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Salivomics: Unlocking New Frontiers in Non-Invasive Diagnostics

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ABSTRACT:

Saliva, often termed as the "mirror of the body," is emerging as a valuable non- invasive diagnostic fluid reflecting a wide range of systemic and oral health conditions. The field of salivomics, which involves the comprehensive analysis of salivary biomarkers, has enhanced early disease detection across medical and dental disciplines. Rich in proteins, enzymes, hormones, cytokines, nucleic acids, and metabolites, saliva provides insights into various physiological and pathological states.

Technological advancements in genomics, proteomics and molecular biology have improved the accuracy and clinical applicability of salivary diagnostics. Key advantages include non-invasiveness, cost-effectiveness, patient compliance, and real- time monitoring capabilities. Salivomics shows promise in the detection and management of cancers, cardiovascular and autoimmune diseases, metabolic and neurological disorders and infections.

This review highlights the potential of saliva as a diagnostic tool and its increasing importance in making clinical diagnostics more accessible, efficient, and less invasive. It points toward a shift in routine healthcare, with saliva-based testing becoming a key part of future diagnostic methods.

Introduction

Salivomics, the study of saliva-based diagnostics, is gaining significant momentum as a cutting-edge approach in modern healthcare. Saliva, a readily available and non- invasive biological fluid, offers a wealth of diagnostic information through its diverse molecular composition—ranging from enzymes and proteins to RNA and hormones. This makes it an appealing alternative to more invasive diagnostic methods that rely on blood, cerebrospinal fluid or urine, which often require skilled personnel and can cause patient discomfort.

In India, oral health remains a growing concern, with the World Health Organization estimating that around 1.3 million children are affected by dental issues. Oral health is closely linked to an individual's overall well-being, influencing not only physical health but also social, psychological and functional aspects of life. Poor oral hygiene can lead to low self-esteem and social isolation, making early diagnosis essential for preventing such outcomes. Identifying diseases in their initial stages not only improves management but also reduces the risk of severe complications. For instance, ovarian cancer is the fifth leading cause of cancer-related deaths among women in the U.S. If identified in its early stages, the five-year survival rate can be as high as 93% in Stage I and 70% in Stage II. However, once it reaches Stages III or IV, the survival rate drops sharply to 37% and even as low as 10%. Similarly, type II diabetes, a serious but common metabolic disease affecting more than 7% of American adults can often be managed effectively through lifestyle changes like diet and exercise.[1]

Saliva holds promise as a diagnostic tool because it mirrors the body's physiological state and is easy to collect. With recent advancements in 'omics' technologies such as proteomics, transcriptomics, metabolomics, and microbiomics—the diagnostic power of saliva has expanded greatly. These tools enhance our ability to detect disease early, monitor progression, and evaluate treatment responses with greater accuracy. This review focuses on how these salivary 'omics' approaches are transforming the early diagnosis of oral diseases and reshaping the landscape of non-invasive diagnostics .[1]

Discussion and Background

Saliva is a easily available biological fluid, making it a suitable medium for the detection of a wide range of diseases.. In 2004, scientists identified the salivary transcriptome, comprising around 180 core messenger RNAs (mRNAs). Additionally, the fundamental salivary proteome was found to include 1,166 proteins—a discovery made possible through collaborative efforts of research teams supported by the National Institute of Dental and Craniofacial Research (NIDCR), including the group at University of california, Los Angeles. Collaborating with researchers from Keio University in Japan, this team also decoded the salivary metabolome (the collection of small molecules present in saliva, representing the end product of various metabolic pathways) and confirmed its relevance for diagnosing oral and systemic diseases .[2]

Furthermore, research led by Farrell and team highlighted how differences in the salivary microbiome could assist in detecting early-stage pancreatic cancer that is still surgically treatable. They identified two microbial markers—*Neisseria elongata* and *Streptococcus mitis*—which produced a receiver operating characteristic (ROC) curve with an area under the curve (AUC) of 0.90 (95% CI: 0.78–0.96; P < .001), indicating high diagnostic accuracy. This method demonstrated 96.4% sensitivity and 82.1% specificity in distinguishing cancer patients from healthy individuals .[2]

Sub Types of Salivomics

1) Genomics
2) Transcriptomics
3) Proteomics
4) Metabolomics
5) Microbiomics
6) Immunomics

Advantages of Saliva Over Other Biofluids

1) Easy to collect
2) Non-invasive
3) Produced on demand and rich in diagnostic information
4) Inexpensive
5) Does not require specialized training to collect
6) Easy to store and handle because it does not clot like blood

