Relationship between p53 status and the bioeffect of ionizing radiation (Review)

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Abstract. Radiotherapy is widely used in the clinical treatment of cancer patients and it may be used alone or in combination with surgery or chemotherapy to inhibit tumor development. However, radiotherapy may at times not kill all cancer cells completely, as certain cells may develop radioresistance that counteracts the effects of radiation. The emergence of radioresistance is associated with the genetic background and epigenetic regulation of cells. p53 is an important tumor suppressor gene that is expressed at low levels in cells. However, when cells are subjected to stress-induced stimulation, the expression level of p53 increases, thereby preventing genomic disruption. This mechanism has important roles in maintaining cell stability and inhibiting carcinogenesis. However, mutation and deletion destroy the anticancer function of p53 and may induce carcinogenesis. In tumor radiotherapy, the status of p53 expression in cancer cells has a close relationship with radiotherapeutic efficacy. Therefore, understanding how p53 expression affects the cellular response to radiation is of great significance for solving the problem of radioresistance and improving radiotherapeutic outcomes. For the present review, the literature was searched for studies published between 1979 and 2021 using the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) with the following key words: Wild-type p53, mutant-type p53, long non-coding RNA, microRNA, gene mutation, radioresistance and radiosensitivity. From the relevant studies retrieved, the association between different p53 mutants and cellular radiosensitivity, as well as the molecular mechanisms of p53 affecting the radiosensitivity of cells, were summarized. The aim of the present study was to provide useful information for understanding and resolving radioresistance, to help clinical researchers develop more accurate treatment strategies and to improve radiotherapeutic outcomes for cancer patients with p53 mutations.

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Contents

1. Introduction

In 1979, multiple laboratories simultaneously discovered a highly expressed ~53 kDa protein in cancer cells and named this protein the p53 protein. Initially, the p53 gene was considered an oncogene (1,2), but it was later demonstrated to be a tumor suppressor gene by several groups (3,4).

The role of p53 as a tumor suppressor gene is mainly realized through the transcriptional regulatory mechanism of apoptosis and senescence. Under normal conditions, wild-type p53 ($p53^{wt}$) in cells is maintained at a low level due to its interaction with the E3 ubiquitin ligase MDM2. However, once DNA is damaged by radiation, the ataxia telangiectasia mutated (ATM) gene may be activated and ATM directly or indirectly phosphorylates p53 (5-8). In this circumstance, the p53 protein is subjected to numerous posttranslational modifications, such as phosphorylation, acetylation, ubiquitination, SUMOylation, neddylation and methylation. These modifications inhibit p53 from binding to MDM2, making p53 a stable transcription factor that binds to specific DNA sequences, transactivates multiple target genes [such as p21, Bax and

p53-upregulated modulator of apoptosis (PUMA)], repairs DNA through homologous recombination and maintains the integrity of the genome (9-11). In addition, p53 also inhibits the inflammatory response (12), repairs broken DNA double strands (13) and maintains metabolic homeostasis (14).

p53 function depends on its structure. The p53 protein is composed of three major domains. The N-terminal domain is related to the transactivation capacity of p53, and it is a disordered and inherently unfolded region consisting of a trans-activated domain and a proline-rich region. The central domain is the key component of p53, controlling the sequence-specific DNA-binding activity of p53 and promoting the DNA-p53 protein interaction. This region is also the most susceptible to mutations, which are known to occur in >90% of human cancers. The C-terminal domain is also a disordered structural domain that controls the posttranslational modification activity of p53 (15).

