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The role of *TP53* mutations in oral cancer: molecular mechanisms and prognostic implications

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Highlights:

- Mutant p53 causes oral cancer by a gain-of-function mechanism.
- TP53 mutations in OSCC predict poor survival and therapy resistance.
- Reactivation of mutant p53 and synthetic lethality are the two types of therapy.

Abstract: The tumour suppressor gene p53 is required to maintain the integrity of the genome, and mutations in the *TP53* gene are one of the more common types of genetic alterations in oral cancer. Collectively, the above studies have presented many genes and pathways affected by *TP53* mutations in oral squamous cell carcinoma (OSCC). First, we will present the physiological functions of wild-type p53 and the types of *TP53* mutations in oral cancer. Then we will discuss how the mutant *TP53* promotes cancer by both loss-of-function (LOF) and gain-of-function (GOF) mechanisms in cell cycle regulation, apoptosis, DNA damage repair and metabolism. We will also study whether *TP53* mutation status is associated with other characteristics of the clinicopathological features of the tumour, treatment response and patient prognosis. Emerging therapeutic strategies of the p53 pathway include mutant p53 reactivation, synthetic lethality and inhibition of downstream signalling pathways. Finally, I will briefly list the present problems and future directions of P53-based strategies for precision medicine in oral cancer.

Keywords: *TP53* mutation; oral cancer; molecular mechanism; prognostic biomarker; targeted therapy

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1. Introduction

Oral cancer represents a significant global health burden, characterized by high morbidity and mortality rates, particularly in regions with prevalent tobacco use, alcohol consumption, and betel quid chewing [1]. As one of the most common malignancies worldwide, its pathogenesis involves a complex interplay of genetic and epigenetic alterations that drive the transformation of normal oral mucosal cells into invasive carcinomas [2]. Among these genetic changes, mutations in the *TP53* gene stand out as a central event, frequently observed in a substantial proportion of oral squamous cell carcinoma (OSCC) cases [3]. The p53 protein, often termed the "guardian of the genome," plays a pivotal role in maintaining genomic integrity by orchestrating cellular responses to various stressors, including DNA damage, oncogene activation, and hypoxia [4]. Under normal conditions, wild-type p53 induces cell cycle arrest, DNA repair, senescence, or apoptosis, thereby preventing the propagation of damaged cells and suppressing tumorigenesis [5]. However, in the context of oral cancer, this protective mechanism is frequently compromised due to *TP53* mutations, which are among the most common genetic alterations detected, occurring in approximately 50%–80% of OSCC cases depending on the population studied [6]. These mutations not only lead to the loss of p53's tumor-suppressive functions but also often confer gain-of-function (GOF) properties that actively contribute to cancer progression, making p53 a critical driver in oral carcinogenesis.

A relatively high proportion of *TP53* mutations has been found in oral cancer and is therefore likely associated with this disease. Most are missense mutations that alter only one amino acid in the p53 protein, and these stable mutant p53 proteins can accumulate in large amounts within tumour cells [7]. Normally, the amount of wild-type p53 in cells without stress is small and it quickly degrades; however, mutant forms of p53 fail to undergo this degradation process and can promote cancer. Investigate how the specific molecular mechanism of *TP53* mutation promotes the development of oral cancer to find the cause of the disease and new drugs. Mutant p53 promotes the development of oral cancer by changing the chromatin structure and altering the expression of microRNAs and modifying protein-protein interactions and also increases the stability of other oncogenes [8]. Mutant p53 has been shown to bind to and inhibit the function of p63 and p73, which are both members of the p53 family with overlapping tumor-suppressive functions; therefore, they cannot promote apoptosis and differentiation of oral epithelial cells [9]. Mutant p53 promotes Epithelial-to-mesenchymal transition (EMT) by increasing the expression of Snail Family Transcriptional Repressor 1 and Zinc Finger E-Box Binding Homeobox 1 and reducing the expression of E-cadherin [10]. In the presence of therapeutic resistance, mutant *TP53* can enhance the chemoresistance and radio resistance of oral cancer cells through the activation of DNA repair pathways, inhibition of apoptosis, and promotion of survival signals in the PI3K/AKT/mTOR pathway [11]. As shown in the molecular analysis above, mutant *TP53* is associated with the development of oral cancer at the molecular level; therefore, new directions for research have been pursued to inhibit this activity, such as the development of small-molecule inhibitors of wild-type p53 and selective degradation agents for mutant p53 protein.

Mutations of *TP53* that occur in oral cancer are all kinds of problems in practice. Many studies have examined whether *TP53* mutation status is associated with different clinical outcomes in OSCC, and some research indicates that certain *TP53* mutations are linked to advanced stages of the tumour, lymph node metastasis, poor differentiation, and reduced overall survival [12]. The future of *TP53* gene

mutations varies among different people, so specific changes in the position or function-altering mutations will have different effects on the body and thus on the disease course [13]. Many mutations in the DNA-binding region of p53 have led to an aggressive and hard-to-treat type of oral cancer with a poor prognosis. Mutant *TP53* can also affect the response of normal chemotherapy and radiation therapy, so customised treatment strategies are now being employed. Recently, it has been attempted to add the results of *TP53* mutation analysis to the prognostic system and treatment strategies for oral cancer patients [14]. New approaches have been proposed to address mutant p53, including using novel agents to reactivate mutant p53, as well as exploiting synthetic lethality in *TP53*-mutant cells with compounds [15]. Systematically study the role of *TP53* mutations in oral cancer at the molecular and clinical levels to provide an all-encompassing introduction that integrates basic science research and clinical applications, thereby improving patient outcomes by enhancing risk stratification and precision medicine.

To increase the openness of this narrative review, the selection plan for the literature has been shortened as shown below. The first materials for this narrative review were collected from the PubMed and Web of Science databases; at the same time, all kinds of keywords such as "*TP53*," "p53 mutation," "oral squamous cell carcinoma," "oral cancer," "prognosis" and "targeted therapy" were used. Recently, research has also been conducted on the mechanism of OSCC, translational and clinical studies and other related materials have been released.

2. Biology and mutational landscape of p53

2.1. Biological functions of wild-type p53

Wild-type p53 is a master tumour suppressor and transcription factor that coordinates various stress responses in cells to deal with DNA damage, oncogene activation, metabolic imbalances, *etc.*, and thus suppresses the development of cancer. The main tumour-suppressive mechanisms employed by this are divided into transcription-dependent and transcription-independent pathways. p53 is a transcription factor that, upon activation, regulates numerous target genes to suppress cell cycle progression, promote DNA damage repair, induce senescence in damaged cells, or trigger apoptosis [16]. For example, after activation of p53, the gene p21 (CDKN1A) is expressed, which inhibits cyclin-dependent kinases to induce G1/S and G2/M phase arrest for DNA damage repair [17,18]. At the same time, p53 promotes apoptosis by inducing pro-apoptotic genes, such as *BBC3* (PUMA) and *PMAIP1* (NOXA), to inhibit the progress of cancer [19,20]. Besides the above classical roles, recent research has also found that p53 loss simultaneously disturbs numerous other cellular functions in health, such as genome stability and DNA repair, metabolism, cell movement and invasion; thus, it is also a pleiotropic tumor suppressor [16,21]. The activity and stability of the p53 protein are not fixed but are controlled by a network of post-translational modifications (PTMs) and protein-protein interactions. The two primary negative regulators are the E3 ubiquitin ligase MDM2 and the related MDMX (MDM4). MDM2 binds to p53, promotes its ubiquitination and degradation by the proteasome, and MDMX mainly suppresses the transcription of p53; together, they form a necessary autoregulatory feedback loop [22,23]. P53 is regulated in a dynamic way by the four post-translational modifications: phosphorylation, acetylation, methylation and ubiquitination. For instance, when DNA damage occurs, kinases such as Ataxia Telangiectasia Mutated are activated to phosphorylate p53 at specific N-terminal residues (e.g., Ser15); consequently, it

is no longer bound by MDM2 and remains stable and active [24]. At the same time, acetylation of p53 at C-terminal lysines (e.g., Lys382) by histone acetyltransferases such as p300/CBP increases its affinity for DNA and transcription activity [25,26]. USP7 is a deubiquitinase that can inhibit MDM2, thereby stabilizing both p53 and the MDM2/MDMX complex; thus, this regulatory circuit is more intricate [27]. A disruption of this well-organised regulatory network is often caused by mutations in *TP53* itself or overexpression of its negative regulators; thus, many cancers in humans have arisen due to the loss of p53's protective function and uncontrolled cell division and survival [28,29].

2.2. Mutational spectrum and characteristics of TP53 in OSCC

TP53 is a well-known tumour suppressor gene in OSCC, and among all tumour suppressor genes, it has the highest frequency of mutation; roughly 40% to more than 70% of all OSCC cases have been associated with *TP53* mutations and play an important role in the progression of oral cancer [30,31]. The first few types of *TP53* mutations in oral cancer and their molecular and clinical characteristics are presented in Table 1. Most of the above mutations are in the DNA-binding domain (DBD), exons 5–8, and many repeat mutation hotspots have been found in this area. There are relatively many recurrent missense mutations at the codons of R175, R248 and R273; for example, the R248Q mutation has been found in OSCC and oral epithelial dysplasia [32,33]. Most are single amino acid substitutions that change the local and overall structure of the p53 protein, prevent it from binding to DNA, and thus cannot activate target genes; therefore, they have lost the tumour-suppressing function of wild-type p53 [32]. There are several kinds of *TP53* mutations in OSCC, missense mutations are the most common, followed by nonsense mutations, frameshift insertions/deletions and splice site mutations [30]. Many missense mutations are also non-functional, but they can also be dominant-negative; that is to say, they bind to wild-type p53 to form inactive tetramers or acquire a new oncogenic GOF property. Mutant p53 proteins can increase the growth rate, invasion and metastasis, as well as the chemoresistance of tumours, through binding to other transcription factors and signalling pathways independently of the activity of wild-type p53 [34,35]. The Mutational Landscape of *TP53* in OSCC is changed by some carcinogens. New data show that the spectrum of *TP53* mutations is also different in different areas of the mouth. Squamous cell carcinoma of the tongue is frequently associated with damage to the DNA-binding domain, and tumors of the buccal mucosa caused by betel quid are typical cases that exhibit G:C to A:T transition signatures related to areca nut carcinogenesis. Tobacco use (smoking and smokeless) and betel quid/areca nut chewing are serious problems in the South Asian region, and they are associated with a specific mutation signature. The agent causes DNA damage and thus may lead to the production of G:C to A:T transitions or other types of mutations [29,36]. There are differences in geography and causes. Research on the Japanese and Indian populations has shown that there are many mutations in *TP53*; however, there may be different numbers of certain hotspot mutations compared with Western cohorts [30,37].

