Mutant p53 in head and neck squamous cell carcinoma: Molecular mechanism of gain-of-function and targeting therapy (Review)

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Abstract. Head and neck squamous cell carcinoma (HNSCC) is one of the most widespread malignancies worldwide. p53, as a transcription factor, can play its role in tumor suppression by activating the expression of numerous target genes. However, p53 is one of the most commonly mutated genes, which frequently harbors missense mutations. These missense mutations are nucleotide substitutions that result in the substitution of an amino acid in the DNA binding domain. Most p53 mutations in HNSCC are missense mutations and the mutation rate of p53 reaches 65-85%. p53 mutation not only inhibits the tumor suppressive function of p53 but also provides novel functions to facilitate tumor recurrence, called gain-of-function (GOF). The present study focused on the prevalence and clinical relevance of p53 mutations in HNSCC, and further described how mutant p53 accumulates. Moreover, mutant p53 in HNSCC can interact with proteins, RNA, and exosomes to exert effects on proliferation, migration, invasion, immunosuppression, and metabolism. Finally, several treatment strategies have been proposed to abolish the tumor-promoting function of mutant p53; these strategies include reactivation of mutant p53 into wild-type p53, induction of mutant p53 degradation, enhancement of the synthetic lethality of mutant p53, and treatment with immunotherapy. Due to the high frequency of p53 mutations in HNSCC, a further understanding of the mechanism of mutant p53 may provide potential applications for targeted therapy in patients with HNSCC.

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Abbreviations: HNSCC, head and neck squamous cell carcinoma; OSCC, oral squamous cell carcinoma; NSCLC, non-small cell lung carcinoma; OPL, oral precancerous lesions; HSPs, heat shock proteins; AMPK, adenosine monophosphate-activated protein kinase; PUMA, p21/p53 upregulated modulator of apoptosis; Bax, Bcl-2-associated X; YAP, Yes-associated protein; FGFR3, fibroblast growth factor receptor 3; NF-YA, nuclear transcription factor Y subunit α; EV, extracellular vesicle; PD-1, programmed cell death protein-1; NAMPT, nicotinamide phosphoribosyl transfer; CTD, C-terminal domain; DBD, DNA-binding domain; GOF, gain-of-function; lncRNA, long non-coding RNA; miRNA, microRNA; ncRNA, non-coding RNA; IL17, interleukin 17

Key words: head and neck squamous cell carcinoma, mutant p53, gain-of-function, therapeutic target, non-coding RNAs, tumor microenvironment

Contents

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is one of the most widespread malignancies worldwide (1-3). Statistics indicate that >54,010 oral and pharyngeal cancer cases are diagnosed, and >10,850 individuals succumb to the disease annually (4). Numerous risk factors lead to the incidence of HNSCC, including smoking, alcohol consumption, human papillomavirus infection, and genetic disposition (5). Despite the advanced treatment methods, HNSCC has a high recurrence rate (6). Therefore, studying the pathogenic mechanism in HNSCC is of great importance in providing individualized treatment for patients.

p53, as a transcription factor, can play its role in tumor suppression by activating the expression of numerous target genes (7). However, p53 is one of the most commonly mutated genes in human tumors, with mutations detected in 65-85% of HNSCC (8,9). Most p53 mutations in HNSCC are missense mutations, which lead to the substitution of only one amino

acid (10). The missense mutations not only suppress the tumor suppressive role of wild-type p53 but also provide novel functions to promote tumor recurrence and chemoresistance, called gain-of-function (GOF) (11). A previous study revealed that the p53 protein, the translated product of the TP53 gene, is frequently mutated in HNSCC (12); therefore, studying the pathogenic mechanism of mutant p53 in HNSCC is crucial to provide more individualized treatment for patients.

A study has revealed that patients with HNSCC carrying p53 mutations have a high risk of malignancy and a poor prognosis (10). p53 mutation can affect a variety of cellular processes, including drug resistance and carcinogenesis (6). The present study focused on the prevalence and clinical relevance of p53 mutation in HNSCC and further described how mutant p53 accumulates. In addition, the molecular mechanisms by which GOF of mutant p53 can affect the proliferation, migration invasion, immunosuppression and metabolic effects of HNSCC were investigated. Finally, therapeutic strategies to abolish the tumor-promoting effects of mutant p53 were elucidated to provide a basis for further understanding the mechanism of mutant p53 to develop targeted therapies.

2. Literature review methods

A systematic literature search was conducted through the electronic search engine PubMed to find eligible studies published before March 9, 2023. The key words for the search were 'Head and neck squamous carcinoma', 'mutant p53' and 'gain-of-function'. In addition, the references in the retrieved articles were also manually reviewed to identify potentially relevant studies.

