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THE SALIVARY BLUEPRINT OF ORAL CANCER: FROM MOLECULAR CLUES TO CLINICAL APPLICATION

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ABSTRACT

Oral squamous cell carcinoma (OSCC), which is the most prevalent malignancy in the oral cavity, poses a significant health challenge globally due to its high rates of mortality and morbidity. Despite considerable progress in both diagnostic and treatment methods, the survival rates for patients with OSCC have not seen significant improvement over the years. Recent developments in multi-omics technologies have enabled a deeper exploration of salivary components, including DNA, RNA, proteins, metabolites, and extracellular vesicles, which can provide insights into localized tumor behaviour and broader physiological changes in the body. This review summarizes the current evidence related to various types of salivary biomarkers in OSCC, including proteomic, transcriptomic, genomic, epigenetic, metabolomic, and microbial markers. Furthermore, it addresses the clinical implications, challenges, and future potential of saliva-based diagnostics, emphasizing how saliva omics could transform the early detection and continuous monitoring of OSCC.

KEYWORDS: Genomics, Metabolomics, Microbiomics, Proteomics, Salivary biomarker, Transcriptomics.

INTRODUCTION

Oral cancer ranks as the most prevalent malignancy in the head and neck area, with around 90% of cases identified as squamous cell carcinoma histologically.[1] Even with advancements in treatment options, many individuals are still diagnosed at later stages, and there has been little enhancement in the overall 5-year survival rate for patients with OSCC.[2] Currently, the identification of OSCC largely relies on expert clinical evaluations and histopathological assessments of questionable lesions. Saliva, which directly interacts with the oral mucosa and neoplastic lesions, contains enzymes, hormones, antibodies, antimicrobial substances, and cytokines, all of which are found in blood and make their way into saliva through various mechanisms. These biomarkers present a hopeful avenue for the early detection of OSCC. Utilizing saliva for diagnostics could decrease the need for invasive biopsies. The identification and validation of these biomarkers hold significant potential for facilitating early detection, improving diagnostic accuracy, enhancing treatment outcomes, and thereby increasing the overall survival rates of OSCC patients.[3]

Use of saliva for biomarker detection is an easy, non invasive and inexpensive method with minimum risk of cross-contamination. However levels of certain biomarkers are not reliable always compared to those in serum. Also, the composition of saliva may depend upon the time and method of saliva collection, degree of salivary flow stimulation and salivary pH.[4,5]

Types of salivary biomarkers

Classification of salivary biomarkers can be based on various factors. These diagnostic markers may appear at different stages of cancer progression and can be specific to certain tissues, cancer stages, patient follow-up, recurrence, or age groups. Although there is a strong demand to establish a standardized classification system for salivary biomarkers in OSCC, the scientific community has yet to reach a consensus.[6]

With ongoing advances in saliva omics, numerous studies have identified over 100 potential salivary biomarkers relevant to OSCC. These biomolecules reach saliva predominantly through local release from the oral lesion itself, whether OSCC or oral potentially malignant disorders (OPMD). A small proportion is secreted into saliva via systemic circulation in response to the tumor. The pathological changes in tissue manifest across genomic, proteomic, and metabolomic levels. The field of saliva omics encompasses six core diagnostic areas: salivary proteomics, genomics, transcriptomics, metabolomics, microbiomics, and methylomics[5,7] (Figure 1).

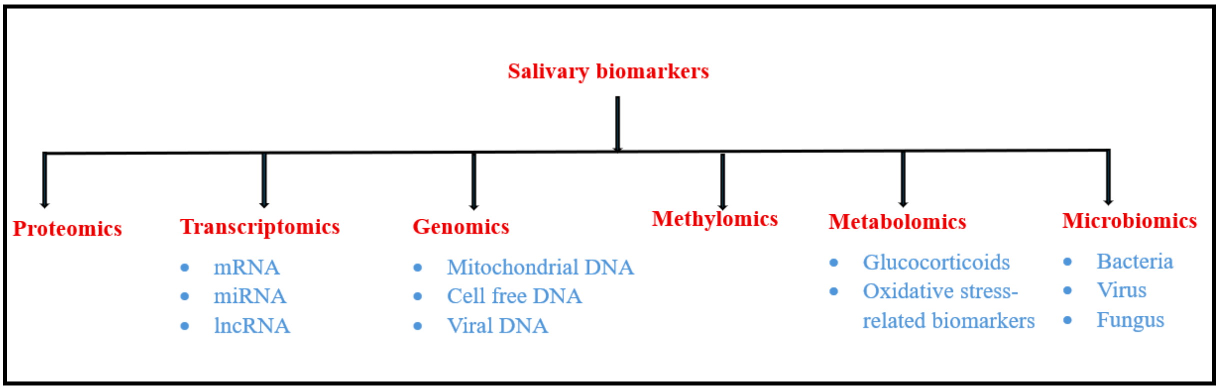

Figure 1: Different types of salivary biomarkers in OSCC.