Table 1. Major *TP53* mutation types and their molecular and clinical significance in OSCC.

Mutation type	Approximate frequency in OSCC	Molecular consequence	Representative examples	Reported clinical associations
Missense mutation	~70%–80%	Dominant-negative effects; GOF activities	R175H, R248Q, R273H	Aggressive phenotype, recurrence, therapy resistance
Nonsense mutation	~10%–15%	Premature truncation and loss of p53 expression	R213	Poor differentiation, unfavorable prognosis
Frameshift insertion/deletion	~5%–10%	Disrupted reading frame and loss of function	Various	Genomic instability
Splice-site mutation	Less common	Aberrant mRNA splicing	Various	Variable clinical significance

Frequencies are not precise and will change with changes in the cohort or sequencing methods.

The status of *TP53* mutation in OSCC is also associated with poor prognosis. Mutations that are considered high-risk or functionally important (e.g., according to the evolutionary action score EAp53) are generally associated with serious clinical signs, such as extracapsular spread of lymph nodes (ECS), perineural invasion and an increased risk of recurrence, and usually have a poor prognosis [6,31,38]. The mutation spectrum of *TP53* in OSCC is relatively well-known, but many problems have yet to be solved in its biological and clinical applications. Not all *TP53* mutations have the same functions. Missense mutations in the DNA-binding domain can be of the dominant-negative or GOF type; truncated mutations usually result in a loss of protein function. The Functions of *TP53* mutations are not uniform and therefore cannot be classified. Second, although Immunohistochemistry (IHC) is often used to detect the gene, it cannot reliably determine whether there has been a mutation in the *TP53* gene; that is to say, an increase in p53 protein expression is not always caused by a genetic abnormality. IHC mainly observes changes in the amount and location of a protein and cannot detect point mutations in the *TP53* gene that are determined by sequencing. Therefore, the above two ways are complementary but not mutually exclusive, and their combination may provide more precise molecular information on OSCC. Different groups of patients, various environments and many sequencing methods have resulted in different rates of mutation discovery in the studies. Given the problems above, a standardised system and function annotations for the *TP53* mutation database should be built to help in clinical classification. Although there are defects, *TP53* mutation analysis should still be conducted to obtain more information about OSCC and improve the risk classification for targeted therapy. Mutations in *TP53* of OSCC are caused by the loss of the tumour-suppressor function of wild-type p53 and the acquisition of new oncogenic traits. The first two are the main biological effects and their mechanisms of *TP53* mutations in Figure 1.

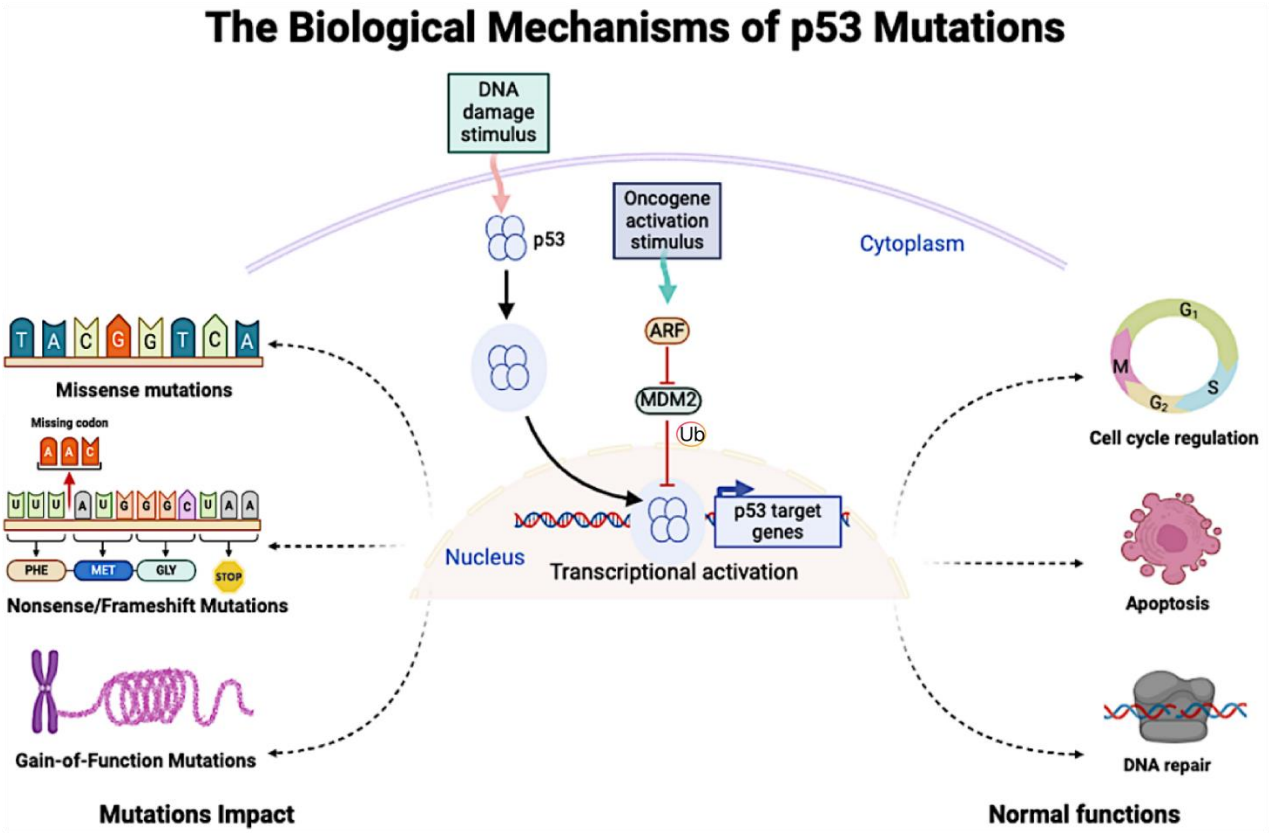

Figure 1. Overview of the biological mechanisms associated with *TP53* mutations in oral cancer. Note: ARF is a tumor suppressor protein encoded by the CDKN2A locus. Its core function is to bind and inhibit MDM2, thereby preventing MDM2-mediated ubiquitination and degradation of p53, which stabilizes and activates p53.

3. Molecular mechanisms of mutant p53 in oral cancer

3.1. Tumor-suppressive functions of wild-type p53

The tumor suppressor p53 generally functions as a transcription factor to coordinate several cellular defensive systems, including cell-cycle arrest, apoptosis and DNA damage repair, and thus maintain the integrity of the genome. At the core of p53's regulation of the cell cycle is the transcription of the cyclin-dependent kinase inhibitor p21 (encoded by CDKN1A) [17]. In the presence of DNA damage or other stress signals, p53 is activated and promotes the expression of p21, which then inhibits cyclin-dependent kinases (CDKs) [17]. Therefore, this inhibition prevents the phosphorylation of retinoblastoma (RB) proteins, leads to the continued formation of RB-E2F repressor complexes, and consequently downregulates many cell cycle-promoting genes to effectively induce a G1 phase arrest [17]. The p53-p21-RB signaling pathway gives cells a time to repair DNA damage before replication and thus avoids transmitting mutations [17]. P21 has been widely studied in the context of the aforementioned gene pathway, as it is induced by wild-type p53 in response to DNA damage and regulates the G1/S phase transition [39]. Trophoblast cells are also regulated in the same way; that is to say, the p53–p21 axis regulates the cell cycle and proliferation of these cells [40]. In addition, p53 can inhibit cell cycle progression via the following ways, rather than just p21, and other transcriptional targets that are also affected include CCNG1, FOXO3B and FBXW7 [18]. Apoptosis triggers the expression

of p53, which in turn induces the production of pro-apoptotic BH3-only proteins such as p53 upregulated modulator of apoptosis (PUMA) and, to a lesser extent, Phorbol-12-myristate-13-acetate-induced protein 1 (NOXA) [41]. PUMA is a strong trigger of the intrinsic apoptotic pathway that binds to and inhibits all the main anti-apoptotic BCL-2 family members (Bcl-2, Bcl-xL, Mcl-1, Bcl-w), thus enabling the activation of BCL-2-associated X protein (BAX) and BCL-2 homologous antagonist/killer (BAK) to induce mitochondrial outer membrane permeabilization and caspase-dependent cell death [42]. This p53-PUMA-BAX axis is a key execution mechanism for the death of cells that have sustained severe, irreversible damage [43]. P53 also functions to repair DNA. Wild-type p53 activates the transcription of DDB2 to promote the function of the NER pathway for DNA damage repair, as shown in Figures 2–3 [44]. At the same time, carcinogens such as arecoline can interfere with the p53-DDB2 axis and thus reduce DNA damage repair in head and neck cancer (HNC) [45]. In addition to transcription, p53 is also rapidly bound to the site of DNA double-strand breaks (DSBs) after they occur to help loosen the chromatin, thereby increasing the efficiency of DSB repair and directing the choice of the early repair pathway, for example, promoting non-homologous end joining (NHEJ) over error-prone alternatives [46]. It is a direct non-transcribed role in the regulation of the DNA damage response that serves to protect the genome [47]. Coordinated Functions help maintain the stability of the genome and prevent cancer. Cell-cycle arrest is to be induced to enable DNA repair, and apoptosis will be triggered for severely damaged cells.

