Review Article

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P53 gene – A salivary biomarker in Oral cancer detection.

Abstract:
Oral cancer remains a major global health burden, with late-stage diagnosis contributing significantly to poor prognosis and high mortality. The identification of reliable, non-invasive biomarkers is crucial for early detection and improved patient outcomes. Among molecular markers, the tumor suppressor gene p53 has emerged as a pivotal candidate due to its central role in regulating cell cycle, apoptosis, and genomic stability. Mutations or altered expression of p53 are frequently observed in oral squamous cell carcinoma (OSCC), making it a promising diagnostic and prognostic indicator. Saliva, as a diagnostic fluid, offers unique advantages: it is easily accessible, non-invasive, and contains a wide array of molecular constituents reflective of systemic and local pathological changes. Recent advances in salivary diagnostics have demonstrated that p53 mutations and protein alterations can be detected in saliva samples of oral cancer patients, correlating with disease progression and severity. The integration of salivary p53 analysis into clinical practice could revolutionize oral cancer screening by enabling early detection, monitoring therapeutic response, and predicting recurrence risk. Furthermore, salivary-based assays are cost-effective and patient-friendly, enhancing their applicability in large-scale population screening programs. This abstract highlights the potential of p53 as a salivary biomarker, emphasizing its clinical relevance in oral cancer detection and the transformative impact of saliva-based molecular diagnostics in oncology.

Key-words: p53 gene; salivary biomarker; oral cancer; oral squamous cell carcinoma; early detection; tumor suppressor; non-invasive screening; prognosis.

Introduction:

Oral cancer represents a major global public health challenge, with incidence and mortality rates continuing to rise across populations. This growing burden underscores the urgent need for innovative strategies in screening and early detection, which remain critical to reducing disease-related morbidity and mortality. Among the available approaches, molecular biomarkers have emerged as highly promising tools for improving the accuracy of diagnosis, staging, prognosis, and post-treatment monitoring.[1]

A unique advantage in oral cancer lies in its anatomical location within the oral cavity, which allows direct interaction between tumor lesions and saliva. This proximity makes saliva an attractive and non-invasive alternative to serum or tissue sampling for biomarker analysis. Saliva contains DNA, RNA, and protein molecules shed from cancer cells, providing a convenient medium for detecting tumor-specific alterations. Consequently, salivary biomarkers offer significant potential for early diagnosis, prognostication, and therapeutic monitoring.

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Advances in post-genomic technologies, including high-throughput genomic and proteomic platforms, have facilitated the identification of altered gene and protein expression profiles in the saliva of oral cancer patients. Among these, TP53 alterations are particularly noteworthy, as they occur early and frequently in oral carcinogenesis. Mutant TP53 DNA fragments, aberrant p53 protein, p53-associated RNAs, and autoantibodies have all been recognized as

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promising salivary analytes for cancer detection and disease surveillance.[1,2]

Mutations in TP53 occur in over 50% of human cancers, including lung, breast, colorectal, and ovarian malignancies, often leading to loss of tumor-suppressive function or gain-of-function oncogenic effects. The p53 gene, encoding the TP53 protein dubbed the "guardian of the genome," serves as a critical tumor suppressor frequently mutated in oral squamous cell carcinoma (OSCC), the predominant form of oral cancer, with salivary detection emerging as a non-invasive diagnostic avenue. Saliva, enriched with tumor-derived biomarkers via genomic DNA shedding from OSCC lesions, enables early p53 mutation and autoantibody (p53-AAb) profiling, surpassing traditional biopsies in accessibility and patient compliance. This review examines p53's molecular role, salivary biomarker validation studies, and clinical translation potential for OSCC screening in high-risk populations like tobacco users.[1,2]

P53 discovery:

- **Historical milestone**: p53 was first identified in the late 1970s as a 53-kDa cellular protein that associated with viral oncoproteins. Early work alternately characterized it as an oncogene and a tumor suppressor until functional studies in the 1980s–1990s established TP53 as a guardian of genomic integrity and a bona fide tumor suppressor gene.[3]

- **Clinical relevance**: Mutational inactivation of TP53 is among the most common genetic events across cancers, including OSCC, where TP53 mutations often appear in premalignant lesions and invasive tumors, linking p53 alterations to both initiation and progression of oral malignancy.[4]