3. p53 mutations in HNSCC

Prevalence of p53 mutations. p53, as a transcription factor, can play its role in tumor suppression by activating the expression of numerous target genes (7). The main functional domains of full-length p53 include two transactivation domains (TAD) at the N-terminus, a proline-rich domain (PRD), a central DNA binding domain (DBD), an oligomerization domain (OD), and a regulatory C-terminal domain (CTD) (7) (Fig. 1A). A missense mutation refers to a substitution of an amino acid in the DBD (10). Most p53 mutations in HNSCC are missense mutations, and the mutation rate of p53 is 65-85% (8,9,13). Furthermore, the mutation rate of p53 was revealed to be as high as 30% in oral precancerous lesions (OPL) (14). In HNSCC, p53 mutations frequently occur at amino acids R248, G245, R273, R175, H179, and R282 among its DBD (10) (Fig. 1A). In addition, a new mutation in exon 7 of the p53 gene has been identified in the tumors of patients with oral squamous cell carcinoma (OSCC) (15). A missense mutation resulting in a codon alteration from 'AGT' to 'ACT' was identified at position 719 of TP53 (15).

Functional effects of p53 mutations in HNSCC. A previous *in vitro* cell function study revealed that the p53 R248Q mutant increased the motility and invasive potential in OSCC cells (16). The p53 R248W mutant was also revealed to inhibit cell proliferation and invasive activity (17). In mouse research models, p53 mutations resulted in GOF properties and experimental mice injected with cells harboring p53 mutations (C176F and E336X) exhibited accelerated growth of oral tongue cancer, a higher incidence of cervical lymph node metastasis and shorter survival time (18). In another study in a mouse model of oral cancer with specific p53 mutations, OSCC model mice expressing the p53 R172H GOF mutation exhibited a higher metastasis rate than wild-type p53 mice (19).

Clinical effect of p53 gene mutations. Clinically, TP53 mutations are associated primarily with a low survival rate, drug resistance, and extranodal extension in patients, which makes p53 mutation status a potential molecular marker for predicting the clinical response of these patients (12,20,21). It was revealed that the mutation rate of p53 in OPL was as high as 30%, indicating that these mutations occur at an early stage of oral tumor development and may influence the development and progression of OPL (14). A previous study reported that in HNSCC, tumors with high-risk p53 mutations are more likely to develop combined resistance to cisplatin and fluorouracil chemotherapy than tumors with low-risk mutations or wild-type TP53 (22). Furthermore, the anticancer effect of cisplatin differs among HNSCC cell lines with different p53 mutation statuses. Further investigation on the association between the mutational statuses of p53 and cisplatin resistance in HNSCC cell lines are required to develop more suitable therapeutic approaches. Notably, serum p53 antibody levels in HNSCC patients have important clinical significance. Mutations in the TP53 gene could lead to the accumulation of mutant p53 protein in cancer cells, which induces the production of serum anti-p53 antibodies (Ap53Ab) in patients with OSCC (23). The results of related assays revealed that the presence of Ap53Ab may reflect p53 mutational status and the aggressive phenotype, which serves as a valid predictive marker for OSCC in clinical practice (23). A previous relevant study reported that the expression of fibroblast growth factor receptor 3 (FGFR3) is highly correlated with the expression of mutant p53 in oropharyngeal squamous cell carcinoma (24). Kaplan Meier analysis of relevant samples showed that patients carrying high expression levels of FGFR3 and mutant p53 had worse disease-free survival (24).

4. Mutant p53 protein accumulation and regulation

Missense mutations not only attenuate the tumor suppressive role of wild-type p53 but also provide novel functions to promote tumor recurrence and chemoresistance, called GOF (11). However, only when the mutant p53 protein remains stable and accumulates to a very high level in tumor tissue can it perform its GOF property (25). At present, the mechanism of mutant p53 aggregation in HNSCC is not completely clear. Previous research has reported that the level of mutant p53 can be regulated by posttranslational modification (ubiquitination, phosphorylation) and molecular chaperone (Fig. 1B).

Mutant p53 protein level can be regulated by phosphorylation modification. R2TP, a molecular chaperone complex containing Pontin, stabilizes substrate proteins (26). Independent of the function of R2TP, Pontin was demonstrated to have the ability to control gene transcription factors, including p53 and mutant p53 (27). A previous study reported that Pontin can promote robust phosphorylation of the GOF