3.2. Loss-and gain-of-function mechanisms of mutant p53

Inactivation of the p53 gene is a typical feature of OSCC that occurs when this tumour-suppressing gene is mutated to a different form, and the resulting tumour cells have acquired new oncogenic properties. Most commonly, the alterations are missense mutations in the DBD; therefore, p53 cannot recognize or bind specific DNA sequences and thus fails to activate transcription [48]. These mutations frequently occur at “hotspot” codons such as R175, G245, R248, and R273 [49]. For example, mutations at codon 248 that change arginine into tryptophan, glycine or proline can cause serious structural problems, reduce DNA-binding ability and lose transcriptional activity, and are features of p53 inactivation in cancer [50]. Structural analysis shows that such missense mutations can be divided into two categories: “contact” mutations (e.g., R248, R273) that directly disturb DNA contacts, and “structural” mutations (e.g., R175, G245) that destabilise the core domain fold; both types result in a loss of function but may be involved in different protein-protein interactions [48]. *TP53* mutations in OSCC are relatively frequent, and among them are missense mutations and truncated mutations of the gene [51]. Truncating mutations (nonsense or frameshift) result in the production of unstable, shortened p53 proteins that lack essential functional domains, such as the DBD and oligomerisation domain, and are thus completely non-functional [51]. These null mutations are frequently associated with a more aggressive disease and a reduced disease-free survival in OSCC patients [51]. In addition to the simple LOF class, many p53 missense mutants that are structurally destabilised but not fully unfolded still show GOF activities that actively promote cancer [52]. GOF mutant p53 proteins can accumulate at high levels and bind to various transcription factors and chromatin regulators to alter gene expression programs that promote cell proliferation, invasion and metastasis, and chemoresistance [53]. For example, in head and neck squamous cell carcinoma (HNSCC), OSCC is a type of HNSCC, and mutant p53 can drive oncogenic changes through regulation of cell migration, immune suppression and metabolism [52]. The specific GOF effects vary by mutation and context; structural mutants (e.g., R175H) and contact mutants (e.g., R273H)

bind to different sets of co-factors to regulate distinct transcriptomes and alter processes such as metastasis [54]. Mutant p53 can also act as a dominant-negative by forming mixed tetramers with wild-type p53, thereby inhibiting the function of the remaining normal-p53 allele, and the effectiveness of this mechanism is influenced by tetramer stability and the cell environment [8]. Accumulation of mutant p53 is frequently due to defective degradation pathways, and thus it remains elevated in a poorer state of health [53]. OSCC has a high frequency of *TP53* mutations, and these mutations have acquired a dual role of abolishing tumour suppression and gaining oncogenic functions; thus, they are now major drivers of the disease that can be targeted in new treatments to restore wild-type function or degrade the mutant protein [52]. Some research has explored the molecular changes associated with p53 mutations in oral cancer to a certain extent, and many other questions have not been answered. Most of the current research is based on *in vitro* studies or non-oral cancer models, and therefore may not fully represent the intricate tumour microenvironment of OSCC. In addition, the functional consequences of mutant p53 are highly context-dependent and vary according to the type of mutation and other gene alterations, cell environment, *etc.* This context-specificity may be the reason why some paths have been activated in some studies but not in others. Furthermore, the cooperation among mutant p53 and the tumour immune microenvironment is still unknown; it is an important subject of research in the future. We need to build a general system to incorporate the above-mentioned mechanisms and apply them in therapy. In short, mutant p53 promotes the development of oral cancer by promoting the proliferation of cells, suppressing apoptosis, inducing the EMT phenomenon, and causing drug resistance. The above processes are shown in Figure 2.

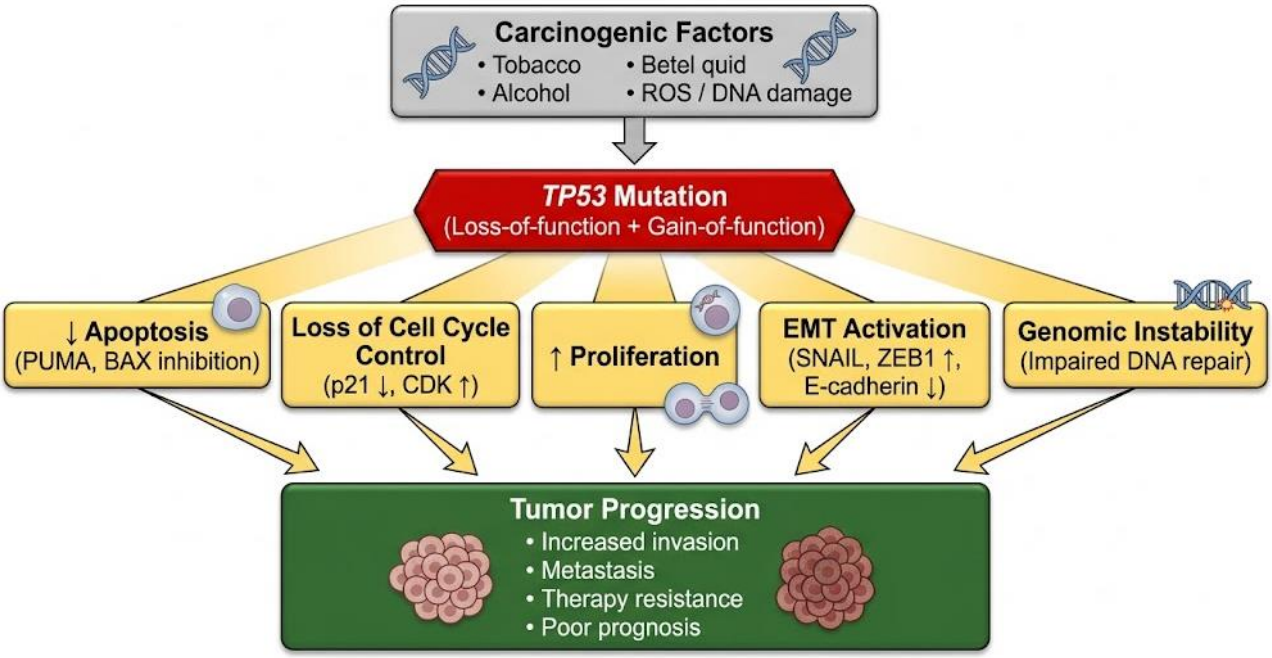

Figure 2. Mutant p53 in a model of oral cancer progression. A schematic illustration of the role of mutant p53 in oral cancer progression. carcinogenic factors cause *TP53* mutations that lose their tumour-suppressive function and acquire oncogenic traits. The above modifications result in the inhibition of apoptosis, uncontrolled proliferation, induction of EMT, genomic instability, and ultimately, tumour progression and drug resistance.

4. Clinical significance of *TP53* mutations

4.1. Association with clinicopathological features

According to a large number of clinical studies, *TP53* mutations are associated with poorer clinical and pathological outcomes for oral cancer; that is to say, they often present in advanced stages, have higher tumour grades and more lymph node metastasis. Overexpression of p53 is often a result of a mutation, and it has been shown that this is associated with an advanced Tumor-Node-Metastasis (TNM) stage in OSCC [55]. Mutant *TP53* is an expression mark of the pathological feature of local invasion and metastasis in high-grade tumors. According to the large-scale database study of patients with oral cavity squamous cell carcinoma (OCSCC), it has been found that mutant *TP53* is associated with the occurrence of extranodal extension and perineural invasion in comparison to wild-type p53, and multivariable analysis has confirmed that both are independent factors [31]. The above characteristics are typical of malignant tumours and directly related to the degree and stage of the tumour. A relatively large proportion has spread to the lymph nodes. A pilot study has found that a severe type of the disease that spreads to the lymph nodes is associated with p53 expression [55]. A typical case of this finding can be seen in the large-scale transcriptomic analysis of HNC, and it has been proposed that the initial growth of tumours is associated with a loss of p53-DREAM-mediated repression of cell-cycle genes [56]. Loss of repression is often caused by a *TP53* mutation, and thus it can lead to the dedifferentiation of epithelial cells and promote the malignant process of stem cell-like proliferation. Mutations in *TP53* can also change the type of differentiation of tumors. Although the specific hotspot mutation R248 is not mentioned in the provided abstracts, there is more general dysregulation of p53 function involved in the development of a highly aggressive form. Research on oral potentially malignant disorders (OPMDs) has found that the level of p53 expression is higher in more severe dysplasia, and it is involved in the development of cancer [57]. The co-expression pattern of p53 and other markers in the developed OSCC is also different based on the aggressiveness of various subtypes, and a basal-like subtype with a characteristic immunomarker profile has been proposed [58]. Taken together, the above evidence suggests that *TP53* mutations or abnormal expressions are not merely passenger mutations but rather drivers of the main malignant characteristics promoting the development of cancer, such as continuous proliferation, invasion and metastasis; thus, they are associated with higher T and N stages and generally more severe clinical diseases.

4.2. Prognostic significance of TP53 mutations

A *TP53* mutation has been found in one of the cases of poor prognosis for oral cancer. Research on OCSCC has not found a direct relationship between *TP53* mutations and the different median overall or disease-free survival in this group [31], but most other studies have also shown that they are associated with a poor prognosis. For instance, in other aggressive cancers, such as ovarian carcinosarcoma, it has been found that the level of the tumor protein p53 is also raised and is associated with a poor prognosis [59]. The p53/apoptosis pathway of response to therapy often affects the survival of oral cancer. The second is that, because of the *TP53* mutation, the developed drugs are losing their effectiveness. A deficiency in the p53 tumour suppressor pathway is a common reason for the decreased response of many treatments to HNSCC [60]. As shown in the figure above, a certain type of resistance is reduced to the standard

chemotherapy drug cisplatin, 5-fluorouracil and radiation therapy. The reason is not obvious and is complex. Mutant p53 can stop apoptosis of cells after chemotherapy and radiation therapy, so these cells do not die. Research on drug combination has also found that epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor resistance is a mechanism, and the condition of *TP53* may affect it [61]. There is no treatment, and the results are not good. Tumours with p53 mutations that do not respond to first-line treatment are more likely to have local recurrence and distant metastasis, and thus have a much shorter lifespan. Based on the above data, p53-positive cells are associated with the recurrence of OSCC [55]. Therefore, the two prognostic values of p53 are that it is associated with an intrinsically more aggressive tumour and reduces the effectiveness of treatment. Based on the above results, it can be concluded that changes in *TP53* are associated with a poor prognosis for some groups of OSCC patients. As a result, the *TP53*-mutant cancer cells are no longer eliminated by the drug and can continue to live and spread; thus, there is a relapse of the disease and a shorter life for the patient. Although many studies have been conducted, the prognosis of *TP53* mutations in OSCC has not been determined yet. Although many studies have linked changes in *TP53* to a poor prognosis, not all of them have found that they are independent prognostic indicators. The reasons for this difference may be other mutations, many detection methods are used, and the patient groups are not the same. Not all mutations of *TP53* are the same, and those in the high-risk area of the DNA-binding domain are more likely to be associated with aggressive cancer than other types of variants. *TP53* is associated with a group of related genes expressed by other genes, such as human papillomavirus (HPV) and EGFR, and it is difficult to accurately predict a person's future health. Therefore, a single indicator of *TP53* mutation may be too arbitrary; thus, many combinations of them are probably necessary for an accurate risk classification model.