P53 Structure & Function:

- **Gene and protein architecture:**

  - TP53 encodes a 393–amino-acid transcription factor with discrete functional domains: the N-terminal transactivation domain, a proline-rich region, the central DNA-binding domain (hotspot for pathogenic mutations), an oligomerization domain, and a C-terminal regulatory domain.[5] (Figure 1)

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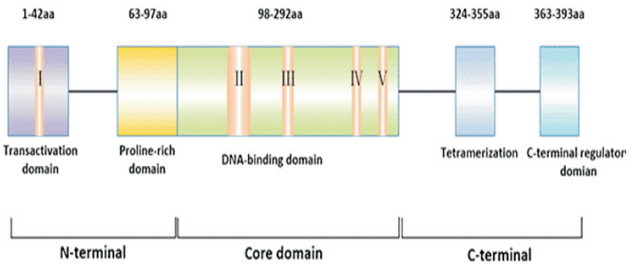

Figure 1- Structure of P53 gene.

- **Molecular activities:**

  - p53 functions primarily as a sequence-specific transcription factor that regulates genes involved in cell-cycle arrest, apoptosis, senescence, DNA repair, metabolism, and antioxidant responses.

  - p53 forms tetramers for DNA binding; post-translational modifications (phosphorylation, acetylation, ubiquitination) tightly regulate stability and activity.

Functions of P53: Diversity and Complexity:

- **Canonical tumor-suppressive programs:**

  - Induction of cell-cycle arrest (e.g., via p21) to allow DNA repair.
  - Activation of apoptosis through transcriptional upregulation of pro-apoptotic genes (e.g., BAX, PUMA).
  - Stimulation of DNA repair pathways and maintenance of genomic stability.[7]

- **Noncanonical and context-dependent roles:**

  - Metabolic reprogramming: p53 modulates glycolysis, oxidative phosphorylation, and lipid metabolism to influence cell fate under stress.
  - Regulation of autophagy and senescence: p53 can invoke protective or deleterious programs depending on cellular context and stress severity.
  - Crosstalk with immune signaling: p53 regulates cytokines, chemokines, and antigen presentation machinery, shaping anti-tumor immunity.

- **Complexity from mutation and isoforms:**

  - Mutant p53 proteins may acquire novel interactions and transcriptional programs that promote invasion, metastasis, and therapy resistance.
  - Alternative splicing and isoform diversity add regulatory layers that influence p53 output in tissue- and stress-specific ways.

Mutational inactivation of P53-

TP53 mutations are a hallmark of human oral cancer pathogenesis, particularly in oral squamous cell carcinoma (OSCC), where they occur in 70-80% of cases, disabling the p53 tumor suppressor's ability to halt cell cycle progression, repair DNA, or trigger apoptosis after damage from tobacco, alcohol, or HPV.[6]

Mutation Prevalence

TP53 mutations are highest in tumors of the larynx (83.5%), hypopharynx, and oral cavity (75.6%), but lower in HPV-positive oropharyngeal sites (28.6%). These mutations often lead to loss-of-function or gain-of-function effects, promoting tumor growth, invasion, and therapy resistance.[7]

Key Pathogenic Steps

The process unfolds sequentially:

- **Initiation**: Mutagens cause TP53 mutations (e.g., R172H, T122N), disabling DNA damage response and apoptosis.[7]
- **Promotion**: Mutant p53 gains oncogenic functions, activating PI3K/AKT/mTOR and MAPK pathways for survival and proliferation; interacts with RB and WNT/β-catenin pathways.[6]
- **Progression**: Enhances invasion, angiogenesis, and metastasis, with high prevalence (70-80%) in oral cavity tumors linked to tobacco/alcohol.[8](Figure 2)

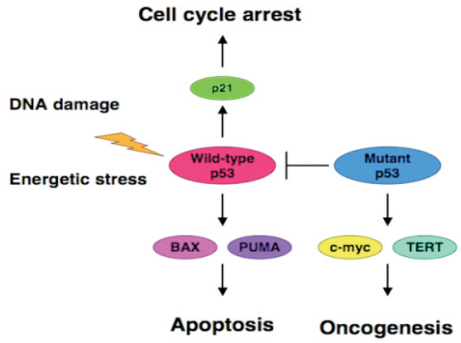

Figure 2- Cell cycle arrest pathway of P53 mutation

Analytical approaches to detect TP53 in saliva:

Analytical approaches for detecting TP53 alterations in saliva provide a promising non-invasive strategy for risk assessment and early detection of oral cancer. These methods target mutant TP53 DNA, p53 protein or antibodies, exosomal nucleic acids, and epigenetic changes within the p53 pathway.[6]

1. Salivary circulating tumor DNA (ctDNA) – mutant Tp53

Targeted analysis of salivary ctDNA focuses on somatic TP53 mutations using amplicon-based next-generation sequencing (NGS), targeted deep sequencing, and droplet digital PCR (ddPCR). Tumor-matched TP53 assays achieve high analytical specificity, and ddPCR in particular provides very low limits of detection for known hotspot variants, enabling sensitive liquid-biopsy monitoring in oral squamous cell carcinoma (OSCC). However, the fraction of tumor-derived DNA in saliva is highly variable, and optimal sensitivity often requires prior knowledge of the dominant TP53 mutation or broad sequencing panels to capture the heterogeneous mutation spectrum.[9]

2. Salivary p53 protein and autoantibody assays:

Protein-based assays, including enzyme-linked immunosorbent assays (ELISA), multiplex bead-based immunoassays, and immunoaffinity enrichment combined with mass spectrometry, have been used to quantify p53 or p53-related markers in saliva. These approaches provide direct evidence of pathway perturbation and can be implemented using relatively straightforward laboratory workflows; p53-specific autoantibody ELISAs have shown higher salivary positivity in OSCC patients compared with healthy or tobacco-exposed controls. Nevertheless, wild-type p53 is typically low-abundance and structurally unstable in extracellular fluids, while mutant p53 predominantly accumulates intracellularly and may not be efficiently released, and enzymatic degradation plus variable total salivary protein content complicate accurate quantification.[10]

3. Exosomal TP53 mRNA and p53-regulated cargo:

Isolation of salivary extracellular vesicles followed by RT-qPCR or RNA sequencing allows detection of TP53 transcripts and downstream p53-regulated microRNAs within exosomes. Because the lipid bilayer protects nucleic acids from degradation, exosomal cargo can more faithfully mirror the tumor transcriptome, and several exosomal miRNAs targeting TP53 have emerged as candidate prognostic markers in head and neck cancer. However, pre-analytical and analytical heterogeneity in vesicle isolation, together with dilution of tumor-derived vesicles by abundant non-neoplastic exosomes, can limit reproducibility and necessitates rigorous standardization.[11]

4. DNA methylation and multi-marker panels involving Tp53-

Bisulfite conversion followed by methylation-specific PCR or sequencing enables interrogation of promoter methylation in TP53 pathway components and broader tumor-specific methylation signatures in salivary DNA. Such epigenetic alterations may be more consistent across individuals than single TP53 point mutations and are compatible with highly sensitive PCR-based assays amenable to clinical workflows. Nonetheless, diagnostic specificity is highly dependent on the choice of methylation markers, and extensive validation in large, ethnically diverse cohorts is required before clinical implementation.[12]

Clinical evidence and diagnostic performance:

- Detection of TP53 mutations and p53-related signals in saliva has been reported in multiple small to medium-sized cohorts. Studies show proof-of-principle that tumor-matched TP53 mutations can be recovered from saliva, and elevated salivary p53-related signals are associated with OSCC in many reports.[7]
- Reported sensitivity and specificity vary widely across studies due to differences in patient selection (stages, tumor size), saliva type (whole, supernatant, stimulated/unstimulated), collection and storage conditions, nucleic-acid extraction methods, and analytical platforms.[8]
- The most consistent finding across the literature is higher positive yield in patients with larger or ulcerated tumors and in post-operative surveillance when tumor burden is higher. Performance for detecting small, early-stage lesions remains limited but promising when ultra-sensitive assays and multimarker panels are used.[9]
- Overall, TP53 alone rarely achieves clinical-grade sensitivity as a single marker; combining TP53 mutation detection with other genomic, epigenomic, or proteomic markers improves discriminatory power.[9]