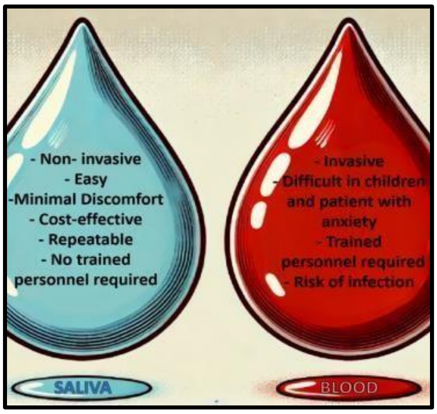

Fig. 1: Advantages of Salivary sample over Blood sample collection

Salivary Biomarkers in various medical conditions

Several cytokines—including IL-1β, IL-1RA, IL-4, IL-6, IL-10, IL-13, IL-17A, IL-

17F, TNF-α, IFN-γ, HGF, CRP, and VEGF—have been extensively investigated in the saliva of oral cancer patients.[3,4] IL-8, along with IL-6, has been found at significantly higher levels in patients, especially in

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advanced stages (III and IV) and after surgery[5]. Elevated IL-17A and IL-17F levels have been linked to advanced oral cancer and lymph node metastasis. TNF-α levels are notably higher in both oral cancer and oral potentially malignant disorders (OPMDs). Elevated levels of VEGF and HGF have also been reported in oral cancer cases .[6]

Markers such as CYFRA 21-1, IL-5, miR-139-5p, and epidermal growth factor receptor (EGFR) have been assessed to predict treatment outcomes in oral cancer.[7] Higher salivary levels of CYFRA 21-1 are associated with tumor recurrence.[8] Increased EGFR expression and elevated IL-5 levels—especially after the first surgery—are also associated with poorer outcomes. Saliva contains both serous and mucous glycoproteins, such as CD44 and carcinoembryonic antigen (CEA), which have been found in greater amounts in individuals with oral cancer. Specific CD44 variants, like CD44v6 and CD44v10, are believed to play a role in the initial development of histopathologically aggressive forms of oral cancer .[8-9]

Multiple studies have shown that salivary levels of microRNAs (miRNAs) differ significantly between individuals with oral cancer, oral potentially malignant disorders(OPMDs), and healthy controls. Specific miRNAs, such as miRlet-7-5p, miR-21, miR-184, miR-30c-5p, miR-302-3p, and others, have been linked to disease status. The expression levels of these miRNAs differ significantly in patients with oral cancer compared to those with OPMD or healthy individuals. However, it has been suggested that variations in salivary miRNA levels may affect diagnostic accuracy due to differences in periodontal health and saliva composition.[10]

Medical Condition	Salivary Biomarkers
Cardiac Events	Troponins I/T, Creatine Kinase, C-Reactive Protein (CRP), TNF-α, MMP-9, Myeloperoxidase
Oral Malignancies	c-Myc, Cytokines (e.g., FGF, IL-8, IL-1β), MMPs (1, 2, 3, 9), Hypoxia markers, CYFRA 21-1
Risk in HNC Patients	EGFR, CRP, Serum Amyloid A, ESR
Breast Cancer	Cancer Antigen CA 15-3
Gastric Carcinoma	Proteins at molecular weights 6856.81 Da and 2081.17 Da
Oral Lichen Planus	Cystatin SA
Sjögren's Syndrome	IgA, β2-Microglobulin, Anti-SSA/SSB, Lysozyme, Lactoferrin
Celiac Disease	Anti-Tissue Transglutaminase (anti-TTG) antibodies
Cystic Fibrosis	Prostaglandins, Electrolytes, Urea, Uric Acid, Salivary Gland Proteins, EGF, Ca, PO4
Bone Turnover Monitoring	Osteonectin, Alkaline Phosphatase (ALP)
Forensic Analysis	DNA evidence, Blood Group Antigens
Cushing's Syndrome	Salivary Cortisol
Diabetes Mellitus	Melatonin, Oxidative Stress Markers, Glucose, α-Hydroxybutyrate
Psychological Stress	Salivary α-Amylase

Table: 1: Salivary Biomarkers in Various Medical Conditons

Emerging Omics Approaches

Genomics

A gene is the basic structural and functional unit of heredity. Genomics applies recombinant DNA technology and bioinformatics to sequence, assemble, and execute mapping of genes. DNA obtained from saliva using the manual purification method (7.8 µg) is comparable to that from blood using the salt precipitation technique (7.4 µg) .[10] Samples can be stored long-term without substantial degradation, and genetic or epigenetic processes are reflected in gene transcription profiles obtained from salivary genetic analysis such as the "*Human Genome Project*."[11] Technologies such as NGS(Next Generation Sequencing) and ddPCR(Droplet Digital Polymerase Chain reaction) are the latest ways to detect circulating tumor DNA (ctDNA) in saliva, which consists of 180–200 base pairs and is shed from tumor cells, indicating oncogenic transformation. EFIRM (Electric Field-Induced Release and Measurement) technology enables the detection of key genetic mutations such as T790M, exon 19 deletions, and L858R—critical biomarkers associated with non-small cell lung cancer. This innovative approach holds significant promise for transforming cancer diagnostics by offering rapid, non-invasive, and highly sensitive mutation detection.

