The status of p53 in cancer cells affects the role of autophagy in tumor radiosensitisation

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Summary

The function of autophagy in cancer has been intensively studied as a possible therapeutic target due to its unique ability to influence the cancer cells’ resistance to chemotherapy and radiation treatment. p53 is a pivotal tumor suppressor that induces apoptosis, cell cycle arrest, and senescence in response to various stresses, also playing an important role in the regulation of radiosensitivity. Autophagy may either promote or inhibit the survival of tumor cells, while it was found to change along with the status of p53 in cancer cells. In this mini review, we aimed to provide an overview of the intricate relationship between autophagy and the status of p53 which plays an important role in radiosensitivity. Since autophagy can react to radiation differently in cancer cells with different p53 statuses, future work elucidating the interaction between autophagy and p53 in response to radiation might provide more insight into targeted cancer radiotherapy.

Key words: autophagy, p53, radiosensitivity, radiotherapy

Introduction

In recent years, the development of novel cancer therapeutics capable of overcoming radioreistance has become a new field of interest in cancer research. The p53 protein is likely the most extensively studied tumor suppressor, and it plays a fundamental role in the response to cellular stress [1,2]. The p53 tumor suppressor pathway serves to protect genomic stability and suppress tumor formation. p53 can play dual roles in the control of autophagy [3].

Autophagy reflects a cellular response to cellular stress. It is often associated with activated oncogenes and cancer therapies, and ultimately targets cytoplasmic proteins and organelles for lysosomal degradation. Accordingly, there is evidence that autophagy can serve either as a cytoprotective or cytotoxic mechanism, depending on the cellular context and the nature of the stress-promoting challenge. Whether autophagy induced by cancer therapy contributes to tumor cell death or represents a mechanism of resistance to therapy-mediated cell death and the role of p53 in regulating autophagy reacting to radiation remains uncertain. Hence, it is important to understand the molecular mechanisms underlying this phenomenon and to search for new therapeutic strategies to overcome radiation resistance.

In this review, we summarise the current knowledge related to the crosstalk between autophagy and p53 in irradiation and delineate the function of autophagy in the modulation of radiosensitivity in cancer cells with different p53 statuses.

p53 plays an important role in radiosensitisation

A. p53 function in tumor radiosensitisation

Irradiation kills cancer cells almost entirely via the induction of radicals that cause DNA damage, while the p53 tumor suppressor protein plays an important role in protecting cells from DNA damage and cellular stressors following radiation [9,10]. p53 has been implicated in multiple aspects of several biological processes, including apopto-
sis, cell cycle arrest, senescence, metabolism, differentiation, angiogenesis and autophagy [11,12]. p53 is a key mediator of an ataxia-telangiectasia mutated gene (ATM)-dependent DNA damage response cascade following cellular exposure to ionising radiation [13]. The p53-family members, p63 and p73, are highly similar to p53, yet they are differentially activated by irradiation (IR) via the ATM and c-abl/ antithrombin receptor (ATR) signalling pathways [14,15]. p53 function is a crucial response to DNA damage. Without a stimulus, p53 is ubiquitinated and targeted for proteosomal degradation with the help of mdm2, mdmx and p300. DNA damage activates ATM/ATR, which can phosphorylate p53, mdm2 and mdmx directly or indirectly through chk1/2 [16]. The outcome of radiotherapy is dependent on the cellular p53 status. In normal cells, p53 acts to stop the cell cycle, activate the DNA repair machinery, and, if the damage persists, initiate the expression of apoptotic genes to remove the damaged cells.

B. p53 mutations that induce radioresistance

p53 is the prototypic tumor suppressor gene; it is well suited as a molecular link between the causes and the development of cancer, and it is mutated in the majority of human cancers. There are more than 26,000 sets of p53 somatic mutation data according to the database from the International Agency for Research on Cancer (IARC) (http://www-p53.iarc.fr/) [17]. Since mutated p53 not only affects the tumorigenic process but also the therapeutic response, p53 mutations in tumors generally indicate a poorer prognosis [18]. Upon loss of p53 function, cancer cells escape from the radiation-induced apoptotic commitment, ignore cell cycle checkpoints and continue through the cell cycle [19-22]. The end-result of these alterations can be the generation of radioresistant mutant tumor cells.

The role of autophagy in the regulation of radiosensitivity is related to p53 status

A. Dual functions of autophagy in radiation

Autophagy is a cellular response to stress in which the fusion of autophagosomes and lysosomes allows the degradation of subcellular organelles to generate energy and metabolic precursors. It may be either cytotoxic or cytoprotective, depending on the cellular context and the nature of the stressful challenge [4,7,23]. Apel et al. genetically inhibited a spectrum of autophagy-related genes in a variety of tumor cell lines and observed inconsistent effects; both radiosensitisation and radiotolerance were observed in different sensitive carcinoma cells [24].

