JBUON 2014; 19(2): 336-341
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

REVIEW ARTICLE

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

Rong Zheng, Qiwei Yao, Shasha Du, Chen Ren, Quanquan Sun, Zhixin Xu, Xiaoshan Lin, Yawei Yuan

Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, P. R. China

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 radioresistance 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-

Correspondence to: Yawei Yuan, MD. Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515, PR China. Tel/Fax: +86 20 61642136, E-mail: yuanyw66@aliyun.com
Received: 01/12/2013; Accepted: 20/12/2013

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 tumorigenetic 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 cytoprotective or cytotoxic, 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, DAPK-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 [3]. 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-

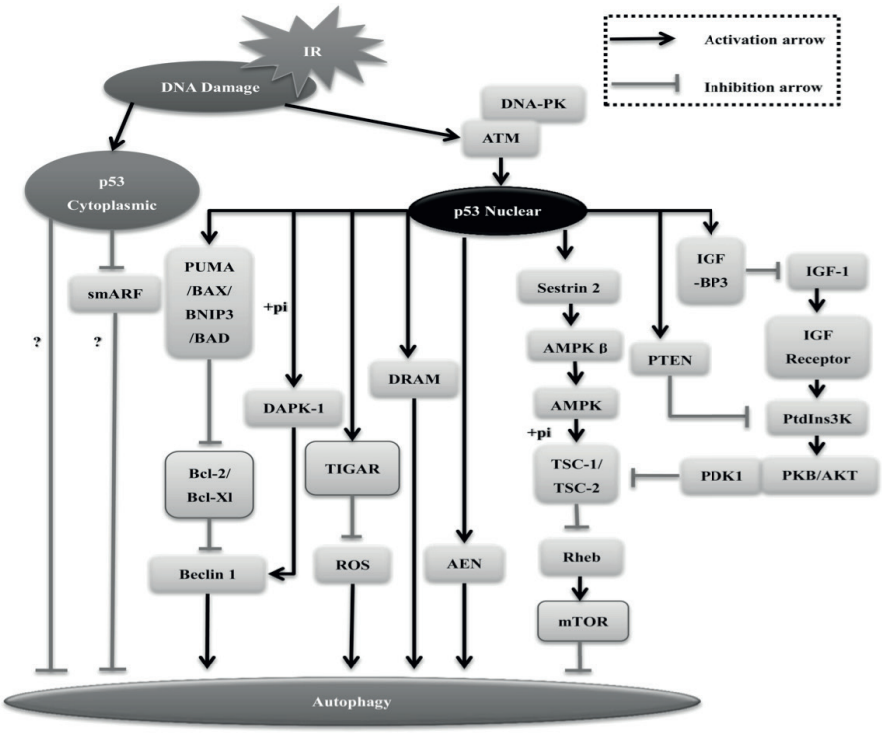

Figure 1. A model for signalling pathways in the molecular regulation of autophagy by p53 following irradiation. Black and blue symbols or lines depict pro- and anti-autophagic factors or interactions, respectively. mTOR: mammalian target of rapamycin, ROS: reactive oxygen species. IR: irradiation.

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.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No.81272508) and the Guangdong Education University-Industry Cooperation Projects (No.2011B090400019).