Proteomics

Proteomics refers to the comprehensive study and characterization of the entire set of proteins expressed in a given biological sample under specific conditions. Proteins are naturally occurring substances consisting of amino acids joined by peptide bonds, represent the functional expression of genes.[11] In 2004, the NIDCR (National institute of Dental and craniofacial research) funded comprehensive studies that identified up to 1,166 proteins in saliva, most synthesized and secreted by salivary gland cells. [11-12] Techniques used include sample collection, pre-treatment, fractionation, identification, characterization, and bioinformatic analysis. New techniques such as PEA (Proximity extension assay) and aptamer-based technologies are becoming popular, while HPLC (High performance liquid chromatography) provides detailed analysis of protein modifications. Saliva contains over 2,300 identifiable minor proteins, despite its overall proteomic content comprising only about 30% of that found in blood.[13] The most abundant salivary proteins include α-amylase, albumin, cystatins, histatins, secretory immunoglobulin A, lactoferrin, mucins, lysozymes, proline-rich proteins, statherin, and transferrin, collectively exceeding 98% of total salivary proteins.[13-14] The presence of salivary proteomic markers can reveal signatures of disease morbidity at early stages and track the progression of the disease.

Transcriptomics

RNA, structurally similar to DNA, is present in all cells. Human saliva contains over 1,000 miRNAs and more than 3,000 mRNA species with 180 mRNAs forming the core transcriptome in healthy individuals. [14] Techniques include 2D-PAGE, MALDI, FT-ICR, QTOF, and HPLC–ESI–MS/MS. Salivary RNA sequencing has revealed gene expression patterns similar to those in other bodily fluids. As of January 2009, researchers identified over 1,000 salivary proteins from major salivary glands, most of them well characterized. For instance, Sjögren's syndrome is an autoimmune disorder marked by xerostomia and keratoconjunctivitis sicca. It has been linked to increased salivary alpha-amylase fragments. In 2009, Park et al. discovered micro-RNA in saliva and its potential as an oral cancer biomarker. Subsequent advanced RNA sequencing of saliva revealed gene expression patterns similar to those in other bodily fluids (Spielmann et al.; Bahn et al.). Saliva also contains coding and non-coding transcripts from human cells and oral bacteria (Beard et al.; Park et al.; Spielmann et al.). In 2013, the NIH (National Institute of Health Common Fund) Common Fund created the Extracellular RNA Communication Consortium (ERCC) to explore the role of extracellular RNA (exRNA), which was found to facilitate intercellular communication. A major achievement of the ERCC has been validating salivary exRNA as a marker for gastric cancer detection, and it is now included in the ERCC's Extracellular RNA Atlas. [15]

Metabolomics

Metabolomics explores the molecular landscape of metabolites which includes amino acids, peptides, nucleic acids, and lipids. The alterations in metabolite profiles can provide unique insights into diagnosis of disease.[14] Recent research has highlighted significant alterations across various metabolite classes including dipeptides, amino acids, carbohydrates, lipids, and nucleotides, when comparing individuals with periodontitis to healthy controls[16]. Comparable studies analyzing salivary metabolic profiles have demonstrated the ability to distinguish individuals with oral, pancreatic, and breast cancers from their corresponding healthy controls, highlighting the diagnostic potential of salivary metabolomics across a range of malignancies.[17-19] Researchers have identified variations in salivary metabolites including acids, carbohydrates, and nucleotides that are associated with various systemic diseases, further accentuating the diagnostic potential of saliva.[14]

Immunomics

A major breakthrough in salivary diagnostics is the discovery of immune system markers in saliva. The FDA has approved (Enzyme Linked immunoassay) ELISA kits to detect HIV-1 and HIV-2 in saliva, while research has expanded to hepatitis A, B, and C demonstrating measurable antigen and antibody levels in saliva.[14] Commercial kits that can identify hepatitis C antibodies in saliva are currently being developed. Despite showing a 97.5% accuracy rate compared to blood-based tests, these kits still await FDA approval.[20,21] Saliva also shows promise for detecting pathogens in global diseases like malaria, dengue, Ebola, tuberculosis, and herpes viruses.

Conclusion

Previously underappreciated, saliva is now emerging as a valuable diagnostic tool. With the advent of advanced analytical technologies, saliva has emerged as a competitive alternative to traditional diagnostic fluids such as blood, offering a noninvasive and efficient means for the detection of systemic diseases. As research progresses and clinical interest expands, salivary diagnostics are poised to become part of routine healthcare, facilitating earlier disease detection, improving clinical outcomes, and enhancing patient quality of life. While its potential in preventive care is substantial, ongoing research remains crucial to fully realize its global impact.

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