4.3. Integrated biomarker models for risk stratification

The prognostic division of oral cancer has been divided more finely by adding other important molecular markers to the *TP53* mutation status in combination with *TP53* mutation status. Combine p53 data with the status of HPV infection in oropharyngeal cancer and extend this approach to stratifying good prognostic factors in other parts of the oral cavity. Research has consistently shown that HPV-positive HNSCC, which is often wild-type for p53 due to viral E6-mediated degradation, has a relatively good prognosis [62]. Conversely, *TP53* mutations frequently occur in HPV-negative tumours and are associated with a poorer prognosis. Immunohistochemical profiling also shows that younger and older patients with OSCC have different levels of biomarker expression; specifically, p53 and p16 (an HPV surrogate) differ significantly, and p16 expression is associated with poor prognosis in young people [63]. Thus, a model has been constructed in which HPV-negative/*TP53*-mutant patients constitute a high-risk group with the poorest prognosis, and HPV-positive/p53-wildtype patients have a relatively good prognosis [60]. P53 is also related to high EGFR expression and an increased risk. Overexpression of EGFR occurs in a relatively high proportion of HNSCC cases and is also associated with an adverse outcome [60]. Research has shown that in co-expression patterns, all p53-positive OSCC cases in one study were also EGFR-co-expressed and likely driven by synergistic pathways promoting aggressiveness [58]. Another cell cycle regulator is Cyclin D1, which can also be added to the model. A characteristic pattern of immunohistochemistry is found in HPV-associated cancers: overexpression of p16 (blocked staining) and low levels of pRb and cyclin D1 are indicative of HPV-driven carcinogenesis and a better prognosis; on the other hand, high expression of pRb and cyclin D1 is associated with HPV-negative disease that is likely *TP53*-mutated [62].

Amplification or overexpression of Cyclin D1 is a typical phenomenon in OSCC, and its expression increases with the degree of dysplasia [57,64]. Therefore, a combined profile of *TP53* mutation, EGFR overexpression and cyclin D1 amplification will be used to identify a subgroup of tumours with enhanced proliferation ability, survival signalling and genomic instability, and thus require aggressive treatment. A few genes have been identified as promoters or inhibitors of different stages in the proliferation cycle of various cancer cells. Such models can better predict the behaviour of tumors, determine the strength of adjuvant therapy, and identify patients who may be suitable for targeted treatment of EGFR-related pathways to achieve personalised treatment strategies for oral cancer.

5. Therapeutic strategies for p53

5.1. Strategies for reactivating mutant p53

A first-line treatment option for p53-mutated oral cancer aims to restore the wild-type structure and transcription function of the mutant protein via small-molecule drugs. Computational and molecular dynamics approaches have been used to design the above compounds, and APR-246 (PRIMA-1Met) serves as a model. This compound and its analogs, such as those found in screening studies (Cmpd-4 and Cmpd-8), function by binding to mutant p53 proteins, and often at specific sites such as cysteine 124, promote the refolding of these proteins into a wild-type-like, functionally active state [65]. Restore the function of p53 in this way to turn on the downstream tumour-suppressive pathway and induce apoptosis and growth inhibition in cancer cells. Therefore, this way will be applied to OSCC, given its high incidence of *TP53* mutations, to restore the function of *TP53* and inhibit oncogenic signaling [65]. Innovative Delivery Systems are being developed to improve both the efficacy and targeting of p53-activating agents beyond small molecules. For example, a thermosensitive hydrogel-nanosystem has been developed to locally and continuously deliver PRIMA-1 (a p53 activator) and other drugs directly to the tumor site in esophageal cancer models, and significant tumour growth inhibition and restoration of p53 activity have been achieved in preclinical studies [66]. Therefore, local delivery will reduce the side effects of systemic poisoning and increase the amount of medicine at the tumour site. CRISPR/Cas9 gene-editing technology can also be employed to correct the *TP53* gene mutation at the level of DNA directly, thus avoiding the need for drugs. Although direct correction of p53 in OSCC is still under investigation, CRISPR/Cas9 has shown good results in related studies; for instance, specific miRNA clusters in OSCC cells can be deleted using CRISPR, leading to p53 activation and increased sensitivity to chemotherapy, thus confirming that this pathway is relevant [67]. Another way to raise the activity of the wild-type p53 protein is to avoid correcting the mutant. The nuclear export inhibitor selinexor blocks XPO1, causes nuclear accumulation and functional activation of tumor suppressors such as p53 and p73, and thus induces apoptosis in cancers with wild-type p53 [68]. Similarly, new chiral-peptide supramolecular structures that are orally available have also been developed to restore the p53 signalling pathway in living cancer models [69]. The above many paths, such as small-molecule correctors and advanced delivery systems, gene editing and indirect activation, *etc.*, have all been deployed to tackle the oncogenic effects of *TP53* mutations in oral cancer.

5.2. Synthetic lethality-based therapeutic approaches

To select only the p53-deficient oral cancer cells for killing and spare the normal tissue, exploit synthetic lethal interactions. Therefore, a loss of p53 function leads to the emergence of particular deficiencies in alternative cell cycle arrest and DNA-damage-response pathways that compromise cell viability. WEE1 kinase is a typical target of these drugs, involved in the G2/M phase control checkpoint. Based on the preclinical and clinical data above, p53-mutated and p53-deficient cancer cells are more susceptible to WEE1 inhibition [70]. MK-1775, a WEE1 inhibitor, enhances the radiosensitising effect of radiation in oral tongue squamous cell carcinoma (OTSCC) by blocking the G2/M phase arrest of cancer cells and inducing mitotic catastrophe and apoptosis; this radiosensitisation has been observed even in *TP53*-mutated cells, although it is generally stronger in the presence of *TP53* mutations [71]. Clinical trials have been conducted on the combination of adavosertib (AZD1775) and chemotherapy for *TP53*-mutant ovarian cancer to extend progression-free survival and have validated the translational potential of this synthetic lethal approach [72]. The mechanism does not only involve p53 inactivation, but as shown in HPV-positive HNSCC, the E6 oncoprotein sensitizes cells to WEE1 inhibition by activating a FOXM1-CDK1 circuit; thus, synthetic lethality can be induced through pathways that converge on cell cycle dysregulation [73]. Besides WEE1, other kinases of the DNA damage response (DDR) pathway, such as ATR and CHK1, are also good synthetic lethal targets. ATR inhibitors such as AZD6738 can enhance the effect of S-phase drugs (e.g., trifluridine) in colorectal cancer models, and this combination is effective in both p53 mutant and wild-type contexts; thus, it may be broadly applicable [74]. Another way is the induction of replication stress; drugs such as gemcitabine that cause replication stress are synthetically lethal with p53 deficiency, and *TP53*-mutant cells cannot mount an appropriate checkpoint response to this injury [75]. Not all of the synthetic lethality involves kinase inhibitors. For example, Werner syndrome helicase (WRN) has been identified as a synthetic lethal target in microsatellite instability (MSI) cancers, and pharmacological inhibition of WRN by compounds such as HRO761 can induce DNA damage and suppress tumor growth in a p53-independent manner [76]. An increasing number of synthetic lethal partners for p53 deficiency have been found to develop targeted treatments. Some new drugs that have not yet been tested in clinical trials include WEE1 inhibitors combined with other agents, such as ATR/PARP inhibitors or immunotherapy (anti-PD-L1); a patient with OSCC who also has *TP53* mutations is at risk of this rare type of leukaemia and may also have a worse prognosis [70].

5.3. Targeting mutant p53-associated signaling pathways

Since mutant p53 often gains oncogenic GOF characteristics and activates several pro-survival and proliferative pathways, another treatment strategy has been to directly inhibit these downstream effector cascades. Mutant p53 can disrupt the signalling pathways of PI3K/Akt/mTOR and RAS/RAF/MEK/ERK to drive treatment resistance and tumour growth. Therefore, a combination of inhibitors for the above pathways can be used to inhibit the oncogenic effect of mutant p53. For example, in esophageal cancer, new procaine-derived hybrid compounds that are selective PI3K/mTOR inhibitors (e.g., compound 8e) have shown strong anti-cancer effects by inhibiting the PI3K/Akt/mTOR signaling pathway to induce apoptosis and modify the expressions of essential apoptotic genes such as Bcl-2, Bax, and p53 [77]. In oral cancer, re-expression of the tumour-suppressive microRNA miR-34 can increase sensitivity to chemotherapy by inducing DNA damage and apoptosis through the p53-dependent pathway [78]. An