2. p53 and malignant disease

The p53 protein status is correlated with the p53 gene status. Cancer cells may have three different p53 gene states: $p53^{wt}$, mutant-type p53 ($p53^{mt}$) and p53 deletion (null-type p53 or $p53^{null}$) (16). p53 mutation is common, occurring in ~50% of human cancers (17,18). The most common and well-characterized p53 mutations are missense mutations (75%). Other alterations include frameshift insertion and deletion (9%), nonsense mutation (7%), silent mutation (5%) and rare changes (19,20). $p53^{mt}$ gene encodes $p53^{mt}$ protein. $P53^{mt}$ prevents apoptosis and promotes the proliferation and metastasis of cancer cells (21). $p53^{mt}$ deactivates sequence-specific DNA-binding activity, thereby causing the loss of normal p53 tumor suppressor function and the inability of the $p53^{wt}$ heterodimer to form a tetramer complex, thereby damaging dimer function (22). In addition, $p53^{mt}$ causes another 'gain of function' (GOF) that not only promotes tumor progression, migration and metabolism but also increases tumor cell resistance to radiotherapy (23,24). This outcome is ascribed to the upregulation of multiple genes by $p53^{mt}$, including phosphatase and tensin homolog, c-myc, NF-κB, $p16^{INK4A}$, p63 and p73 (25-30).

Studies have also indicated that certain tumors have $p53^{null}$ status (31). The absence of p53 leads to failure of G1-S checkpoint blockade, making tumors more resistant to radiotherapy (32).

In general, cancer cells carrying $p53^{wt}$ are more sensitive to radiation than cells carrying $p53^{mt}$ or $p53^{null}$ (6,33,34). An in-depth understanding of the relationship between p53 and radiosensitivity will help enhance the efficacy of radiotherapy and improve the prognosis of patients.

3. p53 states and radiosensitivity

Radiotherapy is one of the most common cancer treatments and it may be used in combination with chemotherapy or surgery to treat various malignant tumor types (35). Radiation kills tumor cells by causing DNA damage. Once DNA damage is identified, cellular sensor proteins, such as ATM, deliver damage signals to effectors and phosphorylate certain targets, such as p53 (7).

Radioresistance is a key factor limiting radiotherapeutic efficacy (36). Several cellular signaling pathways and factors are involved in radioresistance, such as the p53-p21 and p53-Bcl-2 pathways (37,38). Among these pathways, the p53 pathway is considered the most crucial regulator (39,40).

$p53^{mt}$ and radioresistance. The mechanism by which $p53^{mt}$ causes radioresistance was first proposed by Brachman *et al* (41) when they irradiated head and neck squamous cell carcinoma and determined that $p53^{mt}$ cells were more resistant to radiation than $p53^{wt}$ cells. This result was also verified by Hinata *et al* (42), who used bladder cancer cell lines to demonstrate that $p53^{wt}$-mediated cell cycle arrest in G1 phase increases radiosensitivity. Similarly, Williams *et al* (43) reported that the radioresistance of $p53^{mt}$ Li-Fraumeni syndrome fibroblast cells is associated with reduced G1 phase-blocking ability.

However, certain studies have suggested that $P53^{mt}$ may increase radiosensitivity (44). Biard *et al* (45) established four types of rat lung epithelial cells to test cell survival after radiation exposure and showed that the survival rate of $p53^{mt}$ cells is significantly lower than that of other cell lines. Kawashima *et al* (46) observed a similar phenomenon and speculated that this outcome is attributed to $P53^{mt}$ being unable to induce cell cycle arrest, indicating that $p53^{mt}$ cells are more susceptible to DNA damage than $p53^{wt}$ cells.

$p53^{wt}$ and radiosensitivity. Numerous cytological experiments have indicated that $p53^{wt}$ cells are more radiosensitive than $p53^{mt}$ cells (42,47). By assessing the survival rate of human ovarian cancer cell lines irradiated by 12 Gy ^{60}Co rays, Concin *et al* (48) demonstrated that $p53^{wt}$ cells were more radiosensitive than $p53^{mt}$ cells with cell survival rates of 0.4 and 0, respectively. In agreement with the above study, Cheng *et al* (49) determined that radiation-induced apoptosis was significantly higher in $p53^{wt}$ than in $p53^{mt}$ lung cancer cells. In addition, Pirollo *et al* (50) indicated that the introduction of $p53^{wt}$ increased the radiosensitivity of $p53^{null}$ cells. *In vivo* experiments have also confirmed this result. Gallardo *et al* (51) introduced $p53^{wt}$ and $p53^{mt}$ into $p53^{null}$ mice and then subjected the mice to irradiation, and they reported that tumor growth was slower in $p53^{wt}$ mice than in $p53^{mt}$ mice.