B. Signalling pathways between p53 and autophagy

Autophagy is a multistep process, and p53 plays a dual role in the crosstalk signalling pathways that mediate the link between cellular damage and autophagy following radiation [25]. The exact role of p53 seems to depend on its localization within the cell. As shown in Figure 1, ATM signalling in the nucleus appears to play an important role in IR-induced autophagy, which suggests a multitude of therapeutic targets both in vitro and in vivo [26]. Following exposure to IR, nuclear p53 undergoes post-translational modifications by the ATM pathway, which ultimately leads to accumulation of p53 [27]. p53 transactivates several genes that may ultimately modulate autophagy, and may induce autophagy through transcriptional activation of the AMP-activated protein kinase (AMPK) pathway and inhibition of the mTOR pathway [28,29], which is the central regulatory mechanism for autophagy. p53 may also bind to the promoter region of multiple genes that code for pro-autophagic modulators (e.g., the β1 and β2 subunits of AMPK, DAKP-1, DRAM, PTEN, IGF-BP3, pro-apoptotic Bcl-2 proteins such as BAD, BAX, BNIP3 and PUMA, sestrin 2, and TSC2), and may subsequently induce autophagy [30,31]. Nuclear p53 may also inhibit autophagy via transcriptional mechanisms (i.e., p53-mediated transactivation of TIGAR), as well as transcription-independent mechanisms [32]. However, the exact mechanism through which cytosolic p53 suppresses autophagy is poorly understood, although it may involve the extra-nuclear pro-autophagic functions of small mitochondrial ARF (smARF) [33].

C. Function of autophagy in cells with functional p53

It is reported that physiological levels of p53 repress autophagy, but over-activation of p53 could induce autophagy and could be either cytotoxic or cytoprotective [5]. Apel et al. [24] found that the activation or re-expression of p53 was associated with induction of autophagy in tumor cells that survived radiation. Inhibition of autophagy enhanced the ability of p53 activation to induce tumor cell death. Inhibition of this autophagy may enhance the efficacy of therapeutic
strategies through enhancing tumor cell apoptosis and suppressing tumor cell recovery in vivo [34]. However, it is also reported that the IR-induced autophagy, which provides a pro-survival mechanism, was potently abrogated by p53 to regulate radiosensitivity in lung cancer cells [35]. These studies provide evidence that autophagy serves as a survival pathway in tumor cells treated with apoptosis activators and suggest a rationale for the use of autophagy inhibitors like chloroquine in combination with apoptosis-inducing therapies.

Autophagy seems to be a cytoprotective factor in the sensitising effect mediated by p53, but it has been shown that p53 could target damage-regulated autophagy modulator (DRAM) to induce macroautophagy and facilitate p53-mediated death, which demonstrates the cytotoxic role of autophagy [30,36]. Broz et al. [37] found that p53 activates autophagy through an extensive transcriptional network. Although is not involved in p53-dependent cell cycle arrest, autophagy contributes to both p53-driven apoptosis and p53-mediated transformation suppression in primary cells subjected to DNA damage.

This autophagic response to p53 may either help suppress tumor cell outgrowth or constitute a cellular defence response which causes resistance of radiation in the induction of cell death in cancer cell lines.

D. Function of autophagy when p53 is inhibited or deficient

In the tumor microenvironment, an enhanced level of baseline autophagy may improve the fitness of malignant cells. It seems plausible that autophagy linked to p53 inhibition is cytoprotective [38-41]. The latter study showed that depletion, inhibition or loss of p53 could lead to the induction of autophagy and increase cell survival in response to stress, such as IR-induced DNA damage. Aberrant autophagy is often apparent in p53-deficient human tumors and can be triggered by exogenous and endogenous stress, which may confer irinotecan resistance [42]. The mechanisms of autophagy-induced resistance are being actively explored. Some investigators believe that autophagy is a catabolic mechanism by which cells struggle to survive under nutrient-poor conditions, such as loss of growth factor signalling that governs the uptake of nutrients [39], which explains why cells lacking p53 tend to be resistant to ATP depletion and cell death induced by metabolic stress, and inhibition of autophagy can eliminate this resistance. Other studies show that the pharmacological stimulation of autophagy could increase the resistance of cells to apoptosis through removal of pro-apoptotic mitochondria [38,40,43], which may ultimately lead to chemo-

![Figure 1](https://example.com/figure1.png)

**Figure 1.** A model for signalling pathways in the molecular regulation of autophagy by p53 following irradiation. Black and blue symbols or lines depict pro- and anti-autophagic factors or interactions, respectively. mTOR: mammalian target of rapamycin, ROS: reactive oxygen species. IR: irradiation.
radiation resistance in tumor cells. The use of autophagy inhibitors in combination with radiation therapies can induce cell death in human cancers. In summary, these studies provide evidence that autophagy can be an adaptive mechanism that contributes to tumor cell survival and resistance to therapy-induced apoptosis in p53 deficient cells.

Conclusion

p53 is a tumor suppressor that can contribute to the enhancement of radiosensitivity and can play dual roles in the control of autophagy. Furthermore, autophagy plays dual roles in the survival mechanism as well as cell death following irradiation. Autophagy can lead to radioresistance via interference with apoptosis or by affecting cell survival following radiation through autophagy-induced cell death (Figure 2). In summary, autophagy can be either induced or inhibited by intact p53 and then ultimately enhance or inhibit the radiosensitivity of the whole cell in the presence of p53. However, autophagy is only induced (not inhibited) upon p53 loss, and ultimately leads to resistance to apoptosis and contributes to cell survival in conditions with IR stress.

In general, autophagy is clearly involved in the pathway that p53 uses to regulate radiosensitivity, and the function of autophagy is influenced by the p53 status. The outcome depends on a series of binary decisions that are probably determined by cellular signals, as well as by the intensity of these signals, but the exact mechanisms are still unclear. Further research is needed to explore how the p53 status affect the function of autophagy and how autophagy works in different p53 statuses during irradiation. Understanding these mechanisms may present new therapeutic targets for the treatment of cancer by irradiation.

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Figure 2. Autophagy in p53-mediated radiosensitisation. IR: irradiation.
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p53, autophagy and tumor radiosensitisation