introduction to the current and emerging therapeutic strategies for p53 is shown in Table 2, including methods for mutant p53 reactivation, synthetic lethality and pathway-targeted therapies. *TP53* status and the tumour immune microenvironment (TIME) have been widely studied in the context of immunotherapy. Mutant p53 can lead to an immune-excluded or "cold" tumor microenvironment (TME) that is immunosuppressive and does not respond well to immune checkpoint inhibitors (ICIs) such as PD-1/PD-L1 blockers [79]. Mutant p53 may also modify the adaptive immune response by changing the expression of PD-L1, altering T-cell infiltration and modulating inflammatory cytokine signaling in macrophages. Several studies have indicated that *TP53* mutations can lead to immune evasion and reduced cytotoxic T-cell activity, thus limiting the effectiveness of immune checkpoint blockade in OSCC. Carcinogen-induced *TP53* mutations in OSCC models promote a cold TIME enriched with M2 macrophages and are thus resistant to ICI monotherapy [79]. However, this resistance may be overcome by combination strategies; for example, a PD-1 inhibitor and a STING agonist have restored the therapeutic effect in *TP53*-mutant cold OSCC models [79]. Mutant p53 may also be immunogenic due to neoantigen generation. Local delivery of a PD-1 inhibitor in a hydrogel formulation was effective in inhibiting the malignant progression of premalignant oral lesions, and this effect was observed regardless of the presence of *TP53* mutations; therefore, it can be expected that immune modulation will be beneficial for all genetic backgrounds [80]. In combination with therapy for mutant p53, ICIs have also shown promise. Natural nanovesicles of Scutellaria baicalensis (SB) reduce the expression of PD-L1 and regulate the p53 signalling pathway in colorectal cancer cells, thereby enhancing anti-tumor immunity and demonstrating synergistic effects with anti-PD-1 antibodies [81]. Clinical observation also supports the above, and in advanced non-small cell lung cancer (NSCLC) with coexisting KRAS and *TP53* mutations, a chemotherapy-free regimen of camrelizumab anti-PD-1 antibody plus the multi-targeted tyrosine kinase inhibitor anlotinib has shown good results, demonstrating that immunotherapy and targeted agents can be used together in genetically defined subgroups [82]. Therefore, a multi-faceted strategy that simultaneously addresses the signalling pathways activated by mutant p53 (e.g., PI3K/mTOR) and modulates the immune microenvironment (e.g., ICIs or STING agonists) has good prospects for overcoming therapeutic resistance in *TP53*-mutant oral cancer.

Table 2. Therapeutic strategies for p53 in oral cancer.

Strategy/Agent	Mechanism of action	Clinical development status	Potential applications
APR-246 (Eprenetapopt)	Restores wild-type p53 conformation	Phase I/II clinical trials	Reactivation of mutant p53
WEE1 inhibitors	Synthetic lethality in *TP53*-mutant cells	Early-phase clinical trials	Enhances sensitivity to DNA-damaging therapy
MDM2 inhibitors	Blocks p53 degradation	Investigational	Restores p53 signaling in selected settings
Gene therapy	Delivery of wild-type *TP53*	Preclinical/early clinical	Functional restoration of p53 pathway

Based on the results of the additional studies, its stage of clinical development will be reclassified.

Although many therapeutic methods for mutant p53 have shown some promise in preclinical studies, none have been approved for clinical use yet. APR-246 is a representative small-molecule activator that has shown good results, but its effect is only present in some people and has not yet been confirmed by large-scale clinical trials. Although the idea of synthetic lethality-based approach is good, it also has

problems of toxicity and resistance development. There is also a large number of different causes for *TP53* mutations, and thus no single treatment has been found to be universally effective. Thirdly, there are no good-enough biomarkers that can predict whether a person will respond well to the treatment. In the future, we will increase the level of detail in patient stratification, strengthen combination therapy strategies, add molecular and immunological tests, *etc.*, to improve the efficacy of treatment.

6. Challenges and future prospects

6.1. Standardization of TP53 mutation detection technology and clinical application

Given that *TP53 mutation* data in oral cancer patients has been applied to clinics, standardised collection methods and uniform analysis of the test results are still lacking. Although all of them have some advantages and disadvantages, such as Sanger sequencing, next-generation sequencing (NGS) and IHC, an all-encompassing clinical workflow has not been established yet. IHC is relatively convenient and often shows an increase in p53 protein; however, it cannot distinguish between mutant p53 accumulation due to stabilisation and that caused by stress on wild-type p53, so the interpretation may be subjective [83]. Therefore, the detection of p53 overexpression by IHC should be treated cautiously and is not to be considered the same as *TP53* mutation status. Therefore, to enhance the accuracy of molecular information, more integrated immunohistochemistry-gene expression studies are being used in both clinical and translational research. Research shows that the over-expression of p53 by IHC is not consistently related to some clinical factors, such as age or tumour differentiation; therefore, more specific molecular analyses are required [83]. Sanger and NGS are also sequencing technologies; they offer highly accurate mutation data but differ in sensitivity, cost and speed. The *TP53* mutation detection platforms have different strengths and weaknesses in analytical sensitivity and specificity, as well as turnaround time, cost and clinical applicability. A table showing some typical detection methods is presented below (Table 3). Studies on the Spanish population have used PCR-based scanning of exons 5, 6, 8 and 9 to identify pathogenic mutations, such as a C.613 T > A change in exon 6, and have shown the usefulness of targeted sequencing [84]. Based on the research conducted in [85], it has been shown that a specific combination of *TP53* mutation analysis and polymorphism data (such as p53 codon 72 and MDM2 SNP309) can identify expressions of certain prognostic and therapeutic genes, such as hTERT, VEGF and MMPs, that are significantly altered *in vitro*. Although not the only way to achieve this, researchers have recently started identifying *TP53* mutations in ctDNA of circulating tumours through liquid biopsy. Non-invasive ways can be used to detect early changes, follow how much the remaining disease has decreased after treatment, and see if the treatment is having an effect. Research has shown that a serum biomarker of p53 dysfunction is likely to be used early in the diagnosis of oral and pharyngeal squamous cell carcinoma, as evidenced by studies on the serum p53 antibody (s-p53-Ab) [86]. It shows high specificity, especially for p16-negative cancers involving *TP53* mutations, and is a good early diagnostic indicator in the initial stage of disease. The development of a high-sensitivity, clinically practical test for the *TP53* mutation can be used to better individualize the treatment of OSCC.

Table 3. Comparison of *TP53* mutation detection methods in OSCC.

Method	Advantages	Limitations	Sensitivity
IHC	inexpensive, rapid	indirect assessment	moderate
Sanger sequencing	accurate hotspot detection	low sensitivity	moderate
Targeted NGS	high sensitivity	higher cost	high
Whole-exome sequencing	comprehensive profiling	expensive	high
Digital PCR	highly sensitive	limited mutation coverage	very high

6.2. In-depth analysis of mutant p53 functional heterogeneity

The functional effects of *TP53* mutations in oral cancer are not uniform; instead, there is a large number of different mutations at different locations and with various structural changes. Different missense mutations can have different GOF activities and downstream transcriptional programs; therefore, a single category of "mutant *vs.* wild-type" is no longer suitable and more nuanced functional groupings are required. Mutations are generally divided into "contact" mutations (e.g., R248Q) that alter the specificity of DNA binding or "structural" mutations (e.g., R175H) that cause a whole-domain unfolding of the DNA-binding domain; these two categories have different oncogenic effects and different interactions with other pathways in the cell [65]. Calculations and structural analysis have begun to reveal the causes of this. For example, an integrated in silico study of *TP53* mutations in a Senegalese population found that mutations in exon 5 across oral, prostate and breast cancers were mainly destabilizing; on the other hand, certain recurrent exon 6 mutations in prostate and breast cancer (e.g., V217L, V218M) were predicted to be stabilizing and thus affect the structure of p53 in a context- and exon-specific manner [37]. The different mutants can change the tumour's biological behaviour by regulating the crotonylation of non-histone proteins in different ways, which may drive the tumour's growth in the absence of p53 through the MDM2/HDAC3/HNRNPC axis [87]. Build a top-down preclinical model to study the function of single *TP53* mutations in oral cancer. Organoid models based on genes and patient-derived xenograft (PDX) models provide good platforms for this purpose. Organoid models of oral mucosal tissue with specific driver mutations, such as *TP53* and CDKN2A knockouts, have been used to study the early stage of malignant transformation and identify new targets for therapy [88]. Furthermore, synergistic mouse models with specific Trp53 mutations have been developed to study how different mutant types alter the tumor immune microenvironment, and it has been shown that carcinogen-induced *TP53* mutations can promote an immune- "cold" and ICI-resistant state rich in M2 macrophages [79]. Patient-derived organoids (PDOs) that retain the mutational profile of the tumour, such as *TP53* status, are also suitable for functional studies and drug-response assessment, and can bridge the gap between molecular characterisation and personalised therapy [89]. Build a system to characterize the functions of various p53 hotspot mutations by employing these models, and thus learn more about their role in the onset of tumours, spread, metastasis and treatment resistance of oral cancer.

6.3. Development of novel combination treatment modalities

Given the *P53* mutation in target oral cancer cells, new treatment methods are needed, and at present, only combination therapy aims to restore tumour suppressor function or leverages reduced p53 activity. One typical strategy is to employ compounds that can restore the activity of mutant p53, such as APR-246

(PRIMA-1Met), and in combination with conventional chemotherapy or immunotherapy. Preclinical studies have also shown that small molecules that can bind to and stabilise the mutant p53 core domain can restore function, as demonstrated by APR-246 [65]. For example, 4-Hexylresorcinol (4HR) has been identified as a pharmacological chaperone that increases the transcriptional activity of p53 and induces apoptosis in oral cancer cells with a particular DNA-binding domain mutation (Glu258Ala) [90]. In conjunction with chemotherapy, radiation therapy and immunotherapy have shown good results in overcoming drug resistance and enhancing the effects of other treatments for these reactivators. *TP53* mutations are linked to an aggressive phenotype and poor prognosis in OSCC, so this is of interest [55]. Based on the above research, p53 status is likely related to the treatment response; for example, capsaicin induces autophagic apoptosis in *TP53*-mutant HSC-3 cells but only autophagy in p53-functional SAS cells, showing that these cells respond differently to treatment after mutation [91]. Furthermore, the immunosuppressive tumor microenvironment driven by mutant p53 in syngeneic OSCC models may be overcome by combining PD-1 inhibitors and STING agonists [79]. The future direction of therapy will be individualised and use high-precision medicine; that is to say, a full spectrum of molecular data and other genes may be studied for targeted intervention. The new type of orally available, target-specific agents is promoting this change. Novel compounds, such as the p53-targeting arsenical AcGlcAs that shows strong cellular uptake and efficacy in *TP53*-mutant xenograft models, and the MDM2-p53 antagonist brimonidine (BI 907828) designed for intermittent dosing to reduce toxicity, are considered promising clinical candidates [92,93]. First-in-class reactivators such as rezatapopt (PC14586) have shown some clinical efficacy in initial trials for the p53-Y220C mutant, but acquired resistance through secondary *TP53* alterations at the same site (cis) has also occurred; thus, new-generation drugs or rational combinations may be required [94,95]. The present therapeutic strategies for mutant p53 are introduced in Figure 3. Ultimately, the effective treatment may need to combine various strategies, such as direct targeting of the p53 pathway and the simultaneous exploration of collateral vulnerabilities and immune modulation; for example, studies have combined nimbolide and cisplatin in PDX models or employed metformin to restore p53 function in HPV-positive cancers [96,97].