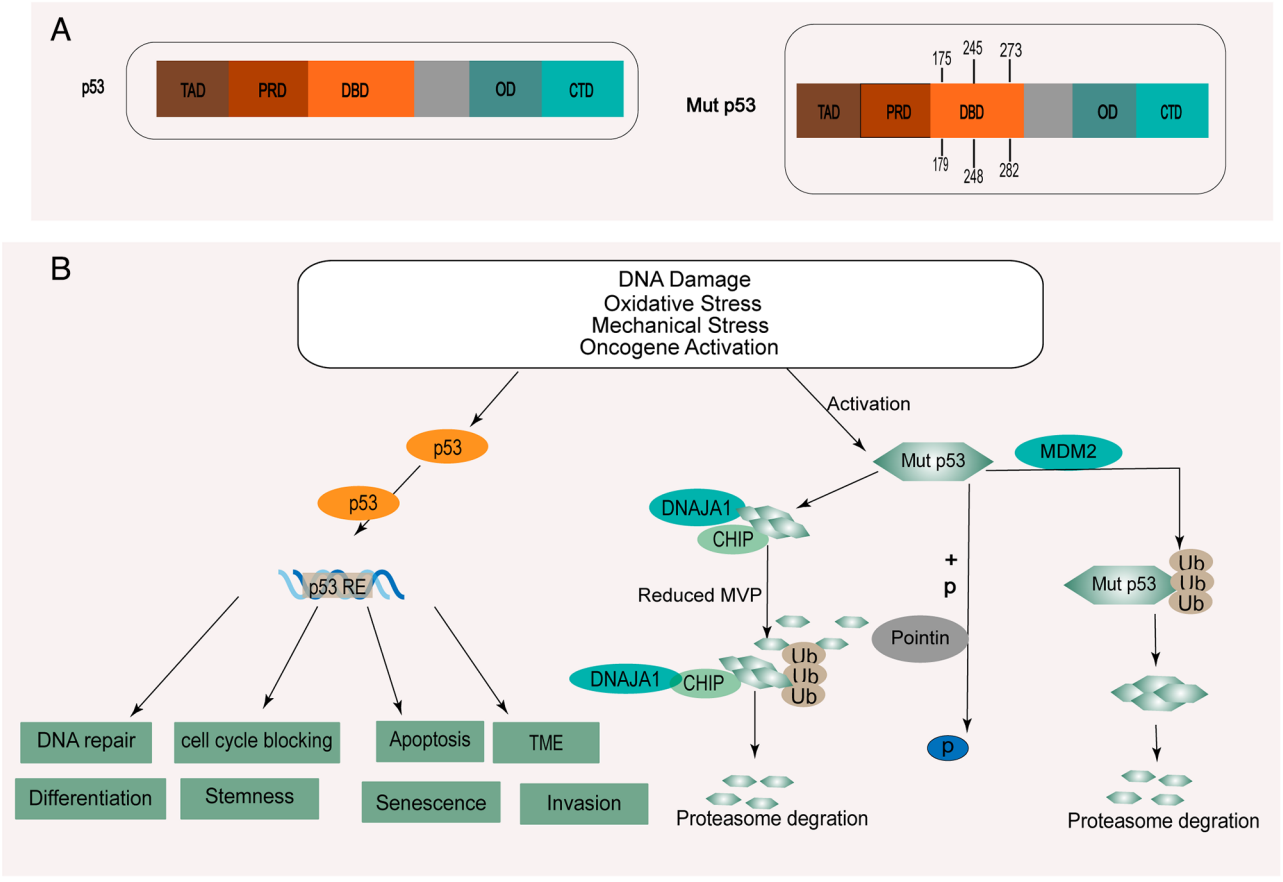

Figure 1. Background introduction of wild-type p53 and mutant p53. (A) The main functional domains of full-length wild-type p53 and mutant p53. I) Full-length wild-type p53 contains the main functional domains: TAD at the N-terminus, PRD, central DBD, OD and CTD. II) p53 mutations in HNSCC, also frequently occur at the locations R248, R273, G245, R175, R282, and H179 in its DBD. (B) The regulation of mutant p53 protein and wild-type p53 in HNSCC. Under some stress signals (DNA damage, oxidative stress, mechanical stress and oncogene activation), p53 can regulate target genes by binding p53 consensus DNA binding elements, termed p53 REs, which are involved in a large number of downstream reactions, such as DNA repair, cell cycle blocking, apoptosis, differentiation, stemness, senescence and invasion. Mutant p53 protein levels are regulated by different mechanisms in HNSCC, including post-translational modifications (ubiquitination and phosphorylation), chaperones (DNAJA1), as well as different stress signals. TAD, transactivation domain; PRD proline-rich domain; DBD, DNA binding domain; OD, oligomerization domain; CTD, C-terminal domain; HNSCC, head and neck squamous cell carcinoma; REs, response elements; TME, tumor microenvironment.

mutant p53-R248Q at Ser15 and Ser46 by interacting independently with mutant p53-R248Q (28).

Chaperones, such as heat shock proteins (HSPs), interact with newly synthesized proteins to restore the correct structure of damaged or misfolded proteins (29). A previous study revealed that MDM2 can inhibit p53 expression by mediating the ubiquitin-proteasome pathway to reactivate a negative feedback loop to strictly regulate p53 activity. Therefore, it is possible to reactivate the function of wild-type p53 as a tumor suppressor after blocking the interaction between MDM2 and p53 (30). Notably, a previous study demonstrated that MDM2 can ubiquitinate mutant p53 and lead to its degradation *in vitro* (31). Another previous study revealed that the heat shock protein 90 (HSP90) chaperone protein can inhibit the activity of MDM2 and CHIP, thereby enhancing the stability of mutp53 (31).

DNAJA1, a member of the HSP40 family, stabilizes mutant p53 by competing with the ubiquitin ligase CHIP for binding to p53, thus rendering mutant p53 more stable (29). Further study has revealed that DnaJA1 can stabilize unfolded mutant p53 and promote mutant p53-mediated activation of Yes-associated protein (YAP)/TAZ signal, which can regulate Cdc42/Rac1 and promote the metastasis of HNSCC (32,33). It was revealed that specific reduction in the level of mevalonate-5-phosphate, a metabolic intermediate in the sodium mevalonate pathway, can promote the degradation of p53 conformational mutants by inhibiting the interaction between mutants and DNAJA1 (34).