Pre-analytical and analytical challenges:

- **Pre-analytical variability:** collection method (stimulated vs. unstimulated saliva), time of day, oral hygiene, food intake, and use of mouthwash markedly affect yield and background.[13]
- **Matrix complexity:** saliva contains abundant host DNA/RNA, microbial nucleic acids, proteases, and inhibitors that can reduce assay sensitivity.[14]
- **Low tumor fraction and heterogeneity:** early tumors shed little DNA; TP53 mutation spectra are highly diverse across patients, requiring broad panels or tumor-informed assays.[15]
- **Assay sensitivity and specificity:** deep sequencing reduces false negatives but risks false positives from sequencing artefacts or clonal hematopoiesis; ddPCR requires prior mutation knowledge.[13]
- **Standardization and reproducibility:** lack of consensus on sample stabilization, extraction protocols, internal controls, and cutoffs limits interstudy comparability.[13,14]
- **Clinical validation gaps:** many published studies are retrospective, single-center, or small; prospective, blinded, multicenter validations are scarce.[14,15]

The Role of P53 to regulate tumor micro environment:

- **Immune modulation:**
  - Wild-type p53 promotes anti-tumor immunity by enhancing antigen presentation, reducing immunosuppressive cytokines, and supporting immune cell recruitment. Conversely, mutant p53 can foster an immunosuppressive milieu via upregulation of pro-tumor cytokines and recruitment of regulatory cells.[16]
- **Stromal interactions:**
  - p53 status in tumor cells influences stromal fibroblast activation, extracellular matrix remodeling, and angiogenesis. Loss of p53 or gain-of-function mutants can induce cancer-associated fibroblast phenotypes and pro-angiogenic signaling.[17]
- **Inflammation and oxidative stress:**
  - p53 attenuates chronic inflammatory signaling and oxidative damage; its dysfunction amplifies inflammatory cascades that facilitate tumor progression.[17]
- **Metastatic niche and invasion:**
  - Mutant p53 contributes to epithelial–mesenchymal transition (EMT), secretion of proteases, and extracellular vesicle cargo that primes distant niches for metastasis.[18]
- **Implication for saliva-based biomarkers:**
  - Microenvironmental changes driven by p53 status (e.g., increased shedding, necrosis, exosome release) can modulate the quantity and quality of tumor-derived analytes in saliva, affecting assay sensitivity and temporal dynamics.[18,19]

P53 in Physiology and Pathology: Guardian Is an All-Rounder:

- **Homeostatic roles:**
  - Beyond tumor suppression, p53 maintains tissue homeostasis through roles in development, stem cell regulation, metabolic balance, and response to physiological stressors. Its transient activation facilitates tissue repair without inducing permanent growth arrest.[20,21,22]
- **Pathological consequences of dysregulation:**
  - Loss or mutation of p53 contributes to unchecked proliferation, genomic instability, impaired apoptosis, metabolic shifts favoring survival, and therapy resistance. In oral epithelium, TP53 alterations commonly mark progression from dysplasia to carcinoma.[21,22]

- **Duality in therapy and aging:**

  - Chronic p53 activation can accelerate tissue aging and impair regenerative capacity, illustrating a trade-off between tumor suppression and organismal maintenance. This balance complicates therapeutic strategies that modulate p53 activity systemically.[23,24]

Targeting P53 for Disease Treatment: All roads lead to Health:

- **Therapeutic strategies:**

  - Reactivating wild-type p53 pathways in tumors: small molecules that restore mutant p53 conformation/function or disrupt negative regulators (e.g., MDM2 inhibitors) to stabilize endogenous p53.
  - Exploiting synthetic lethality: targeting vulnerabilities selectively lethal in TP53-deficient contexts (e.g., cell-cycle checkpoint inhibitors).
  - Immunotherapeutic approaches: vaccines or adoptive strategies targeting neoantigens generated by p53 mutations and harnessing anti-p53 immune responses.
  - Gene therapy and peptide-based strategies: delivery of wild-type TP53, p53-mimetic peptides, or modulators of p53 isoforms.[25]