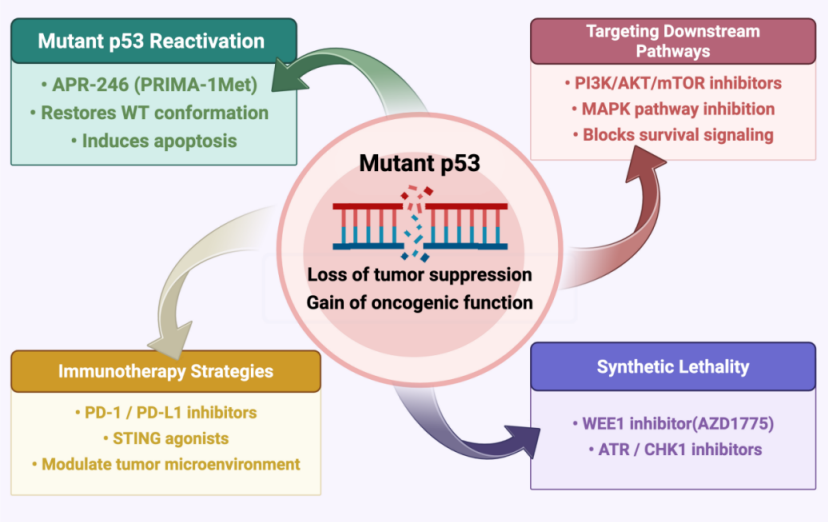

Figure 3. Therapeutic strategies for mutant p53. Overview of therapeutic strategies targeting mutant p53 in oral cancer. The four types are: activation of mutant p53, induction of synthetic lethality, suppression of downstream signaling pathways, and alteration of the tumour immune microenvironment.

7. Conclusion

A typical case showing how a gene mutation affects the necessary attributes and prognosis of tumours is *TP53* mutation in oral cancer. As one of the most common types of genetic alterations in this kind of cancer, p53 dysfunction has occurred via both dominant-negative and GOF mechanisms and is now a main reason for the initiation of cancer, its spread and development of drug resistance. Pathologically, according to clinical data, mutant p53 can be a strong and independent prognostic indicator for poor prognosis in cancer patients, is strongly associated with reduced sensitivity to radiotherapy and chemotherapy and is thus linked to the bad course of the disease. Now, it has been known that *TP53* is a gene responsible for life and disease, and many research efforts have been made in the field of cancer therapy.

All the various research directions and results in this area need to be distributed reasonably. On the one hand, there has been a continuous link between *TP53* mutations and adverse events, so treatment research urgently needs to be conducted. At the same time, due to all kinds of *TP53* mutations (missense and truncation), various functions are realised (GOF and LOF), and thus a single treatment strategy cannot be adopted. Therefore, the general and consistent prognostic indicators of the study should be related to the specific biological mechanisms of the variation. Among the new therapeutic strategies that have appeared, one of the many ways to solve this problem is to restore the wild-type function of the mutant p53 protein by targeting key downstream pathways of synthetic lethality. There are also problems in the use of drugs, such as drug delivery issues, lack of tumour specificity and strong resistance of cancer cells to compensatory pathways.

In the future, many joint efforts will be made to promote the health of the people. First, in order to guarantee the standardisation and verification of robust methods for *TP53* mutation detection in clinical samples, precise patient stratification and reproducible research need to be achieved; thus, such methods must be established. Second, we need to learn about the function differences of the various p53 mutants in more detail. Move beyond mutation status to identify which oncogenic networks are affected by specific variants and thus find new subtype-specific vulnerabilities. Finally, strengthen the translation link and other reasons. In the future, the focus of efforts will be on the clinical development of p53-targeting drugs and intelligent combinations with traditional treatments such as radiotherapy or chemotherapy and other targeted drugs to overcome resistance mechanisms. At present, the model links *TP53* mutations only to treatment resistance; going forward, we will use this mutation for individualised cancer treatment and revise this model accordingly.

TP53 mutations are difficult-to-treat for oral cancer at present, but they are now also regarded as promising targets for treatment. The convergence of advanced molecular diagnostics, in-depth research on mutant p53 biology, and new designs for clinical trials can all be used to make this genetic defect a target for treatment. The above work can improve the survival rate of patients with oral cancer and provide a reference for targeting transcription factor dysregulation in other cancers.

With the development of high-throughput sequencing and single-cell analysis in the future, AI-driven models will help us learn more about the different types of *TP53* gene mutations and the diseases they cause. Collect data from all kinds of ‘omics technology and functional experiments to improve the accuracy of *TP53* mutation classification and develop personalised treatment plans. With the desire to help more people with oral cancer, research has also been carried out at the molecular level.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used generative AI tools only to improve language and readability. Specifically, the authors used ChatGPT for language polishing only. The authors take full responsibility for the content of the manuscript.

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Authors' contribution

Conceptualization, Lei Ma and Zhibin Liu; investigation, Ke Huang, Shuang Zhao and Yafang Li; writing—original draft preparation, Lei Ma and Zhibin Liu; writing—review and editing, Myoung Ok Kim and Qiuhong Duan; visualization, Lei Ma; supervision, Myoung Ok Kim and Feng Zhu; project administration, Juanjuan Xiao and Feng Zhu; funding acquisition, Juanjuan Xiao and Feng Zhu. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

[1] Tran Q, Maddineni S, Arnaud EH, Divi V, Megwalu UC, *et al.* Oral cavity cancer in young, non-smoking, and non-drinking patients: a contemporary review. *Crit. Rev. Oncol. Hematol.* 2023, 190:104112.

[2] Rapado-González Ó, López-Cedrún JL, López-López R, Rodríguez-Ces AM, Suárez-Cunqueiro MM. Saliva gene promoter hypermethylation as a biomarker in oral cancer. *J. Clin. Med.* 2021, 10(9):1931.

[3] Tessier-Cloutier B, Pors J, Thompson E, Ho J, Prentice L, *et al.* Molecular characterization of invasive and *in situ* squamous neoplasia of the vulva and implications for morphologic diagnosis and outcome. *Mod. Pathol.* 2021, 34(2):508–518.

[4] Wang H, Guo M, Wei H, Chen Y. Targeting p53 pathways: mechanisms, structures, and advances in therapy. *Signal. Transduct. Target. Ther.* 2023, 8(1):92.

[5] Mijit M, Caracciolo V, Melillo A, Amicarelli F, Giordano A. Role of p53 in the regulation of cellular senescence. *Biomolecules* 2020, 10(3):420.

[6] Gleber-Netto FO, Neskey D, Costa AFM, Kataria P, Rao X, *et al.* Functionally impactful TP53 mutations are associated with increased risk of extranodal extension in clinically advanced oral squamous cell carcinoma. *Cancer* 2020, 126(20):4498–4510.

[7] de Bakker T, Journe F, Descamps G, Saussez S, Dragan T, *et al.* Restoring p53 function in head and neck squamous cell carcinoma to improve treatments. *Front. Oncol.* 2021, 11:799993.

[8] Gencel-Augusto J, Lozano G. p53 tetramerization: at the center of the dominant-negative effect of mutant p53. *Genes. Dev.* 2020, 34(17–18):1128–1146.

[9] Aberdam E, Roux LN, Secrétan PH, Boralevi F, Schlatter J, *et al.* Improvement of epidermal covering on AEC patients with severe skin erosions by PRIMA-1(MET)/APR-246. *Cell Death Dis.* 2020, 11(1):30.

[10] Tang Q, Lento A, Suzuki K, Efe G, Karakasheva T, *et al.* Rab11-FIP1 mediates epithelial-mesenchymal transition and invasion in esophageal cancer. *EMBO Rep.* 2021, 22(2):e48351.

[11] Pifer PM, Yang L, Kumar M, Xie T, Frederick M, *et al.* FAK drives resistance to therapy in hpv-negative head and neck cancer in a p53-dependent manner. *Clin. Cancer Res.* 2024, 30(1):187–197.

[12] Basyuni S, Nugent G, Ferro A, Barker E, Reddin I, *et al.* Value of p53 sequencing in the prognostication of head and neck cancer: a systematic review and meta-analysis. *Sci. Rep.* 2022, 12(1):20776.

[13] Bhandarkar AA, Kelly-Foleni NE, Sarkar D, Jeffs A, Slatter T, *et al.* TP53 splice mutations have tumour-independent effects on genomic stability and prognosis: an in silico study. *Int. J. Mol. Sci.* 2025, 26(24):12080.

[14] Rodriguez CP, Kang H, Geiger JL, Burtness B, Chung CH, *et al.* Clinical trial development in tp53-mutated locally advanced and recurrent and/or metastatic head and neck squamous cell carcinoma. *J. Natl. Cancer Inst.* 2022, 114(12):1619–1627.

[15] Fujihara KM, Corrales Benitez M, Cabalag CS, Zhang BZ, Ko HS, *et al.* SLC7A11 is a superior determinant of apr-246 (eprenetapopt) response than tp53 mutation status. *Mol. Cancer Ther.* 2021, 20(10):1858–1867.

[16] Valente LJ, Tarangelo A, Li A, Naciri M, Raj N, *et al.* p53 deficiency triggers dysregulation of diverse cellular processes in physiological oxygen. *J. Cell Biol.* 2020, 219(11):e201908212.