A previous study confirmed that various stress signals, including DNA damage and oncogene activation signals, can stabilize and activate wild-type p53 (35). Notably, previous research indicated that different stress signals, including signals related to oxidative stress, DNA damage related to excessive proliferation, hyperoxia, and oncogene activation, can regulate the stability and accumulation of mutant p53 in HNSCC, thus contributing to the acquisition of GOF activity (32).

5. Mutant p53 GOF activities and mechanisms in HNSCC

p53 mutations can promote tumor progression, enhance metastatic potential or promote drug resistance through the effects of GOF activity (10,36,37). Mechanistically, mutated p53 proteins can perform complex and important functions by interacting with other transcription factors and cofactors or directly binding to relevant target genes (Fig. 2A). The

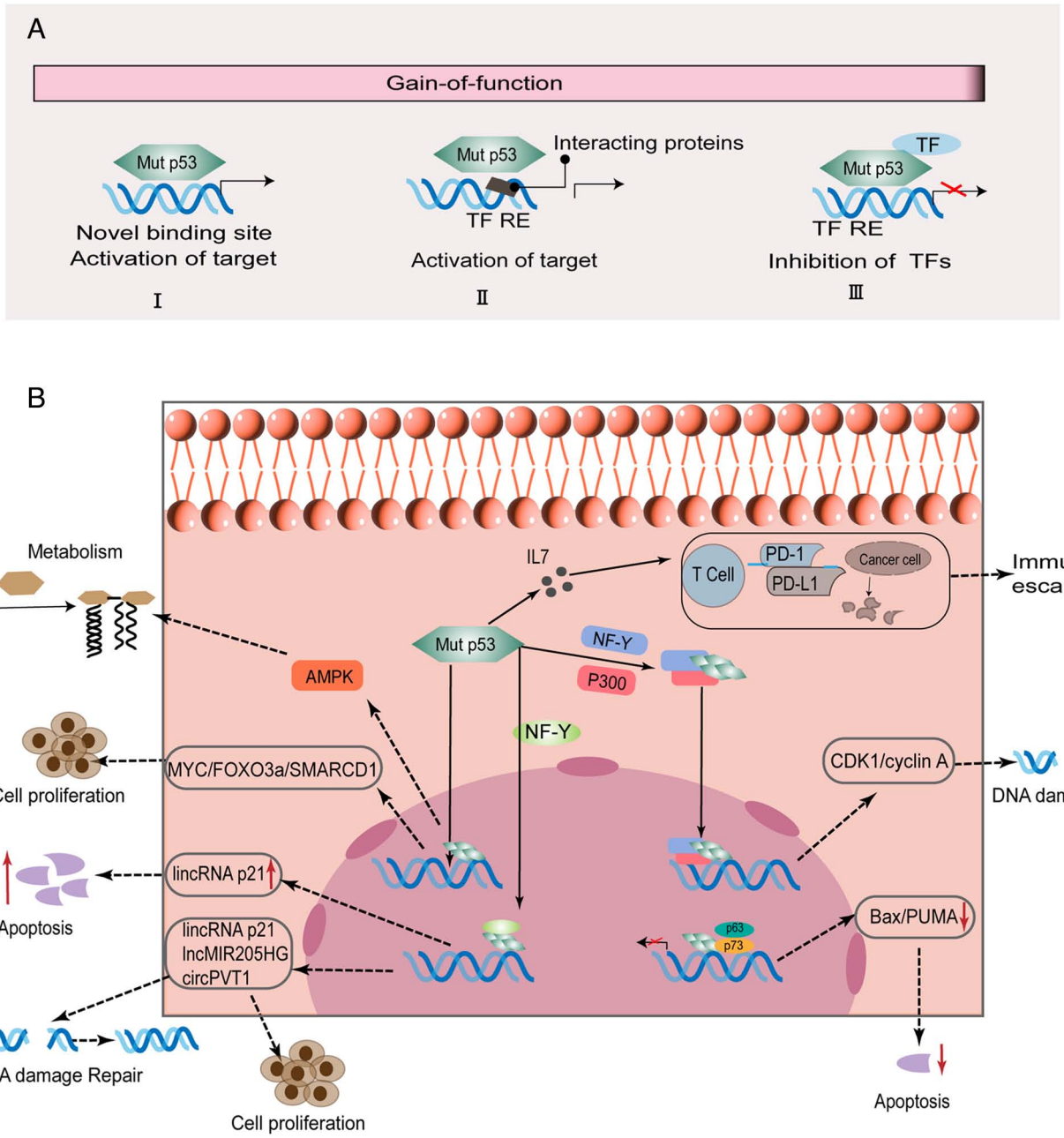

Figure 2. Mechanisms involved in mutant p53 exerting GOF effects. (A) The functional modes involved in mutant p53 exerting GOF effects. I) Mutant p53 binds novel sites to induce transactivation of target genes. II) Mutant p53 interacts with other TFs to induce transactivation of target genes. III) Mutant p53 inhibits other TFs via protein-protein interactions to disrupt the expression of genes targeted by those TFs. (B) The effects of GOF produced by mutant p53 in tumors. The triple complex formed by NF-Y, mutant p53 and P300 proteins can promote the expression of NF-Y target genes, including cyclin A and CDK1, thus enhancing DNA synthesis to copy with DNA damage. In head and neck squamous cell carcinoma, mutant p53 participates in transcriptional regulation of its target genes including MYC, SMARCD1 and AMPK to promote cell proliferation by binding to their DNA domains. By binding to DNA regions, mutant p53 can regulate the expression of particular ncRNAs, including lincRNA-p21, lncMIR205HG, miR-205-5p and circPVT1, leading to apoptosis, proliferation and DNA damage repair. p53 regulates the upregulation of the IL17 signaling pathway in the tumor microenvironment and depletes $CD8^+$ cells, thus abolishing the immunotherapeutic effect of anti-PD-1 antibody treatment in OSCC. Mutant p53 exerts GOF activity by interacting with p63 and p73 to inhibit the expression of related proteins, including PUMA/Bax, to inhibit apoptosis. GOF, gain-of-function; TF, transcription factor; NF-Y, nuclear transcription factor Y subunit α; CDK1, cyclin dependent kinase 1; ncRNAs, noncoding RNAs; IL17, interleukin 17; OSCC, oral squamous cell carcinoma; RE, response element; PD-1, programmed cell death protein-1; AMPK, adenosine monophosphate-activated protein kinase; Bax, Bcl-2-associated X; PUMA, p21/p53 upregulated modulator of apoptosis.

molecular mechanisms by which p53 mutations exert GOF effects in HNSCC are presented in Table I and Fig. 2B.

Effects of mutant p53 on protein interactions. Mutant p53 can promote HNSCC proliferation and invasion by interacting with other transcription factors, including nuclear transcription factor Y (NF-Y), p63 and p73 (38,39). It was demonstrated that mutant p53 can bind to NF-Y-targeted promoters, recruit P300, and contribute to histone acetylation after DNA damage (40). The resulting complexes containing p53 mutants (P151S, R175H, G245C and R282W) and nuclear transcription factor Y subunit α (NF-YA) can