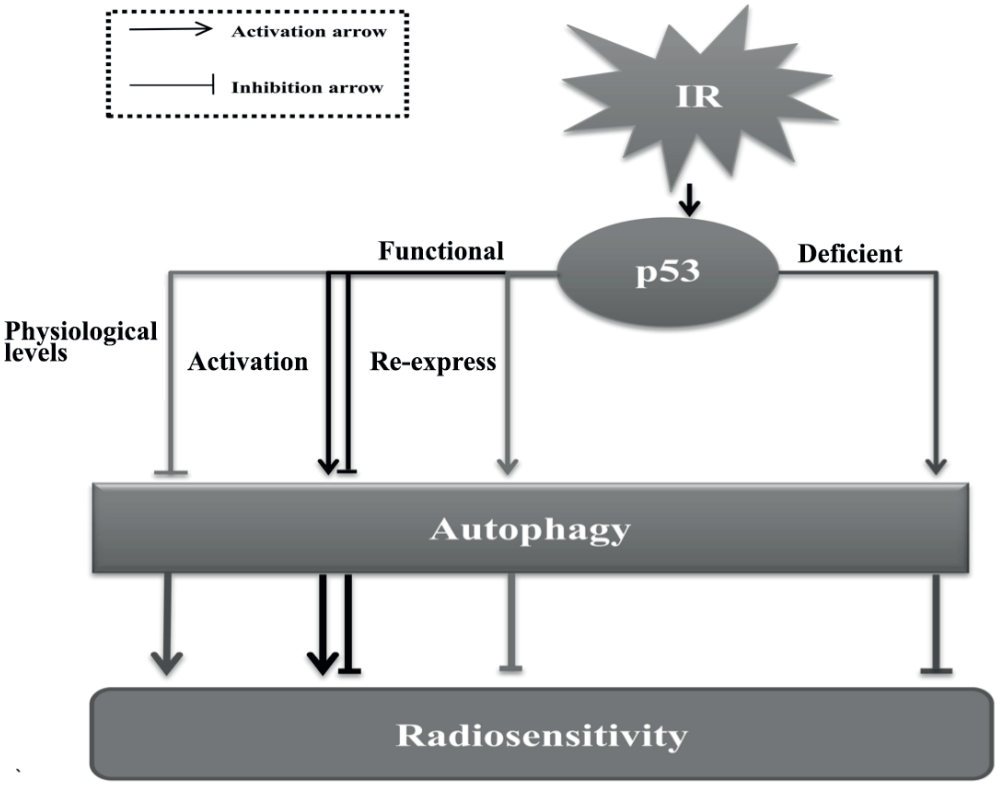

Figure 2. Autophagy in p53-mediated radiosensitisation. IR: irradiation.

References

1. Laptenko O, Prives C Transcriptional regulation by p53: one protein, many possibilities. Cell Death Differ 2006;13:951-961.
2. Chumakov PM Versatile functions of p53 protein in multicellular organisms. Biochemistry (Mosc) 2007;72:1399-1421.
3. Tasdemir E, Maiuri MC, Galluzzi L et al. Regulation of autophagy by cytoplasmic p53. Nat Cell Biol 2008;10:676-687.
4. Livesey KM, Tang D, Zeh HJ, Lotze MT. Autophagy inhibition in combination with cancer treatment. Curr Opin Investig Drugs 2009;10:1269-1279.
5. Wilson EN, Bristol ML, Di X et al. A switch between cytoprotective and cytotoxic autophagy in the radiosensitization of breast tumor cells by chloroquine and vitamin D. Horm Cancer 2011;2:272-285.
6. Klionsky DJ, Abdalla FC, Abeliovich H et al. Guidelines for the use and interpretation of assays for monitoring autophagy. Autophagy 2012;8:445-544.
7. Boya P, Gonzalez-Polo RA, Casares N et al. Inhibition of macroautophagy triggers apoptosis. Mol Cell Biol 2005;25:1025-1040.
8. Lambert LA, Qiao N, Hunt KK et al. Autophagy: a novel mechanism of synergistic cytotoxicity between doxorubicin and roscovitine in a sarcoma model. Cancer Res 2008;68:7966-7974.
9. Levine B, Abrams J. P53: the janus of autophagy? Nat Cell Biol 2008;10:637-639.
10. Rutkowski R, Hofmann K, Gartner A. Phylogeny and function of the invertebrate p53 superfamily. Cold Spring Harb Perspect Biol 2010;2:a1131.
11. Riley T, Sontag E, Chen P, Levine A. Transcriptional control of human p53-regulated genes. Nat Rev Mol Cell Biol 2008;9:402-412.
12. Zilfou JT, Lowe SW. Tumor suppressive functions of p53. Cold Spring Harb Perspect Biol 2009;1:a1883.
13. Brady CA, Attardi LD. P53 at a glance. J Cell Sci 2010;123:2527-2532.
14. Levine AJ, Tomasini R, McKeon FD, Mak TW, Melino G. The p53 family: guardians of maternal reproduction. Nat Rev Mol Cell Biol 2011;12:259-265.
15. Cuddihy AR, Bristow RG. The p53 protein family and radiation sensitivity: yes or no? Cancer Metastasis Rev 2004;23:237-257.
16. Lehmann BD, McCubrey JA, Terrian DM. Radiosensitization of prostate cancer by priming the wild-type p53-dependent cellular senescence pathway. Cancer Biol Ther 2007;6:1165-1170.
17. Petitjean A, Achatz MI, Borresen-Dale AL, Hainaut P, Olivier M. Tp53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. Oncogene 2007;26:2157-2165.
18. Zhao J, Lu Y, Shen HM. Targeting p53 as a therapeutic strategy in sensitizing trail-induced apoptosis in cancer cells. Cancer Lett 2012;314:8-23.
19. Burdak-Rothkamm S, Prise KM. New molecular targets in radiotherapy: DNA damage signalling and repair in targeted and non-targeted cells. Eur J Pharmacol 2009;625:151-155.
20. Lowe SW, Schmitt EM, Smith SW, Osborne BA, Jacks T. P53 is required for radiation-induced apoptosis in mouse thymocytes. Nature 1993;362:847-849.
21. Tamura T, Ishihara M, Lamphier MS et al. DNA damage-induced apoptosis and ice gene induction in mitogenically activated T lymphocytes require irf-1. Leukemia 1997;11 (Suppl 3):439-440.
22. Tamura T, Ishihara M, Lamphier MS et al. An irf-1-dependent pathway of DNA damage-induced apoptosis in mitogen-activated T lymphocytes. Nature 1995;376:596-599.
23. Bristol ML, Di X, Beckman MJ et al. Dual functions of autophagy in the response of breast tumor cells to radiation: cytoprotective autophagy with radiation alone and cytotoxic autophagy in radiosensitization by vitamin d 3. Autophagy 2012;8:739-753.
24. Apel A, Herr I, Schwarz H, Rodemann HP, Mayer A. Blocked autophagy sensitizes resistant carcinoma cells to radiation therapy. Cancer Res 2008;68:1485-1494.
25. Sui X, Jin L, Huang X, Geng S, He C, Hu X. P53 signaling and autophagy in cancer: a revolutionary strategy could be developed for cancer treatment. Autophagy 2011;7:565-571.
26. Chaachouay H, Ohneseit P, Toulany M, Kehlbach R, Multhoff G, Rodemann HP. Autophagy contributes to resistance of tumor cells to ionizing radiation. Radiother Oncol 2011;99:287-292.
27. Pan J, Song E, Cheng C, Lee MH, Yeung SC. Farnesyltransferase inhibitors-induced autophagy: alternative mechanisms? Autophagy 2009;5:129-131.
28. Alexander A, Cai SL, Kim J et al. ATM signals to TSC2 in the cytoplasm to regulate mTORc1 in response to ROS. Proc Natl Acad Sci U S A 2010;107:4153-4158.
29. Feng Z, Zhang H, Levine AJ, Jin S. The coordinate regulation of the p53 and mTOR pathways in cells. Proc Natl Acad Sci U S A 2005;102:8204-8209.
30. Crighton D, Wilkinson S, O'Prey J et al. Dram, a p53-induced modulator of autophagy, is critical for apoptosis. Cell 2006;126:121-134.
31. Feng Z. P53 regulation of the igf-1/akt/mtor pathways and the endosomal compartment. Cold Spring Harb Perspect Biol 2010;2:a1057.
32. Galluzzi L, Morselli E, Kepp O, Maiuri MC, Kroemer G. Defective autophagy control by the p53 rheostat in cancer. Cell Cycle 2010;9:250-255.
33. Pimkina J, Humbey O, Zilfou JT, Jarnik M, Murphy ME. Arf induces autophagy by virtue of interaction with bcl-xl. J Biol Chem 2009;284:2803-2810.
34. Amaravadi RK, Yu D, Lum JJ et al. Autophagy inhibition enhances therapy-induced apoptosis in a myc-induced model of lymphoma. J Clin Invest 2007;117:326-336.
35. Guanghui C, Dejuan K, Xue H et al. The tumor suppressor p53 contributes to radiosensitivity of lung cancer cells by regulating autophagy and apoptosis. Cancer Biother Radiopharm 2012;28:153-159.
36. Maiuri MC, Galluzzi L, Morselli E, Kepp O, Malik SA, Kroemer G. Autophagy regulation by p53. Curr Opin

