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Salivary Biomarkers – A Review

Sharmila Devi Devaraj

Saveetha Dental College and Hospitals ,
Chennai -600077,India.

Abstract
Saliva , a biological fluid serves as the diagnostic tool in health and disease. Salivary transcriptomic biomarkers , exosomes, salivary micro RNA, Cytokines which include interferons ,tumour necrosis factor, interleukins serves as diagnostic tool. Increased salivary levels of cell cycle regulatory proteins such as cyclin D1,Ki67,glycotic enzyme like lactate dehydrogenase(LDH),matrix metallo proteinase (MMP) in oral cancer is reviewed.
Key Words- Biomarker, Cytokines, Oral cancer,Saliva

INTRODUCTION

The term, **biomarker,** refers to measurable and quantifiable biological parameters than can serve as indicators for health and physiology-related assessments, such as pathogenic processes, environmental exposure, disease diagnosis and prognosis or pharmacologic responses to a therapeutic intervention[1].

A **cancer biomarker** for a specific tumor type can provide vital information needed to successfully treat cancer. The ultimate goal in the discovery of biomarkers is to enhance the survivability of cancer through improved diagnostics and treatment.[2]

Salivary diagnostics is a dynamic and emerging field utilizing nanotechnology and molecular diagnostics to aid in the diagnosis of oral and systemic diseases and using the **salivary biomarkers** for disease detection[3].

SALIVA THE DIAGNOSTIC TOOL

Human saliva is a clear, slightly acidic (pH=6.0-7.0) biological fluid containing a mixture ofsecretions from multiple salivary glands, including the parotid, submandibular, sublingual gland other minor glands beneath the oral mucosa as well as gingival crevice fluid[1].

Salivary diagnostics has evolved into a sophisticated science, and serves as a subset of the larger field of molecular diagnostics, now recognized as a central player in a wide variety of biomedical basic and clinical areas[3]

Saliva is a readily available specimen, which can be collected by non-invasive procedures and contains many hormones, drugs and antibodies in screening and diagnosis.[5].

With a salivary specimen, one can collect multiple specimens from the same individual at the optimum times for diagnostic information[5].

Molecular diagnostics reveals a wide range of disciplines including drug development, Pharmacogenomics and plays an important role in the discovery of salivary biomarkers for the diagnosis of oral and systemic diseases.[3]

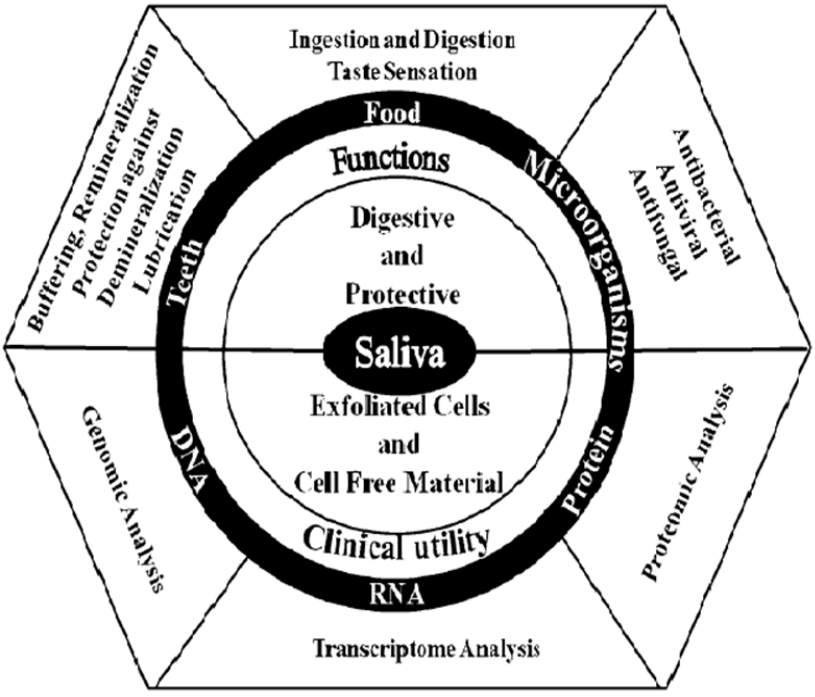

Figure 1: Functions and Clinical Utility of Saliva[4]

ROLE OF SALIVARY BIOMARKERS

Till date, most of the biomarkers have been identified from various body fluids. Among which blood and saliva are the most widely studied body fluids that may contain reliable biomarkers for detecting cancer . It is an informative body fluid containing an array of analytes (Protein, mRNA and DNA) that can be used as biomarkers for translation and clinical applications.[4]

Clinical significance of salivary biomarkers in various malignancies is studied by several investigators. They explored for the presence of salivary proteomics and genomics signatures for breast cancer.[4] The Functions and clinical utility of saliva authors reported Her2/neu as the first salivary biomarker for breast cancer and also documented raised levels of CA15-3 and Her2/neu as well as low levels of p53 in patients with breast cancer. Then elevated salivary levels of CA 125 in patients with ovarian cancer. The salivary leptin was expressed in much higher amount in salivary gland tumors than in healthy parotid tissue. It has been reported that gastric cancer can also be identified at an early stage by using saliva proteome analysis .[4]

Identification of the combination of three mRNA biomarkers (acrosomal vesicle protein 1, ACRV1; DMX like 2,DMXL2 and dolichyl phosphate mannosyltransferase polypeptide 1, catalytic subunit, DPM1) could differentiate pancreatic cancer patients from chronic pancreatitis and healthy individuals.[4]

SALIVARY TRANSCRIPTOMIC BIOMARKERS

Messenger (m) RNA is the direct precursor of proteins and in general the corresponding levels are correlated in cells and tissue samples[1] .At present, the main strategy to identify salivary transcriptomic biomarkers is through microarray technology. After profiling the transcriptomic biomarkers by microarray, they are validated by quantitative (q)PCR, the gold standard for quantification of nucleic acids.[1].