Table I. Mutant p53 in head and neck squamous cell carcinoma: Molecular mechanism of gain-of-function.

Gain-of-function	Molecular mechanism	Mutant version	(Refs.)
Metabolic reprogramming	Increasing AMPK activity	G245D	(45)
Radioresistance	Increasing MYC activity	H193L and 278S	(46)
	Increasing SMARCD1 activity	291R	(47)
Proliferation	Binding NF-YA to inhibit lincRNA-p21	R175H and H193L	(39)
	Binding NF-Y/E2F1 to upregulate lncMIR205HG	R248L	(54)
	Inhibiting miR-27a expression	R172H	(55)
	Increasing miR-205-5p expression	H193L and R248L	(56)
	Binding YAP/TEAD to promote circPVT1	R175H	(57)
	Downregulating p21/PUMA genes	R175H	(38)
Immune evasion	Regulating the function of IL-17 and CD8 cells	R172H	(19)

AMPK, AMP-activated protein kinase; NF-YA, Nuclear transcription factor Y subunit α; E2F1, E2F transcription factor 1; YAP, Yes-associated protein; PUMA, p21/p53 upregulated modulator of apoptosis; IL-17, interleukin 17.

transcriptionally regulate lincRNA-p21, which inhibits G1 arrest in HNSCC cells (39). Moreover, mutant p53 can interact with p73, which inhibits the expression of apoptotic target genes [p21/p53 upregulated modulator of apoptosis (PUMA) and Bcl-2-associated X protein (Bax)], thus giving rise to chemoresistance (38). In HNSCC with mutations or inactivation of p53, the imbalance between p63 and p73 may have particular importance for apoptosis and drug resistance. Research has shown that ΔNp63α is overexpressed mainly with TAp73 in HNSCC with p53 mutations (41). Tumor necrosis factor-α can promote the nuclear translocation of p63 and c-Rel, which affects the translocation of TAp73 to the cytoplasm (42-44).

In HNSCC, mutant p53 participates in transcriptional regulation of target genes, including MYC, SMARCD1, and AMPK, by binding their DBD (45-47). Studies have shown that mutant p53 can alter metabolism pathways, including reactive oxygen species, autophagy, and lipid metabolism pathways (48,49). A previous study revealed that AMPK can sense energy stress to stimulate the transmission of relevant information and regulate metabolic homeostasis (50). Mutant p53 can participate in metabolic reprogramming by affecting related energy conduction-related protein kinases to perform its GOF (45). Under energy stress, p53 GOF mutants (P151S, R282W, G245C, and R175H) preferentially inhibit AMPK activation, thereby enhancing metabolism and cell invasive growth, unlike wild-type p53 (45). A study by Tanaka *et al* revealed that GOF mutant p53 G245D could reduce the phosphorylation of FOXO3a mediated by AMPK, leading to proliferation in HNSCC (51). MYC is an essential target of tumorigenicity mediated by mutant p53 and the simultaneous expression of mutant p53 and MYC proteins is a more accurate predictor of the clinical outcome of HNSCC than the expression of either alone (52). In OSCC, it was confirmed that mutant p53 291R can transcriptionally activate SMARCD1, and overexpression of SMARCD1 enhances tumorigenic characteristics, including cell viability and the ability to form colonies (47,53).