$p53^{null}$ and radiosensitivity. Certain studies have indicated that $p53^{null}$ cells are more radiosensitive than $p53^{wt}$ cells. Servomaa *et al* (52) compared the survival of head and neck tumor cells with different p53 states and determined that cells with a loss of p53 were more sensitive to γ-irradiation, suggesting that a p53-independent apoptosis pathway may be triggered in these cells during radiotherapy.

However, opinions on this mechanism are contradictory. $p53^{null}$-associated radioresistance is also observed in tumor cells. Lowe *et al* (53) injected three types of tumor cells with different p53 variants into rats and irradiated tumor-burdened rats, and they indicated that the tumors in $p53^{null}$ rats were larger and that the apoptotic cell number was significantly lower in $p53^{wt}$ rats. Merritt *et al* (54) and Matsui *et al* (55) also determined that p53 deletion prompts cell radioresistance. It is speculated that this radioresistance is generally considered to involve the inhibition of p53-dependent apoptosis.

Other hypotheses and clinical trials. Certain studies have suggested that $p53^{mt}$ is not associated with radioresistance (56,57). Tchelebi (34) suggested that the differences are correlated with the genetic background of the cell lines and the type of p53 mutation. Certain clinical investigations have focused on p53 mutants and radiation efficacy. Tada *et al* (58) suggested that $p53^{mt}$ may prolong the survival rate of cancer patients receiving radiotherapy. Koch *et al* (59) determined that after radiotherapy, the overall survival of patients carrying $p53^{mt}$ cells was not affected, but they exhibited a risk of regional recurrence.

4. p53 mutant sites and radiosensitivity

Although p53 mutations are observed in the whole gene, there are six mutation hotspots distributed in the DNA-binding domain. These six hotspots are located in codons 175, 245, 248, 249, 273 and 282 (60). Different p53 mutation types may lead to distinctly different cellular functions and effects on radiotherapeutic efficacy even when the mutations are in the same domain. Menendez *et al* (61) indicated that different p53 mutations produce different cellular phenotypes after transfection, leading to cell survival or apoptosis. After cells are exposed to radiation, the expression levels of target genes, such as p21, MDM2, Bax and mutS homolog 2, which correlate with the cell cycle and cell apoptosis, induced by different $p53^{mt}$ mutants are different; therefore, the biological activities of these transfectants are completely different. Okaichi *et al* (62) transferred four types of mutant p53 genes distributed separately at codons 123 (Thr→Ala), 143 (Val→Ala), 175 (Arg→His) and 273 (Arg→His) into human osteosarcoma Saos-2 cells ($p53^{null}$) and irradiated the cells with X-rays. The results indicated that the radiosensitivity of cells expressing mutant p53 proteins (123Thr→Ala) is higher than that of cells expressing proteins with other mutation types, while the expression of p53 proteins mutated at amino acids 143, 175 and 273 does not affect cellular radiosensitivity. In addition, the same group performed a similar experiment with 12 different types of p53 mutations and determined that mutations in hotspots may cause loss of p53 binding ability to DNA and, thus, loss of transcription function. However, mutations in loop domains do not change the conformation of the p53 protein and its normal functions are retained. They also demonstrated that mutations occurring at the N-terminus of the p53 protein affect downstream $p21^{WAF1}$ expression and radiosensitivity (63,64).

5. Mutant p53 and its target genes

$p53^{mt}$ alters the normal intracellular pathway and functions through interactions with various factors and enhances the radioresistance of cancer cells by inhibiting apoptosis or promoting repair. Elucidation of the relationship between these genes and $p53^{mt}$ may enhance the understanding of tumorigenesis and discover additional methods to treat tumors.