[17] Engeland K. Cell cycle regulation: p53-p21-RB signaling. *Cell Death Differ.* 2022, 29(5):946–960.

[18] Wang J, Li Z, Thomas HR, Fan K, Thompson RG, *et al.* p21, ccng1, foxo3b, and fbxw7 contribute to p53-dependent cell cycle arrest. *iScience* 2025, 28(6):112558.

[19] Lees A, McIntyre AJ, Crawford NT, Falcone F, McCann C, *et al.* The pseudo-caspase FLIP(L) regulates cell fate following p53 activation. *Proc. Natl. Acad. Sci. U. S. A.* 2020, 117(30):17808–17819.

[20] Lieschke E, Thomas AF, Kueh A, Atkin-Smith GK, Baldoni PL, *et al.* Mouse models to investigate *in situ* cell fate decisions induced by p53. *EMBO J.* 2024, 43(19):4406–4436.

[21] Boutelle AM, Attardi LD. p53 and tumor suppression: it takes a network. *Trends Cell Biol.* 2021, 31(4):298–310.

[22] Yang J, Jin A, Han J, Chen X, Zheng J, *et al.* MDMX recruits UbcH5c to facilitate MDM2 E3 ligase activity and subsequent p53 degradation *in vivo*. *Cancer Res.* 2021, 81(4):898–909.

[23] Yang J, Zhang Y. New insight into the role of MDMX in MDM2-mediated p53 degradation and anti-cancer drug development. *Oncoscience* 2021, 8:94–96.

[24] Barber AE, Meek DW. Detection of post-translationally modified p53 by western blotting. In *Post-Translational Modifications of Tumor-Related Proteins*, Cham: Springer Nature, 2021. pp. 7–18.

[25] Margiola S, Gerecht K, Müller MM. Semisynthetic ‘designer’ p53 sheds light on a phosphorylation-acetylation relay. *Chem. Sci.* 2021, 12(24):8563–8570.

[26] Wu Y, Sun Y, Xu B, Yang M, Wang X, *et al.* SCARNA10 regulates p53 acetylation-dependent transcriptional activity. *Biochem. Biophys. Res. Commun.* 2023, 669:38–45.

[27] Qi S, Cheng G, Cheng X, Xu Z, Xu B, *et al.* Targeting USP7-Mediated deubiquitination of mdm2/mdmx-p53 pathway for cancer therapy: are we there yet? *Front. Cell Dev. Biol.* 2020, 8:233.

[28] Moxley AH, Reisman D. Context is key: understanding the regulation, functional control, and activities of the p53 tumour suppressor. *Cell Biochem. Funct.* 2021, 39(2):235–247.

[29] Das R, Kundu S, Laskar S, Choudhury Y, Ghosh SK. In silico assessment of DNA damage response gene variants associated with head and neck cancer. *J. Biomol. Struct. Dyn*. 2023, 41(6):2090–2107.

[30] Osawa Y, Aoyama KI, Hosomichi K, Uchibori M, Tajima A, *et al.* Somatic mutations in oral squamous cell carcinomas in 98 Japanese patients and their clinical implications. *Cancer Treat. Res. Commun.* 2021, 29:100456.

[31] Celidonio J, Chinta S, de Armas JS, Roden D. Genetic landscape of oral cavity squamous cell carcinoma. *OTO Open* 2026, 10(1):e70194.

[32] Bizzarri AR. Conformational heterogeneity and frustration of the tumor suppressor p53 as tuned by punctual mutations. *Int. J. Mol. Sci.* 2022, 23(20):12636.

[33] Krishnan RP, Pandiar D, Ramani P, Jayaraman S. Molecular profiling of oral epithelial dysplasia and oral squamous cell carcinoma using next generation sequencing. *J. Stomatol. Oral Maxillofac. Surg.* 2025, 126(4):102120.

[34] Hu W, Feng Z. Hypothermia is a potential new therapy for a subset of tumors with mutant p53. *Cancer Res.* 2021, 81(14):3762–3763.

[35] Asl ER, Rostamzadeh D, Duijf PHG, Mafi S, Mansoori B, *et al.* Mutant P53 in the formation and progression of the tumor microenvironment: friend or foe. *Life Sci.* 2023, 315:121361.

[36] Zaidi SAA, Chughtai N, Abbassi ZA, Alam J, Malick TS, *et al.* TUSC3, p53 and p21 genetic association with development of oral submucous fibrosis and oral squamous cell carcinoma among addictive tobacco chewers of Pakistan. *BMC Oral Health* 2024, 24(1):780.

[37] Mbaye M, Mbaye F, Sembene M. Integrative computational analysis of tp53 exon 5-6 mutations in oral cavity, prostate, and breast cancers in a senegalese population. *Genes* 2026, 17(2):245.

[38] Shi L, Tao F, Liu RM, Liu QR. Correlation between high-risk TP53 mutation and extracapsular spread in oral squamous cell carcinoma (In Chinese). *Shanghai J. Stomatol.* 2019, 28(6):644–647.

[39] Xiao B, Zhao Y, Jia X, Wu J, Wang Y, *et al.* Multifaceted p21 in carcinogenesis, stemness of tumor and tumor therapy. *World J. Stem. Cells* 2020, 12(6):481–487.

[40] Meng M, Wu X, Qin T, Mo W, Long X, *et al.* Shp2 regulates the trophoblast cell cycle progression through p53–p21 pathway modulation. *Biochem. Biophys. Res. Commun.* 2025, 776:152209.

[41] Sabirzhanov B, Makarevich O, Barrett J, Jackson IL, Faden AI, *et al.* Down-regulation of mir-23a–3p mediates irradiation-induced neuronal apoptosis. *Int. J. Mol. Sci.* 2020, 21(10):3695.

[42] Mansour MA, El-Salamoni MA, Mostafa HN. Harnessing PUMA's lethal potential: BCL-2 family dynamics and novel strategies to combat cancer recurrence. *Cancer Treat. Res. Commun.* 2025, 44:100975.

[43] Yang L, Wang C, Shu J, Feng H, He Y, *et al.* Porcine epidemic diarrhea virus induces vero cell apoptosis via the p53-PUMA signaling pathway. *Viruses* 2021, 13(7):1218.

[44] Tang J, Chu G. Xeroderma pigmentosum complementation group E and UV-damaged DNA-binding protein. *DNA Repair* 2002, 1(8):601–616.

[45] Wang Y, Huang J, Lee K, Lu H, Lin Y, *et al.* Downregulation of the DNA repair gene DDB2 by arecoline is through p53's DNA-binding domain and is correlated with poor outcome of head and neck cancer patients with betel quid consumption. *Cancers* 2020, 12(8):2053.

[46] Chen H, Shan J, Qi W, Chen L, Zeng X. p53-dependent chromatin relaxation is required for DNA double-strand break repair. *Acta Biochim. Biophys. Sin.* 2025, 57(5):701–711.

[47] Wang Y, Ho TLF, Hariharan A, Goh HC, Wong Y, *et al.* Rapid recruitment of p53 to DNA damage sites directs DNA repair choice and integrity. Proc. *Natl. Acad. Sci. U. S. A.* 2022, 119(10):e2113233119.

[48] Loh SN. Follow the mutations: toward class-specific, small-molecule reactivation of p53. *Biomolecules* 2020, 10(2):303.

[49] Malhotra L, Singh A, Kaur P, Ethayathulla AS. Phenotypical mapping of TP53 unique missense mutations spectrum in human cancers. *J. Biomol. Struct. Dyn.* 2025, 43(18):10693–10706.

[50] Balasundaram A, Doss CGP. Unraveling the structural changes in the DNA-binding region of tumor protein p53 (tp53) upon hotspot mutation p53 Arg248 by comparative computational approach. *Int. J Mol. Sci.* 2022, 23(24):15499.

[51] Hyodo T, Kuribayashi N, Fukumoto C, Komiyama Y, Shiraishi R, *et al.* The mutational spectrum in whole exon of p53 in oral squamous cell carcinoma and its clinical implications. *Sci. Rep.* 2022, 12(1):21695.

[52] Li M, Sun D, Song N, Chen X, Zhang X, *et al.* Mutant p53 in head and neck squamous cell carcinoma: molecular mechanism of gain-of-function and targeting therapy. *Oncol. Rep.* 2023, 50(3):162.

[53] Chiang Y, Chien Y, Lin Y, Wu H, Lee DF, *et al.* The function of the mutant p53-R175H in cancer. *Cancers* 2021, 13(16):4088.

[54] Chachad D, Patel LR, Recio CV, Pourebrahim R, Whitley EM, *et al.* Unique transcriptional profiles underlie osteosarcomagenesis driven by different p53 mutants. *Cancer Res.* 2023, 83(14):2297–2311.

[55] Deshmukh AV, Gupta A, Chaudhari AG, Gangane NM. Correlation of p53 expression with clinical presentation and prognosis of oral squamous cell carcinoma patients: a pilot study. *Indian J. Otolaryngol. Head Neck Surg.* 2022, 74(Suppl 2):1836–1840.

[56] Brennan K, Espín-Pérez A, Chang S, Bedi N, Saumyaa S, *et al.* Loss of p53-DREAM-mediated repression of cell cycle genes as a driver of lymph node metastasis in head and neck cancer. *Genome Med.* 2023, 15(1):98.

[57] Das D, Issac AS, Sangala BN, Jerry A, Jankar A, *et al.* Longitudinal study of oral precancerous lesions: transformation rate and predictive markers for malignancy. *J. Pharm. Bioallied Sci.* 2024, 16(Suppl 3):S2555–S2557.

[58] Niculescu Talpoş IC, Rumel RC, Scurtu AD, Dinu Ş, Miron MI, *et al.* Oral squamous cell carcinomas: a histopathological review of multiple cases from Western Romania. *Rom. J. Morphol. Embryol.* 2021, 62(4):929–937.

[59] Ismail A, Choi S, Boussios S. Frontiers of ovarian carcinosarcoma. *Curr. Treat. Options Oncol.* 2023, 24(12):1667–1682.

[60] Gupta S, Pandey P, Verma S, Verma A. p16, p53 and EGFR expression in head and neck squamous cell carcinoma and their correlation with clinicopathological parameters. *J. Cancer Res. Ther.* 2024, 20(3):881–887.