Effects of mutant p53 on RNA expression. Mutant p53 is able to regulate the expression of specific non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) by binding to DNA regions (39,54-57). Therefore, p53 mutation may alter the wtp53/ncRNA networks to promote cancer (58).

LncRNAs are RNAs that are >200 nucleotides in length and have no translation capability (54,59). Functionally, lncRNAs can sponge miRNAs and competitively interact with target mRNAs to interfere with the role of miRNAs (60). Research has indicated that lncRNAs are correlated with tumor development, lymph node metastasis, advanced clinical stage, and poor prognosis in OSCC (61). Mutant p53 and NF-YA complexes can promote lincRNA-p21 expression, which inhibits STAT3-regulated downstream genes (MYC and cyclin D1), thereby suppressing cell proliferation in HNSCC (39). Moreover, elevated expression of lincRNA-p21 regulated by mutant p53 and NF-YA complexes can significantly promote the cleavage of PARP and caspase-3, which in turn promotes apoptosis in HNSCC cells (39). Another study has reported that NF-Y and E2F1 can recruit mutant p53 to the MIR205HG promoter and significantly upregulate the expression of lncMIR205HG and miR-205-5p (54). Notably, lncMIR205HG was revealed to sponge miR-590-3p, and then increased the expression of cyclin B, CDK1 and YAP, promoting the proliferation of HNSCC cells (54).

Furthermore, studies have revealed that the function of mutant p53 proteins can be enhanced via regulation of miRNA expression in numerous cancers, such as non-small cell lung carcinoma (NSCLC), breast cancer, and HNSCC (62-64). A previous study demonstrated that the p53 R175H mutant can induce miR-128-2 expression to exert an antiapoptotic effect in

response to anticancer drug therapy in NSCLC (64). A study by Masciarelli *et al* revealed that the association of mutant p53 with the ZEB-1 transcriptional suppressor protein complex could regulate the activity of the miR-223 promoter and inhibit its transcriptional response, which leads to the acquisition of drug resistance in breast cancer (63). Mutant TP53 was found to suppress the activity of the miR-27a promoter, thereby promoting the survival of patients with HNSCC (55). In HNSCC, mutant p53 can maintain the high expression level of miR-205-5p, which could reduce the expression of BRCA1 and Rad17, resulting in abnormal DNA repair activity, thus promoting the proliferation of HNSCC cells (56). In addition, TP53 mutation-associated miRNAs (miR-17-3p, miR-21-3p, miR-21-5p) have become recognized as influential prognostic factors in HNSCC treatment (65).

CircRNAs are endogenous RNAs with important roles in regulating gene expression (66,67). Functionally, they can play multiple roles in regulating alternative splicing and miRNA expression (68,69). A previous study reported that circPVT1 was enriched in tumors expressing mutant p53 protein compared with normal tissues, based on sequencing data from HNSCC tissue samples (57). The study reported that the transcription factor complex (mutant p53/YAP/TEAD) transcriptionally enhanced the expression of circPVT1, which regulated the expression of miR-497-5p and its target genes, thereby promoting the proliferation in HNSCC cells (57).

Effects of mutant p53 on exosomes and immunosuppression. Mutant p53 can alter the extracellular matrix microenvironment through extracellular vesicles (EVs) to exert GOF effects (70). EVs can transfer important bioactive molecules (protein, DNA, mRNAs, and ncRNAs) between cells (71). Through this process, they can affect the tumor microenvironment and alter the related response of recipient cells, which promotes tumor growth, metastasis, and drug resistance (71). A previous study revealed that mutant p53 can be transported between cells through EVs to alter the tumor microenvironment, which could trigger immunosuppression (71). A previous study has shown that mutant p53 proteins are expressed in pancreatic, lung, and colon cancer cell lines; these proteins can be selectively packaged into EVs and then affect the reprogramming of the tumor microenvironment (72). It has been shown that exosomal miR-1246 can transfer the mutant p53 protein product from cancer cells to neighboring cancer cells and macrophages, leading to alterations in the tumor microenvironment (73). Immunosuppressant molecule, programmed cell death protein-1 (PD-1)-blocking antibody has been utilized in the clinical trial treatment of patients with HNSCC, improving the survival rate of patients with advanced HNSCC (74). Furthermore, a previous study reported that p53 R172H regulates the upregulation of the interleukin 17 (IL17) signaling pathway in the tumor microenvironment and depletes $CD8^+$ cells, thereby abolishing the immunotherapeutic effect of anti-PD-1 antibody in OSCC (19).

6. p53 as a therapeutic target

Therapies targeting mutant p53 are very promising for a wide range of human tumors since almost 50% of tumors carry mutant p53 (75). The main strategies include normalizing the activity of wild-type p53, inhibiting new protein-protein interactions of factors related to the response of mutant p53, exploiting synthetic lethal vulnerabilities, inducing selective degradation, and administering immunotherapy (Figs. 3 and 4).