Radiation disrupts the DNA structure and activates certain protein kinase pathways, which block cell cycle progression and initiate DNA repair processes. p53 is the major downstream effector in DNA damage-activated kinase pathways and the main role of p53 is to promote cellular apoptosis induced by radiation. Activated p53 triggers G1 phase arrest by transactivating $p21^{Waf1}$, allowing cells additional time for DNA repair (65). In addition, p53 upregulates the proapoptotic molecules PUMA and NADPH oxidase activator 1, and activates the Bcl family member Bax to promote the apoptosis of nonrepairable cells and the recovery of tissue homeostasis (66).

In the case of p53 mutations, $p53^{mt}$-mediated transactivation, cell cycle arrest and apoptosis responses may be abrogated. Furthermore, $p53^{mt}$ accelerates the rate of tumor proliferation and induces radio/drug resistance (67-70). This mechanism of resistance may be attributed to the regulation of $p53^{mt}$. MYC is a major mediator of mutant p53 GOF in head and neck squamous cell carcinoma (HNSCC), leading to radioresistance and a high local recurrence rate of HNSCC. Recruitment of $p53^{mt}$ to the MYC promoter increases MYC stability and continuous expression (71). Ganci *et al* (72) demonstrated that inhibition of the $p53^{mt}$/MYC-dependent signature alters the radiosensitivity of HNSCC cells. Cellular inhibitor of PP2A (CIP2A) activates various oncogenic proteins and promotes the proliferation of various cancer cells. p53 inhibits the expression of CIP2A. Kim *et al* (73) indicated that CIP2A modulates the radioresistance of cancer cells by attenuating cell senescence in HNSCC through disruption caused by $p53^{mt}$. They irradiated HNSCC cell lines carrying different p53 mutants to determine their effects on cell survival and CIP2A expression levels, and they observed that CIP2A is highly expressed in radioresistant HNSCC cells carrying disruptive $p53^{mt}$. Inhibition of CIP2A enhances the radiosensitivity of these $p53^{mt}$-disrupted cells. Nitric oxide (NO) synthase 2 (NOS2) produces high levels of NO, acting as either a cytotoxic or a cytoprotective agent. Matsumoto *et al* (74) indicated that after irradiation of human glioblastoma cell lines carrying $p53^{mt}$, NO is upregulated by $p53^{mt}$. In addition, upregulated NO expression led to the increased accumulation of p53 in $p53^{wt}$-transfected cells through the intercellular signaling/transduction pathway. These results suggested that the reduced radiosensitivity may be attributed to the increased cell survival rate caused by the presence of p53-triggered cancer cell repair during NO-induced G1-phase arrest.

6. p53-microRNA interaction in radiotherapy

miRNAs constitute a class of small noncoding RNA molecules involved in the regulation of multiple cell behaviors, such as gene expression, cell division, differentiation, apoptosis, metabolism and cancer development (75-77). The communication of miRNAs with various signaling factors provides an ingenious entry point for improving the efficacy of radiotherapy. Further understanding the role of miRNAs in tumor radiosensitivity, particularly their relationship with p53, is helpful for forming novel ideas to solve the ubiquitous radiation resistance problem in cancer treatment and for providing more effective therapeutic strategies for patients who are suitable for radiotherapy.

p53 and miRNA interactions have key roles in modulating the cellular response to radiation. For instance, p53 induces the expression of miR-34 in cells with DNA damage and overexpression of miR-34 enhances radiosensitivity (78,79). miRNAs bind to the 3'UTR of p53 mRNA and suppress p53 translation, negatively regulating p53-related genes,

Table I. Summary of the history of p53 research and the association between p53 expression and radiation response.