Cell Biol 2010;22:181-185.

37. Broz DK, Attardi LD. Trp53 activates a global autophagy program to promote tumor suppression. Autophagy 2013;9:1440-1442.
38. Rubinsztein DC, Gestwicki JE, Murphy LO, Klionsky DJ. Potential therapeutic applications of autophagy. Nat Rev Drug Discov 2007;6:304-312.
39. Lum JJ, DeBerardinis RJ, Thompson CB. Autophagy in metazoans: cell survival in the land of plenty. Nat Rev Mol Cell Biol 2005;6:439-448.
40. Brahimi-Horn MC, Chiche J, Pouyssegur J. Hypoxia signalling controls metabolic demand. Curr Opin Cell Biol 2007;19:223-229.
41. Feng Z, Hu W, de Stanchina E et al. The regulation of ampk beta1, tsc2, and pten expression by p53: stress, cell and tissue specificity, and the role of these gene products in modulating the igf-1-akt-mtor pathways. Cancer Res 2007;67:3043-3053.
42. Paillas S, Causse A, Marzi L et al. Mapk14/p38alpha confers irinotecan resistance to tp53-defective cells by inducing survival autophagy. Autophagy 2012;8:1098-1112.
43. Hanahan D, Weinberg RA The hallmarks of cancer. Cell 2000;100:57-70.