- **Relevance to oral cancer and saliva diagnostics:**

  - p53-targeted therapies that reduce tumor burden should be monitorable via salivary analytes (mutant ctDNA decline, change in exosomal cargo, disappearance of anti-p53 antibodies). Conversely, saliva assays may identify candidates for p53-directed therapies by confirming tumor p53 status noninvasively.[26]

- **Challenges and safety:**

  - Tumor heterogeneity, dominant-negative mutants, and systemic toxicity pose hurdles. Restoring p53 in non-malignant tissues carries aging or degenerative risks; selective delivery and tumor-specific activation are active research priorities.[27]

Analytical and clinical pathway for salivary p53 assays:

- **Sample collection best practices:**

  - Standardize collection (unstimulated saliva preferred unless justified), instruct patients on pre-collection abstinence (food, smoking, dental hygiene), collect

    atconsistent times, and use validated stabilizers or immediate processing to preserve nucleic acids and proteins.[28]

- **Assay selection and design**

  - For mutant TP53 detection: tumor-informed ddPCR or targeted deep sequencing with unique molecular identifiers (UMIs) to minimize artefacts and increase sensitivity. For protein/antibody detection: validated ELISA or multiplex platforms with spike-in controls and matrix-matched calibrators. Exosomal assays require standardized vesicle isolation or capture workflows.[30]

- **Clinical validation:**

  - Prospective, blinded studies in well-defined cohorts (high-risk populations, symptomatic patients, post-treatment surveillance groups) comparing salivary results to gold-standard histopathology and matched tumor sequencing. Define clinically meaningful endpoints (early-stage detection rate, lead-time, recurrence detection).[28,30]

- **Interpretation and integration:**

  - Use multimodal panels combining TP53 mutation, methylation signals, and protein/antibody markers to improve sensitivity and specificity. Integrate saliva results with clinical exam and imaging; treat salivary assays as adjunctive tools that may triage patients for biopsy or more intensive surveillance.[29,30]

Clinical Applications:

- **Early detection**: Salivary p53 testing could identify precancerous lesions before clinical manifestation.
- **Screening tool**: Potential for community-level screening in high-risk populations (e.g., tobacco users)
- **Prognosis**: Salivary p53 mutations may predict recurrence or metastasis.
- **Therapeutic monitoring**: Dynamic changes in salivary p53 levels could reflect treatment response.

Future directions and research priorities:

- Harmonize pre-analytical SOPs for saliva collection, stabilization, and storage to reduce interstudy variability.[20]
- Develop regulatory-grade, multiplexed saliva assays that combine mutant ctDNA, methylation markers, exosomal RNAs, and protein/autoantibody signals, validated in multicenter prospective trials.[31]
- Explore tumor-informed approaches where tumor tissue sequencing guides personalized saliva assays for surveillance and minimal residual disease detection.[13]
- Investigate biological determinants of salivary shedding (tumor size, ulceration, location) to model detection probability and optimize sampling timing.[13]

- Assess cost-effectiveness and implementation pathways in low- and middle-income settings where noninvasive screening could have major public-health impact.[24]
- Study the kinetics of salivary p53 analytes during treatment to define thresholds for response and early relapse detection.[32]

Challenges and Limitations:

- **Sensitivity and specificity**: Variability in detection methods may affect accuracy.
- **Standardization**: Lack of uniform protocols for saliva collection and analysis.
- **Biological variability**: Saliva composition influenced by diet, oral hygiene, and systemic conditions
- **Clinical translation**: Need for large-scale validation studies before routine use.

Conclusion:

TP53 represents a biologically robust and clinically pertinent candidate for salivary biomarker development in oral cancer. By integrating multiple p53-related salivary analytes—including mutant circulating tumor DNA, p53 protein or autoantibodies, and exosomal p53-axis RNAs—future multimodal panels may achieve the sensitivity and specificity required for non-invasive early detection and longitudinal monitoring. To translate these concepts into practice, stringent pre-analytical standardization, analytically ultra-sensitive and clinically validated assays, and large, prospective studies in diverse at-risk populations are essential. With such coordinated translational efforts, p53-based salivary diagnostics have the potential to complement existing clinical and imaging pathways, enabling earlier diagnosis, refining risk stratification, and improving treatment guidance and surveillance in oral oncology.

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