Item	Details and (Refs.)
p53 discovery	Misidentification as an oncogene (1,2)
	Role as a tumor suppressor gene (3,4)
	p53 structure (15,18,19,21,63)
p53 function	Regulators of p53 (5-8)
	Target genes of p53 (9-11,21,24-29,60,64,65,70-72)
	p53 and the inflammatory response (12), DNA double-strand breaks (13) and metabolic homeostasis (14)
$p53^{mt}$ and radiation	$p53^{mt}$ increases radioresistance (22,23,40-42)
	$p53^{mt}$ increases radiosensitivity (43-45,61)
$p53^{wt}$ and radiation	$p53^{wt}$ increases radiosensitivity (32,33,41,46-50)
$p53^{null}$ and radiation	$p53^{null}$ increases radioresistance (31,52-54)
	$p53^{null}$ increases radiosensitivity (44,51)
p53-associated pathways in radiation	p53-p21 pathway (36)
	p53-Bcl-2-caspase pathway (37)
p53-miRNA interaction in radiotherapy	p53 induces the expression of miR-34 and enhances radiosensitivity (76,77)
	miR-375 regulates p53 expression and reduces radiosensitivity (78)
	miR-300 reduces radiosensitivity by inducing p53 (79)
	miR-375 inhibits p53 degradation and increases radiosensitivity (82)
	Let-7 decreases the radiosensitivity of $p53^{wt}$ cells (86)
p53-lncRNA interactions in radiotherapy	lncRNA ROR increases radioresistance by inhibiting p53 (90)
	lncRNA CCAT2 promotes radioresistance by inhibiting p53 (91)
	p53 modulates radiation-induced cellular apoptosis by regulating lncRNA Trp53cor1 and Tug1 (92)

$p53^{mt}$, mutant p53; $p53^{wt}$, wild-type p53; $p53^{null}$, p53 deletion; lncRNA, long non-coding RNA; miR/miRNA, microRNA; CCAT2, colon cancer-associated transcript 2; Trp53cor1, tumor protein p53 pathway corepressor 1; Tug1, taurine-upregulated 1; ROR, regulator of reprogramming.

such as p21 and MDM2, and inducing cell cycle arrest and radioresistance. Liu *et al* (80) reported that the presence of miR-375, which is associated with the recurrence of gastric cancer, reduces the radiosensitivity of tumor cells by regulating the expression of p53. He *et al* (81) observed that in human lung cancer cells, radiation upregulates the expression level of miR-300 and reduces radiosensitivity by inducing p53/apaf1-related G2-phase cell cycle arrest and apoptosis. By contrast, miRNAs may stimulate the expression of p53 and increase tumor radiosensitivity (82,83). Song *et al* (84) indicated that in patients with cervical cancer, miR-375 is overexpressed after radiotherapy. miR-375 inhibits the degradation of p53 and leads to cell cycle arrest in G1-phase, thereby increasing radiosensitivity.

Radiation-induced p53 overexpression also inhibits the level of miRNAs and negatively affects radiation efficacy (85). miRNA let-7 family members function differently in different cells after irradiation (86). One of the targets of let-7 is KRAS, which induces radioresistance (87). In certain cancer cells, miRNAs such as let-7a and let-7b (let-7 family members) are inhibited after irradiation and their inhibition is correlated with $p53^{wt}$ expression. Saleh *et al* (88) irradiated $p53^{null}$ and $p53^{wt}$ mouse colon cancer cell lines and observed that let-7 decreases the radiosensitivity of $p53^{wt}$ cells but not $p53^{null}$ cells. In addition, experiments have revealed that functional p53 directly interacts with Drosha, a miRNA-processing enzyme, and inhibits the expression of let-7a and let-7b through transcriptional regulation in cells after irradiation.

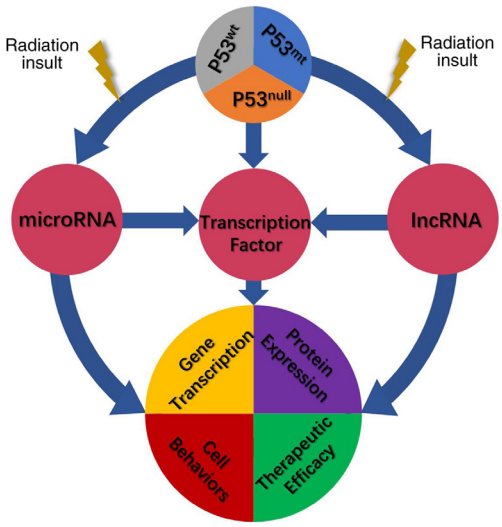

Figure 1. Schematic of the molecular mechanisms of p53 regulating radiation response. $p53^{mt}$, mutant p53; $p53^{wt}$, wild-type p53; $p53^{null}$, p53 deletion; lncRNA, long non-coding RNA.