EXOSOMES

Exosomes are small, right-side out cell-secreted vesicles of about 30–100 nm, derived from fusion of multivesicular bodies to plasma membranes.[12]

More recently, salivary mRNA were localized inside salivary exosomes and these nucleic acids were protected against ribonucleases in saliva ;Moreover, saliva exosomes have been discovered to regulate the cell-cell environment by altering their gene expression allowing us to better understand the molecular basis of oral diseases.[1]

SALIVARY MICRO RNA

MicroRNAs (miRNAs) are encoded by genes but are not translated into proteins.[1] Hundreds of miRNAs from various organisms have been discovered, and functional assays have established that miRNAs serve important functions in cell growth, differentiation, apoptosis, stress and immune response as well as glucose secretion [1].

Proteins, mRNAs and microRNAs before and after pharmacological interventions may provide important information on drug efficacy and toxicity in the context of therapeutic responsiveness.[1].

CYTOKINES

The cytokines, which include the interferons, tumour necrosis factor, and the interleukins, are a burgeoning and diverse family of peptide cell regulators[6]. The availability of natural and recombinant cytokines has led to the use as anti-tumour agents and in limiting the myelo suppressive effects of cytotoxic chemotherapy.[6].

In 2004,one group have published that analysis of supernatant of mRNA of IL-8,IL-1beta,dual specificity protein phosphatise-1(DUSP-1)H3 histone family 3A(H3F3A or HA3),S100 calcium binding protein P(S100P),ornithine decarboxylase antizyme-1(OAZ-1),spermidine or spermine N1-acetyl tranferase 1(SAT-1), as combination will have a specificity and sensitivity of 91 % in the diagnosis of oral squamous cell carcinoma[7].

SALIVARY BIOMARKERS IN ORAL CANCER

Oral cancer [more than 90% are oral squamous cell carcinomas (OSCC)] is the sixth most common cancer worldwide with an average 5-year survival rate of approximately 60%. Global profiling of disease-associated molecules, such as proteins, DNA, mRNA, micro RNA, and metabolites is becoming the state-of-the-art method to provide promising disease biomarker candidates. [8]

The first report of saliva as a diagnostic tool for oral cancer detection was published in 2000.The authors claimed that exon 4, codon 63 of the p53gene was mutated in salivary DNA from five of eight(62.5%) oral cancers patients[4].

The ability to globally profile these molecules in saliva, through transcriptomic and proteomic approaches, as well as the ability to detect specific molecules in saliva will greatly enhance the opportunities to identify reliable oral cancer biomarkers. The prior salivary transcriptomic studies have discovered 7 OSCC-associated salivary RNAs (IL-8, SAT, IL-1B, OAZ1, H3F3A, DUSP,S100P).[8]

Report of increased salivary levels of cell cycle regulatory proteins including Cyclin D1 and ki67, glycolytic enzyme lactate dehydrogenase (LDH), matrix metalloproteinase (MMP)-9, as well as reduction in DNA repair enzyme, 8-oxoquanine DNA glycosylase (OGG1) and Maspin, a tumor suppressor protein in oral cancer patients. [4].

Protein concentrations of both MMP1 and MMP3 were observed to be highly elevated in the saliva of OSCC patients compared to saliva from cancer-free controls[9].

Significantly higher salivary levels of IL-1, IL-6, IL-8 and TNF-a in oral cancer patients as compared to the patients with dysplastic oral lesions and controls[4] After using laser-capture micro dissection, have identified the expression of 2 cellular genes that are uniquely associated with OSCC: interleukin (IL) 6 and IL-8 . 75% positive expression of telomerase in saliva of oral cancer patients suggesting its usefulness as a supportive marker to diagnose oral cancer and also suggested that human telomerase reverse transcriptase (hTERT) analysis may be a potential biomarker for the diagnosis of oral cancer[4]

p53 Autoantibodies Presence of p53 autoantibodies in saliva as well as serum of oral cancer patients demonstrated that its detection in saliva can offer a non-invasive method for the detection of a subset of tumors with p53 aberrations[4]

A biomarker that can indicate lymphnode metastasis would be valuable to classify patients with OSCC for optimal treatment. In one study, have performed a serum proteomic analysis of OSCC using 2-D gelelectrophoresis and liquid chromatography/tandem mass spectrometry. One of the down-regulated proteins in OSCC was identified as tetranectin, which is a protein encoded by the *CLEC3B* gene (C-type lectin domain family 3, member B).[10].

NID2 and HOXA9 promoter hypermethylation as biomarkers for prevention and early detection in Oral Cavity Squamous Cell Carcinoma tissues and saliva.[11].

CONCLUSION

Saliva has been analyzed for diagnostic purposes .Salivary biomarkers is useful in the diagnosis of variety of diseases .It is a non invasive , uncomplicated, diagnostic tool.

Oral cancer that can be monitored by assaying salivary biomarkers opens to a wider view. More studies on salivary biomarkers may prove greater insight in to various systemic diseases in human population.

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