The function of mutant p53 is abolished by preventing the interaction between mutant p53 and related proteins (Fig. 3A). The drug RETRA and NSC59984 (p53 pathway activator) reactivate p73 by blocking the biological interaction between mutant p53 and p73 or promoting the degradation of mutant p53 (76). Nicotinamide phosphoribosyl transfer (NAMPT) can regulate the aggregation of mutant p53, as determined by comparison of the gene expression profiles of several regulatory factors in HNSCC cells (77). Furthermore, combination treatment with NAMPT inhibitor and a p73 activator can inhibit the proliferation of HNSCC cells with p53 GOF mutations (77). Another essential drug is PI3K inhibitor. Mechanistically, mutant p53 facilitates the binding of MYC to its target promoter, thus enhancing MYC-mediated carcinogenesis (46). PI3K inhibitors eliminate the GOF effect of mutant p53 by preventing the interaction between MYC, mutant p53, YAP proteins with MYC target promoter (46).

The purpose of restoring the function of wild-type p53 is to restore the natural construction of the DBD (Fig. 3B). It has been reported that several compounds can reactivate wild-type p53 to restore the p53-induced biological functions; these drugs are either cysteine-targeting compounds or Zn^{2+} agents (78,79). A previous study revealed that significant p53 reactivation was observed in HNSCC cells with mutant p53 treated with a p53 reactivator (80). In combination therapy, the p53-reactivation molecule enhanced the antitumor activity of cisplatin, 5-fluorouracil, and paclitaxel against HNSCC cells (80). Another method developed was the use of Zn^{2+} agents to restore the wild-type conformation of p53. The p53 structure contains a zinc ion, an essential cofactor, which stabilizes the DBD to support the role of p53 in inhibiting carcinogenesis (81,82). The Zn^{2+} binding ability of mutant p53 is easily lost (82). The clinical application of the Zn^{2+} pharmaceutical agents is represented by COTI-2. COTI-2 is a novel associated third-generation thiosemicarbazone that binds to the misfolded mutant conformation of the p53 protein to induce conformational changes (83,84). A previous study reported that COTI-2 could normalize the expression of wild-type p53 target genes and restore the DNA binding ability of GOF p53 mutant proteins in HNSCC (84). COTI-2 may bring new promise for the treatment of patients with HNSCC carrying p53 mutations.

Inducing the degradation of mutant p53 is another strategy, which therapeutically targets mutant p53 (Fig. 3B). HSP90, a chaperone molecule, is capable of inactivating p53 ubiquitin ligase MDM2 (85). Therefore, HSP90 inhibitor treatment can destabilize mutant p53, thereby increasing tumor cell apoptosis in HNSCC (85).

Research has identified anti-p53 antibodies in cancer patients (including patients with HNSCC), and it has also revealed that p53 mutants were able to be recognized by antibodies and T cell receptors, thus vaccines for the mutant p53 gene were evaluated and assessed in clinical trials for the treatment of various types of cancer, including patients with HNSCC (86,87) (Fig. 3B).