[61] Ragab AE, Al-Ashmawy GM, Afify SRE, El-Feky OA, Ibrahim AO. Synergistic anticancer effects of cisplatin and phenolic aglycones of the aerial part of Rumex dentatus L. in tongue squamous cell carcinoma: insights from network pharmacology and biological verification. *BMC Complement Med. Ther.* 2025, 25(1):25.

[62] Becker AS, Merkel J, Bozkurt I, Strüder DF, Maletzki C, *et al.* p16 overexpression identifies oncogenic high-risk HPV infection in non-oropharyngeal squamous cell carcinoma of the head and neck. *Head Neck* 2024, 46(10):2569–2581.

[63] Csurgay K, Zalatnai A, Benczik M, Csomó BK, Horváth F, *et al.* A Study of prognostic factors in young patients with non-HPV oral cancer in central Europe. *Pathol. Oncol. Res.* 2021, 27:1609991.

[64] Wan Z, Zheng Z, Huang M, Chen Y, Yao L. Expression of Ki-67, Cyclin D1, P53, and p16 in patients with oral leukoplakia and leukoplakia cancerization with spicy diet in Chengdu. *West China J. Stomatol.* 2021, 39(4):434–440.

[65] Shah HD, Saranath D, Murthy V. A molecular dynamics and docking study to screen anti-cancer compounds targeting mutated p53. *J. Biomol. Struct. Dyn.* 2022, 40(6):2407–2416.

[66] Gong K, Lin J, Chen X, Duan Y, Zhang J, *et al.* Thermosensitive gel-nano system against esophageal cancer via restoring p53 activity and boosting T-cell immunity. *J. Control. Release* 2024, 371:111–125.

[67] Lin S, Wu H, Yeh L, Yang C, Kao S, *et al.* Activation of the miR-371/372/373 miRNA cluster enhances oncogenicity and drug resistance in oral carcinoma cells. *Int. J. Mol. Sci.* 2020, 21(24):9442.

[68] Bogani G, Monk BJ, Coleman RL, Vergote I, Oakin A, *et al.* Selinexor in patients with advanced and recurrent endometrial cancer. *Curr. Probl. Cancer* 2023, 47(6):100963.

[69] He W, Zhang Z, Yang W, Zheng X, You W, *et al.* Turing milk into pro-apoptotic oral nanotherapeutic: de novo bionic chiral-peptide supramolecule for cancer targeted and immunological therapy. *Theranostics* 2022, 12(5):2322–2334.

[70] Kong A, Mehanna H. WEE1 Inhibitor: clinical development. *Curr. Oncol. Rep.* 2021, 23(9):107.

[71] Al-Jamaei AH, de Visscher J, Subramanyam VR, Forouzanfar T, Sminia P, *et al.* WEE1 kinase inhibitor MK-1775 sensitizes oral tongue squamous cell carcinoma cells to radiation irrespective of TP53 status. *Oral Dis.* 2023, 29(7):2640–2649.

[72] Oza AM, Estevez-Diz M, Grischke EM, Hall M, Marmé F, *et al.* A biomarker-enriched, randomized phase ii trial of adavosertib (AZD1775) plus paclitaxel and carboplatin for women with platinum-sensitive TP53-mutant ovarian cancer. *Clin. Cancer Res.* 2020, 26(18):4767–4776.

[73] Diab A, Gem H, Swanger J, Kim HY, Smith K, *et al.* FOXM1 drives HPV+ HNSCC sensitivity to WEE1 inhibition. *Proc. Natl. Acad. Sci. U. S. A.* 2020, 117(45):28287–28296.

[74] Harata S, Suzuki T, Takahashi H, Hirokawa T, Kato A, *et al.* AZD6738 promotes the tumor suppressive effects of trifluridine in colorectal cancer cells. *Oncol. Rep.* 2023, 49(3):52.

[75] Choi EK, Kim HD, Park EJ, Song SY, Phan TT, *et al.* 8-Methoxypsoralen induces apoptosis by upregulating p53 and inhibits metastasis by downregulating MMP-2 and MMP-9 in human gastric cancer cells. *Biomol. Ther.* 2023, 31(2):219–226.

[76] Ferretti S, Hamon J, de Kanter R, Scheufler C, Andraos-Rey R, *et al.* Discovery of WRN inhibitor HRO761 with synthetic lethality in MSI cancers. *Nature* 2024, 629(8011):443–449.

[77] Sheng Y, Wu B, Li F, Zhang C. Design, synthesis, and biological evaluation of procaine-based triazole-isoxazoline hybrids as selective PI3K/mTOR inhibitors for esophageal cancer therapy: *in vitro* and *in vivo* studies. *RSC Med. Chem.* 2026.

[78] Mortezagholi B, Nasiri K, Movahed E, Dadgar E, Nejati ST, *et al.* MiR-34 by targeting p53 induces apoptosis and DNA damage in paclitaxel-resistant human oral squamous carcinoma cells. *Chem. Biol. Drug Des.* 2023, 102(2):285–291.

[79] Shi Y, Xie T, Wang B, Wang R, Cai Y, *et al.* Mutant p53 drives an immune cold tumor immune microenvironment in oral squamous cell carcinoma. *Commun. Biol*. 2022, 5(1):757.

[80] Shi Y, Xie TX, Leach DG, Wang B, Young S, *et al.* Local anti-PD-1 delivery prevents progression of premalignant lesions in a 4NQO-oral carcinogenesis mouse model. *Cancer Prev. Res.* 2021, 14(8):767–778.

[81] Cui D, Qiao W, Chen W, Li P, Wang S, *et al.* Anti-tumor immunotherapy of scutellaria baicalensis-derived vesicles on immune checkpoint modulation in colorectal cancer. *Aging. Dis.* 2026.

[82] Qi W, Xi D, Bai Y, Liu L, Ma Y, *et al.* Case report: chemotherapy-free treatment with camrelizumab and anlotinib for elderly patients with KRAS and TP53 mutated advanced lung cancer. *Front. Pharmacol.* 2023, 14:1026135.

[83] Agarwal VK, Sharma R, Gahlot G, Arnav A. Clinical and histopathological correlation of p16 and p53 expression in oral cancer. *Indian J. Surg. Oncol.* 2021, 12(Suppl 1):164–168.

[84] Martín-Lozano G, Gómez-Díaz R, Iglesías-Martín F, Torres-Lagares D, Gutiérrez-Corrales A, *et al.* Mutations in p53 gene exons in a sample from the south of spain in oral cancer. *J. Clin. Exp. Dent.* 2021, 13(10):e1001–e1005.

[85] Singh RD, Patel KA, Patel JB, Patel PS. Alterations in p53 Influence hTERT, VEGF and MMPs expression in oral cancer patients. *Asian Pac. J. Cancer Prev.* 2022, 23(9):3141–3149.

[86] Hirokawa S, Araki K, Yamashita T, Uno K, Tomifuji M, *et al.* The value of serum p53 antibody as a biomarker in oral and pharyngeal squamous cell carcinoma. *Acta Otolaryngol.* 2023, 143(1):85–90.

[87] Sun L, Gao X, Wang M, Zhang Y, Sun R, *et al.* Gobal crotonylome reveals that HNRNPC and its crotonylation promote p53-deficient tumor growth by stabilizing CCND1 and MCM3 mRNAs. *Cancer Lett.* 2025, 628:217854.

[88] Zhao H, Park YM, Zheng Y, Mao Q, Collet C, *et al.* Genetically defined organoid models reveal mechanisms driving squamous cell neoplastic evolution and identify potential therapeutic vulnerabilities. *BioRxiv* 2025.

[89] Doerfler R, Chen J, Kim C, Smith JD, Harris M, *et al.* Integrating artificial intelligence-driven digital pathology and genomics to establish patient-derived organoids as new approach methodologies for drug response in head and neck cancer. *Oral Oncol.* 2025, 171:107742.

[90] Kang Y, Yang W, Chae WS, Kim DW, Kim SG, *et al.* Administration of 4-hexylresorcinol increases p53-mediated transcriptional activity in oral cancer cells with the p53 mutation. *Oncol. Rep.* 2022, 48(3):1–10.

[91] Chang C, Islam A, Liu P, Zhan J, Chueh P. Capsaicin acts through tNOX (ENOX2) to induce autophagic apoptosis in p53-mutated HSC-3 cells but autophagy in p53-functional SAS oral cancer cells. *Am. J. Cancer Res.* 2020, 10(10):3230–3247.

[92] Liang Y, An Q, Song H, Tang Y, Xiao S, *et al.* AcGlcAs: a novel P53-targeting arsenical with potent cellular uptake and cancer cell selectivity. *J. Med. Chem.* 2023, 66(24):16579–16596.

[93] Gollner A, Rudolph D, Weyer-Czernilofsky U, Baumgartinger R, Jung P, *et al.* Discovery and characterization of brigimadlin, a novel and highly potent MDM2-p53 antagonist suitable for intermittent dose schedules. *Mol. Cancer Ther.* 2024, 23(12):1689–1702.

[94] Fece de la Cruz F, Varkaris A, Patel PS, Kushner EW, Morales-Giron AA, *et al.* Acquired on-target alterations drive clinical resistance to p53-Y220C reactivators. *Cancer Discovery* 2026, 16(4):677–685.

[95] Papavassiliou KA, Vassiliou AG, Papavassiliou AG. Rezatapopt: a promising small-molecule "refolder" specific for TP53(Y220C) mutant tumors. *Neoplasia* 2025, 67:101201.

[96] Arvindh S, Priyadarshini M, Baba AB, Veeravarmal V, Mishra R, *et al.* The neem limonoid nimbolide modulates key components of the DNA damage response signalling in cellular and animal models of oral squamous cell carcinoma. *Curr. Pharm. Biotechnol.* 2025, 26(3):428–442.

[97] Zhang R, Hou F, Gan J, Zhang L, Yang D, *et al.* Metformin-induced E6/E7 inhibition prevents HPV-positive cancer progression through p53 reactivation. *Anticancer Drugs* 2025, 36(6):468–477.