7. p53-lncRNA interaction in radiotherapy

LncRNAs constitute a class of noncoding RNAs with a length of >200 bp that have regulatory roles in chromatin modification, transcription and posttranscriptional gene regulation. An increasing number of lncRNAs have been indicated to have important roles in the development and treatment of tumors. This increase in lncRNAs may be used as a cancer marker to detect specific diseases and improve the rate of early diagnosis of tumors (89).

LncRNAs are involved in various mechanisms in cells to regulate radiosensitivity, such as DNA damage repair, cell cycle arrest and apoptosis. LncRNA and p53 interactions may regulate cellular radiosensitivity. Zhang *et al* (90) and Wang *et al* (91) indicated that lncRNAs participate in the nonhomologous end joining pathway after radiation-induced DNA damage, which accelerates damage repair and reduces radiation sensitivity. Yang *et al* (92) reported that the lncRNA regulator of reprogramming (ROR) increases radioresistance in colorectal cancer cells by inhibiting the p53/miR-145 axis, which is known to be an important pathway for tumor inhibition; they determined that the levels of p53 protein and miR-145, as well as the degree of radiosensitivity of colorectal cells, are increased after X-ray irradiation compared to lncRNA ROR-deficient cells. In esophageal cancer, Wang *et al* (93) observed that lncRNA colon cancer-associated transcript 2 promotes radioresistance by inhibiting the p53 proapoptotic signaling pathway. Beer *et al* (94) indicated that p53 has a central role in the modulation of radiation-induced cellular apoptosis by regulating the expression of several lncRNAs, including tumor protein p53 pathway corepressor 1 (Trp53cor1) and taurine-upregulated (Tug1). They treated human peripheral blood mononuclear cells with high-dose γ radiation and determined that Trp53cor1, as a downstream target of p53, was significantly upregulated after cell irradiation and that the expression of caspase-3 was increased; they also observed that the expression level of lncRNA Tug1 in cells was increased after IR. As a downstream target gene of p53, lncRNA Tug1 increases cell radiosensitivity by promoting cell cycle arrest and apoptosis through the regulation of various miRNAs, including miR-222-3p, miR-221-3p, miR-132 and miR-29a.

8. Conclusions and prospects

Over the past 40 years, with the enhanced understanding of the structure, role and mutations of the p53 tumor suppressor gene, it has become increasingly evident that p53 has an important role in tumor inhibition and treatment, and its importance underlies the carcinogenicity of its deletion or mutation. Deletion or mutation of p53 in tumor cells leads to the loss of normal p53 antitumor function and promotes the occurrence and metastasis of cancer. Summary of the research results of the past 30 years supports that the antiapoptotic properties of $p53^{mt}$ enhance tumor resistance to radiotherapy, which inhibits the efficacy of cancer treatment. The p53 status, to a certain degree, may be considered as a useful biomarker for radiosensitivity, and it is advocated to elevate the irradiation dose, prolong the irradiation time, or select a more suitable treatment strategy, i.e. chemotherapy, targeted therapy and immunotherapy for those patients with $p53^{mt}$.

Identifying the mechanism of p53 in promoting radioresistance may help doctors develop accurate treatment strategies for patients and improve the radiotherapeutic outcomes and prognosis for patients. As part of the present study, a summary of the history of p53 research and the association between p53 expression and radiation response (Table I) and a schematic of the mechanisms related to p53 and radioresistance (Fig. 1) are provided. Specifically, the role of non-coding RNAs in p53-induced radioresistance was summarized, which is rarely mentioned in previous reports and similar reviews. The present review is an extension and supplement to the traditional theories. It is esteemed that these mechanisms serve as a basis to guide further analysis, laboratory studies and clinical practice for cancer patients receiving radiotherapy.

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Authors' contributions

DY and SL contributed to the conception and design of the article. XK drafted the manuscript. ZW drafted the figure and table and revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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