoptotic [71,73,74]. Several antioxidant genes, including p53-induced genes, potentially suppress apoptosis and participate in the autophagic process, such as glutathione peroxidase 1 (GPX1), mitochondrial SOD-SOD2, catalase, and sestrins 1 and 2 [84,85]. In certain cases, p53 stabilization is involved in the transcriptional upregulation of several genes, including mitochondrial (Bax, Noxa, etc.) and death receptor-mediated (CD95, DR5, etc.) apoptosis [86]. In addition, DRAM modulates autophagy in a p53-dependent manner and functions as the upstream of mitochondrial apoptosis mediated by p53 [35], ULK1, transactivated by p53, was suggested to contribute to sustained autophagy activation and DNA-damage-induced cell death [87]. Thus, the p53 network is unclear, and further investigation is urgently required to clarify these issues. Taken together, depending on cellular location, p53 can either promote or inhibit prosurvival autophagy. Nevertheless, strong activation of p53 in response to stress kills cells by activating apoptosis.

Autophagy is closely involved in providing energy requirements and metabolic states to cells under prolonged nutrient deficiency, thus extending their survival in stressful environments, particularly in cancer pathogenesis [2,11]. In summary, autophagy is speculated to have a contextual role in cancer. Autophagy initially inhibits initial tumor growth and then promotes tumor progression [14,16]. Similar to this finding, Rao and Tortola observed that the silence of Atg5, a key mediator of the autophagosome formation, distinctly blocks the progression of KRasG12D-elicited lung carcinoma and prolongs the survival of tumor-bearing mice. However, autophagy deficiency markedly accelerates the initiation of Atg5-deficient KRasG12D-driven lung tumors despite its improved survival at later states of tumor. Given these results, these authors demonstrated a dual role of Atg5-dependent autophagy in the oncogenic process. They speculated that the mechanism of altered immunosurveillance against autophagy-deficient cancer cells could explain why Atg5 deficiency results in the enhanced tumor onset [88]. p53 is known for its tumor-suppressing functions and proapoptotic effects [89]. Recently, p53 is better recognized for its activities in autophagy regulation, especially in maintaining autophagic homeostasis; p53 possesses prosurvival functions, particularly under stress conditions. All of these presumably render p53 in a complicated association with tumorigenesis [82]. Such cytoprotective function of p53 could serve as an anticancer mechanism; this function may be part of its increasingly appreciated role in maintaining genomic stability and intracellular metabolic homeostasis. This function may reduce the incidence of cancer-promoting cellular disorders in a healthy organism. However, some cancer cells may take full advantage of these prosurvival effects of p53 if they successfully complete the canceration process without acquiring a wt p53. Subsequently, wt p53 may render them more resilient in changing nutrient availability, and cancer cells may misuse p53 functions meant to serve the wellbeing of the organism [82]. Rao et al. described that disabled autophagy can markedly impede the progression of lung cancer; nevertheless, the gene knockout of p53 reverts cancer progression of Atg5-deficient tumors, suggesting that the p53 tumor suppressor pathway may be viewed as a crucial barrier in the malignant progression of autophagy-defective lung tumors [88]. Moreover, the role of autophagy in tumor progression is closely related to the status of the tumor suppressor p53 [17,90]. Rosenfeldt and coworkers described a mouse model of pancreatic ductal adenocarcinoma, containing oncogenic Kras but lacking p53. In this model, the loss of autophagy no longer blocks tumor progression but significantly accelerates tumor initiation. Metabolic analysis reveals that the loss of p53 and autophagy result in increased glucose uptake and enrichment of anabolic intermediates, which may be responsible for tumor growth [90]. In line with these results, Guo et al. [91] reported that p53 also controls lung tumor development in Atg7-mutant mice. They observed that the absence of Atg7 reduces lung tumor burden that is partially relieved by deletion of p53 and extends life span. Furthermore, autophagy promotes tumor growth by suppressing the ability of p53 to limit tumor growth, maintaining mitochondrial function, sustaining metabolic homeostasis, and surviving stress [92].

All of these recent findings that autophagy drives tumorigenesis suggest a novel concept of autophagy inhibition as a potential approach for cancer therapy [92]. Meanwhile, autophagy inhibition may also be valuable combined with other anticancer therapeutic approaches [16]. In the context of p53 deletion, autophagy inhibitors may actually spur tumor progression. Conversely, selected patients with intact p53 status are more likely to benefit from autophagy inhibitors as a component of their adjuvant or first-line treatment [17]. In addition, cytoprotective autophagy may serve as a potential basis for therapeutic resistance in cancer [93,94], which may provide a new strategy for improving curative efficacy through interference with autophagy [95–102]. A number of studies have shown that genetic or pharmacological intervention of autophagy can sensitize tumor cells to radiation or chemotherapy [103–107]. However, other data indicated that neither chloroquine (pharmacological inhibition of autophagy) nor knockout of autophagy-related gene is effective in conferring radiosensitization or chemosensitization in cancer [96,108]. These findings seem to conflict with those of other studies and bring about the compelling question concerning whether autophagy inhibition applied in clinical treatment for chemosensitization and radiosensitization may lack sufficient and rigorous supporting preclinical data. Collectively, these studies implicate that chemotherapy or radiation does not always induce the cytoprotective form of autophagy [93,96]. For this reason, radiation-induced autophagy was further demonstrated as either cytoprotective or nonprotective, depending on whether the functional p53 exists in tumor cells. Alternatively, these findings suggest that while radiation can induce autophagy independent of p53 status, inhibition of autophagy enhances radiation sensitivity through a mechanism that requires functional p53. Consequently, if autophagy inhibition strategy is applied in clinical treatment, determining whether the autophagy is cytoprotective or nonprotective is necessary [95,109,110]. Further understanding the interplay of p53 status, autophagy, tumor metabolism, and apoptosis before treatment may provide an opportunity for better selection of a specific therapeutic schedule.

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Conflict of interest

The authors have declared no potential conflicts of interest.

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