Salivary Proteomics

Proteomic analysis is a promising method for identifying biomarkers specific to OSCC because proteins are essential to cellular activity. Recent research demonstrated the possibility for early detection by protein profiling by using sophisticated mass spectrometry-based quantitative proteomics to saliva from individuals with premalignant lesions. Several protein markers, such as interleukins (IL-6, IL-8, IL-1β), matrix metalloproteinases (MMP-2, MMP-9), transforming growth factor-1, Ki-67, cyclin-D1, Cyfra-21.1, transferrin, α-amylase, tumor necrosis factor alpha (TNF-α), and catalase, have been linked to oral squamous cell carcinoma (OSCC) by salivary proteomics.[8]

The aggressiveness and severity of oral squamous cell carcinoma (OSCC) have been associated with cytokines such as IL-6, IL-8, and IL-1RA. In addition, research indicates that patients with OSCC have significantly elevated levels of these markers compared to healthy control individuals.[9] The processes of tumor invasion and metastasis are largely affected by matrix metalloproteinases (MMPs), which break down the extracellular matrix and basement membrane. Stromal cells surrounding the invasive edges of metastasizing tumors show elevated levels of these proteins. A recent investigation found that MMP transcripts are overexpressed in OSCC, with both MMP-1 and MMP-9 linked to the progression from dysplasia to cancer.[10]

Cytoskeletal proteins such as actin and myosin were found to be increased in the saliva of patients with malignant neoplasms, likely because of their abundance in the exfoliated OSCC cells.[11] Jou et al. reported increased salivary transferrin level in OSCC patients, suggesting salivary transferrin is a biomarker of early-stage OSCC. Elevated transferrin levels also showed a significant correlation with tumor size and clinical stage.[12] A distinct expression of the protein biomarker telomerase was noted by Zhong et al. Compared to a positive rate of 6.67% in healthy individuals, telomerase activity was observed in 75% of patients with oral squamous cell carcinoma, indicating a statistically significant difference.[13] The immunoblot analysis of saliva samples from OSCC patients showed notably elevated levels of tissue polypeptide antigen, cancer antigen 125, and the cytokeratin 19 fragment Cyfra21-1. Azurophil granules in polymorphonuclear leukocytes contain peptide molecules known as defensins, which possess both cytotoxic and antibacterial functions. Research has indicated that the concentrations of salivary defensin-1 are higher in patients with OSCC compared to healthy individuals, and this increase has been linked to the presence of tumorigenic cells.[14,15]

Salivary Genomics

Molecular genetic investigations of head and neck squamous carcinoma (HNSC) have revealed frequent alterations in particular chromosomal regions, especially 3p, 9p, 8p, and 17p, in both premalignant and malignant lesions. These alterations signify early events in carcinogenesis, and their identification in oral fluids presents a potential non-invasive approach for early diagnosis, risk evaluation, and monitoring. These include p53, mitochondrial DNA, cell free DNA, viral DNA etc.[16]

Mitochondrial DNA (mtDNA) has its function influenced by both the number of copies in its genome and its molecular integrity. As the number of mitochondria changes with the energy needs of the cell, any damage that affects respiratory function—whether it's genetic or environmental—can give tumor cells a growth advantage. High levels of mtDNA may show a response to problems with respiration. This matches earlier findings that connected oxidative stress to increases in mtDNA. The link between high salivary mtDNA, advanced tumor stages, and more tumor-derived mtDNA supports the idea that salivary mtDNA shows genetic material from tumors that ends up in the upper aerodigestive tract.[17]

The p53 tumor suppressor gene, found on chromosome 17p, plays a vital role in maintaining genomic stability. Its loss of function is commonly seen in head and neck cancers. Research conducted by Liao et al. discovered mutations at codon 63 in exon 4 of the p53 gene present in the saliva of 62.5% of patients diagnosed with oral squamous cell carcinoma (OSCC), in contrast to just 18.5% of healthy subjects. These findings indicate that analyzing p53 mutations in saliva could serve as an effective biomarker for the diagnosis of OSCC.[18]