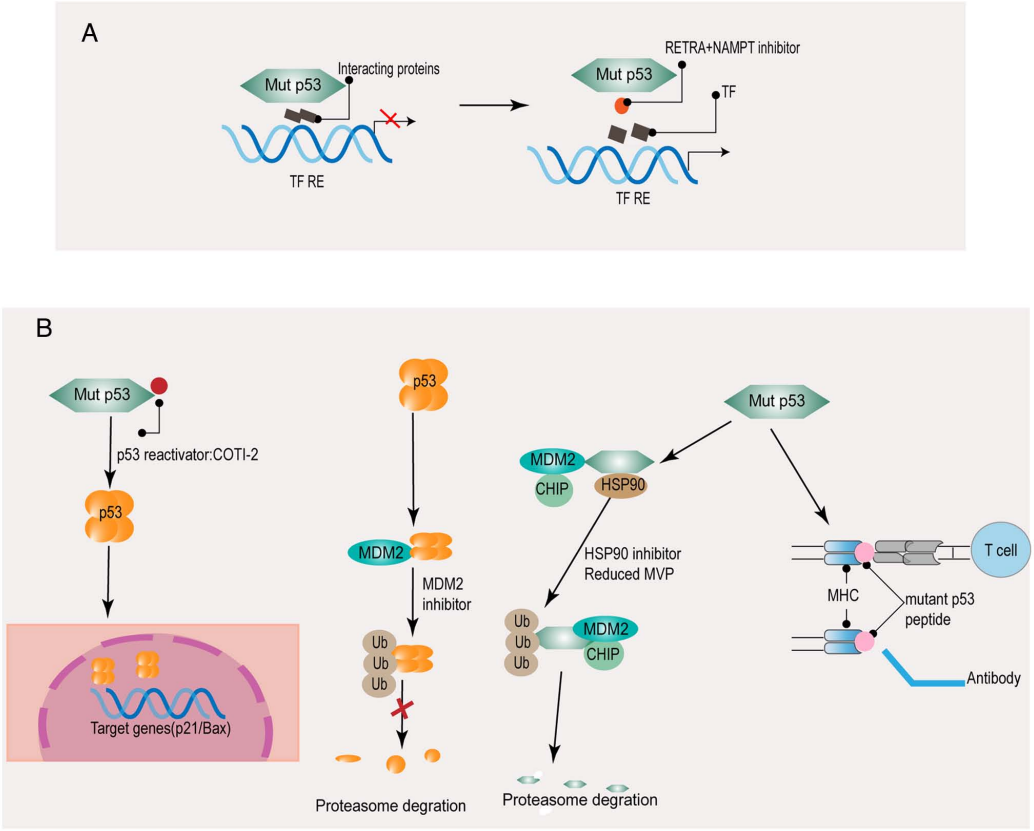

Figure 3. Therapeutic strategies of targeting mutant p53 in head and neck squamous cell carcinoma. (A) Approaches targeting p53 mutant: Inhibition of novel protein-protein interactions involved in mediating gain-of-functions of mutant p53. (B) Approaches targeting p53 mutant: Restoration of mutant p53 activity to wild-type; selective degradation of mutant p53; treatment with immunotherapy based on the recognition of mutant p53 neoantigens. NAMPT, nicotinamide phosphoribosyl transfer; TF, transcription factor; RE, response element; HSP90, heat shock protein 90.

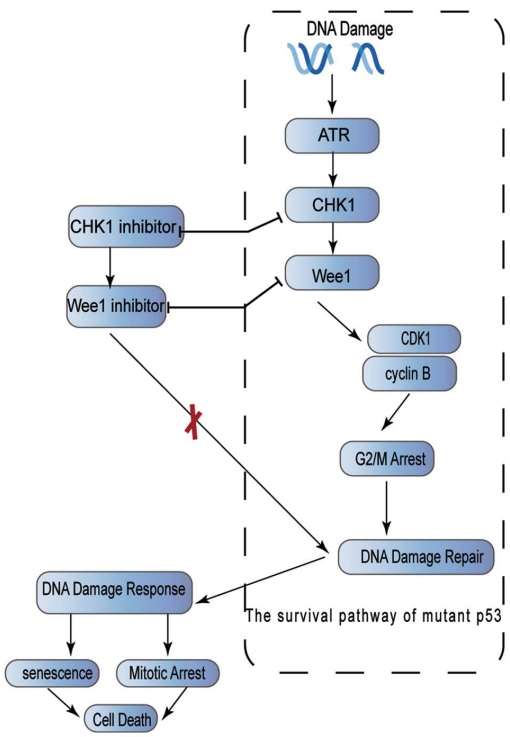

Figure 4. An additional strategy for the management of mutant p53 is exploitation of synthetic lethal vulnerabilities. The G2/M checkpoints (CHK1 and Wee1) were ablated by inhibition of the kinases, which can cause the mutant p53 to lose its ability to promote cell survival.

An additional strategy for the management of mutant p53 is the exploitation of synthetic lethality vulnerabilities, which causes mutant p53 to lose its ability to promote cell survival (Fig. 4). Tumors in which wild-type p53 function cannot be normalized, must rely on the activation of S and G2 checkpoints (ATR, CHK1, MK2, Wee1, etc.) to mediate the repair of DNA damage; thus, these tumor cells are more sensitive to ablation of the G2 checkpoints (88,89). Inhibition of the kinases involved in the G2/M checkpoint, such as CHK1 and Wee1, can cause p53 mutants to lose their ability to promote cell survival (90). The use of abrogation of G2 checkpoints, Wee-1 kinase inhibition and CHK1 inhibition, can significantly induce sensitivity to cisplatin treatment by affecting HNSCC cells expressing high-risk p53 mutations (91,92). The Wee-1 inhibitor, MK-1775, was demonstrated to render tumor cells chemosensitive in p53-deficient tumors (93). A clinical trial has shown that in patients with HNSCC, combined treatment with MK-1775, cisplatin, and docetaxel effectively inhibited the function of mutant p53 and increased the synthetic lethality of mutant p53 (94).

7. Conclusions and future perspectives

p53 is one of the most commonly mutated genes in human tumors, with mutations detected in 65-85% of HNSCC cases, highlighting the critical role of p53 in inhibiting tumorigenesis. It is challenging to directly target the mutant p53 protein. This ability is highly dependent on the unique structure

of the protein, rendering targeted drug development more complex. In addition, with the accumulating research on the role of ncRNAs, the functions of ncRNAs are becoming better appreciated. Mutant p53 can regulate related ncRNAs through transcriptional or posttranscriptional mechanisms; thus, targeted inhibition of the related ncRNAs-mutant p53 network can enhance the synthetic lethality. In the future, the challenge of studying p53 will be at the molecular and cellular levels. With an in-depth understanding of p53, the aim will be to translate this knowledge into clinical application. Notably, the study of p53 mutations has historically been conducted mainly in cell lines and mouse models, which may cause interspecies differences in p53 sequences and signaling pathways. The development of human tumor-like organs that closely reproduce the tumor conditions has offered considerable advantages in understanding the function of p53 and assessing treatment schemes in a more definitive manner.

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Authors' contributions

ML and CH contributed to the selection of the studies. Images were completed by XC and DS, and the table was created by NS, WZ, XZ and YY. The first draft of the manuscript was written by ML, and all authors revised previous versions of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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