CfDNA (cell free DNA) is a type of DNA present in the bloodstream that originates from healthy cells, cancerous cells, or cells in the tumor's microenvironment, resulting from different cellular activities like oncosis, netosis, active secretion, apoptosis, necrosis, and phagocytosis. There are only a few studies available regarding the significance of salivary cfDNA in OSCC.[19] HPV genomic DNA can be readily detected in saliva or oral scrapingscan identify individuals at elevated risk and supports screening of OPMD patients and partners of affected individuals.[20]

Salivary Transcriptomics

Saliva contains proteins and nucleic acids, creating what can be referred to as the “second diagnostic alphabet.” While RNA is typically unstable and subject to degradation by RNases, salivary RNAs are preserved since they are encapsulated within exosomes. These membrane-bound vesicles, measuring between 30 to 100 nm and abundant in mRNA and miRNA, originate from the endoplasmic reticulum and aid in the transport of RNA from tumor tissues into saliva. By influencing gene expression and facilitating communication between cells, exosomes reveal the molecular characteristics of oral diseases. Salivary RNA is derived from either serum or local secretions, with expression levels correlating closely with both physiological and pathological states. Advanced transcriptomic technologies now allow for the effective assessment of various mRNA types, aiding in disease classification and monitoring progression. Numerous mRNA transcripts, such as IL8, IL1B, DUSP1, H3F3A, OAZ1, S100P, and SAT, are consistently found at elevated levels in the saliva of individuals with oral cancer. Their involvement in inflammation, signaling, oxidative stress, DNA binding, polyamine synthesis, and calcium signaling underscores their potential as non-invasive diagnostic markers.[21]

Small non-coding RNAs called miRNAs regulate cellular and tissue programming by either activating or repressing transcription or translation. They are thought to be a possible biomarker for the prognosis and diagnosis of OSCC. MiR-125a and miR200a were found to be downregulated in OSCC patients, while miR-24-3p, miR-31, and miR-21 were found to be significantly increased in comparison to normal healthy controls. The detection and quantification procedures of these indicators must be normalized and standardized, even though the abnormal expression of salivary miRNAs is an adjuvant diagnostic tool. Inflammation is additionally related to alterations in miRNA expression.[22]

Long non-coding RNAs (lncRNAs) are transcripts longer than 200 nucleotides that do not code for proteins but can influence transcription and impact cancer development. The varying levels of these RNAs between normal and malignant cells make them promising candidates for diagnostic and prognostic indicators. Research has examined lncRNAs such as MALAT1, HOTAIR, NEAT-1, HULC, MEG3, and UCA1 in tissues and saliva of oral squamous cell carcinoma (OSCC). Notably, HOTAIR exhibited significantly increased levels in saliva, particularly in patients with lymph node metastasis, indicating its potential to forecast survival outcomes.[23]

Salivary Metabolomics

Salivary metabolomics explores alterations in the metabolic profile of OSCC patients compared to healthy individuals. Wei et al. analysed the salivary metabolomic signatures of OSCC patients. They found that salivary levels of lactic acid and n-eicosanoic acid were significantly elevated, while GABA, phenylalanine, and valine were downregulated. Similarly, taurine and piperidine were identified by Sugimoto et al. as biomarkers unique to oral cancer.[24,25]

Patients with cancer have been shown to have dysregulation of the hypothalamic-pituitary-adrenal axis. According to Bernabé et al., salivary cortisol levels were considerably greater in people with OSCC. They found a positive link between cortisol levels and clinical staging. Their results support the idea that salivary cortisol could be an effective biomarker for head and neck cancers.[26] Additionally, Ma et al. emphasized how oxidative and nitrative stress contribute to cancer development. This happens through mechanisms such as DNA base modification, inactivation of tumor suppressor genes, and activation of proto-oncogenes. Smoking, alcohol consumption, and dietary nitrates are the main sources of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that contribute to the development of oral cancer.[27]

Salivary Microbiomics

The oral cavity hosts a complex microbiome, with saliva serving as a medium that reflects microbial shifts associated with oral carcinogenesis. Advances in sequencing technologies have revealed distinct microbial patterns in oral potentially malignant disorders (OPMDs) and oral squamous cell carcinoma (OSCC). Elevated levels of Prevotella melaninogenica, Capnocytophaga gingivalis, and Streptococcus mitis have shown diagnostic accuracy for OSCC. The oncogenic roles of Fusobacterium nucleatum and Porphyromonas gingivalis are well established, and increased salivary carriage of Candida albicans, along with HPV and EBV detection, further supports their diagnostic value.[28]

For instance, certain oral streptococci, yeast, and Neisseria species are linked to the production of acetaldehyde or exhibit alcohol dehydrogenase activity, contributing to their carcinogenic properties. Likewise, ongoing infections caused by periodontal pathogens such as P. gingivalis and F. nucleatum may enhance the risk of oral squamous cell carcinoma (OSCC) by influencing the inflammatory IL-6/STAT-3 signaling pathway via a mechanism dependent on TLR2. Analysis of microbial communities in saliva, utilizing 16S rRNA sequencing and microarray technologies, presents a promising non-invasive method for the early detection and ongoing monitoring of oral cancer.[29,30]

Salivary Methylomics

Analysis of DNA methylation is a powerful epigenetic method for identifying cancer. The process of adding a methyl group to cytosine residues results in transcriptional silencing, which is vital for normal development but can be harmful when it is disrupted. The abnormal hypermethylation of tumor-suppressor genes during the development of cancer creates unique methylation patterns that can distinguish cancer patients from healthy individuals. These patterns, detectable in saliva, provide a non-invasive method for the early diagnosis and monitoring of the disease.[31]

Research by Lim et al. indicated that the methylation profiles of RASSF1α, p16INK4a, TIMP3, and PCQAP/MED15 can successfully differentiate patients with head and neck squamous cell carcinoma (HNSCC) from healthy controls, as well as distinguish between HPV-positive and HPV-negative cases, with the latter group showing significantly higher levels of hypermethylation.[32] The importance of these biomarkers was emphasized by Liyanage et al., who confirmed that they offer exceptional diagnostic accuracy, with sensitivity and specificity rates exceeding 90%. Additional studies have found frequent methylation in microRNA promoter regions, specifically in mgmiR9-1, mgmiR124 family, mgmiR129-2, mgmiR137, and mgmiR148a, underscoring the extensive effects of epigenetic dysregulation in head and neck squamous cell carcinomas. Giuliano et al. also found that the methylation of EPB41L3 and HPV-16 CpG sites in oral gargle samples correlated significantly with tumor methylation patterns, offering another biomarker system for HPV-related oropharyngeal cancer.[33]

Limitations of salivary biomarkers

One of the challenges with salivary biomarkers is the variability in their levels; There is a need for validation in other oral inflammatory conditions; Many serum markers are also found in whole saliva, which can affect the diagnostic value of specific salivary biomarkers; Various medications, systemic health issues, and radiation can impact salivary gland function, altering both the composition and amount of saliva.[34]

Concluding remarks and future perspectives

The emergence of advanced molecular diagnostics has positioned salivary biomarkers as a promising option for diagnosing and prognosticating oral cancer, making it a dynamic area of scientific research. These biomarkers present several benefits compared to serum, as they are non-invasive, cost-effective, accessible, safe, and allow for multiple sampling opportunities, which are essential for the early detection of oral cancer. Innovations in state-of-the-art technology will bolster the application of saliva as a valuable medium for confirming biomarkers for Point of Care (PoC) uses. The prompt recognition of premalignant lesions and early-stage oral squamous cell carcinoma (OSCC) is associated with better survival outcomes. However, despite novel diagnostic methods being introduced, numerous patients diagnosed with OSCC still exhibit more advanced stages of tumors. At present, there is a deficiency of dependable early-stage diagnostic markers for OSCC. Reliable and precise biomarkers for OSCC would be beneficial in screening high-risk patients, evaluating treatment outcomes, and monitoring for initial signs of recurrence. The potential of salivary diagnostics for OSCC is significant due to saliva's direct contact with the oral mucosa. Nevertheless, in spite of considerable advancements in the field of salivaomics, clinically applicable biomarkers for OSCC are still absent. Future investigations and innovations will require thorough and stringent validation of biomarkers prior to any candidates being suitable for clinical use. Additional research is vital to verify the diagnostic and prognostic capabilities of various salivary biomarkers concerning oral potentially malignant disorders (OPMDs) and oral cancer. Moreover, there is an increasing necessity to direct research to confirm the specificity of different salivary biomarkers using larger populations. More detailed systematic analyses are critical for identifying sensitive and specific salivary biomarkers for the diagnosis and prognosis of OSCC as well as OPMDs.[35,36]

ETHICAL APPROVAL

Ethical approval was not required for this review article as it is based on previously published literature and did not involve any animal or human subjects.

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