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SALIVARY ONCOGENIC BIOMARKERS

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INTRODUCTION

Saliva is more commonly used as a diagnostic medium in the recent years. It is mostly due to its noninvasive nature when compared to blood.[1] smaller sample aliquots, good cooperation with patients, cost effectiveness, easy storage and transportation. repeated sampling for monitoring over time, greater sensitivity and its similarity to the composition of serum.[2] In this review, the salivary genomic and proteomic markers in the diagnosis of various cancers, by beginning with oral cancer followed by cancers far off from the oral cavity.

ORAL SQUAMOUS CELL CARCINOMA

Since saliva is always in contact with oral cavity, it is best to identify oral squamous cell carcinoma.[1] Oral squamous cell carcinoma (OSCC) is a common and lethal malignancy. Thus, improvement in current knowledge of molecular changes associated with OSCC is urgently needed to explore novel avenues of diagnostics and treatment of this disease.[3] Early detection is the key to good prognosis in almost all types of cancer. Saliva has been used as a diagnostic medium for oral squamous cell carcinoma (OSCC), and salivary analytes such as proteins, mRNA, and DNA have been used in their diagnosis.[4]

GENOMIC MARKERS

Certain **long non-coding RNAs (lncRNAs)** has been functionally associated with certain types of cancer, recently it is identified to be potential markers for OSCC.[4] The advantage of lncRNAs is that it is independent of the age and gender of the patient.

In a study conducted by Tang et al with tumour tissue samples, HOTAIR, NEAT-1 and UCA1 were expressed at higher levels in tumors that subsequently metastasized than in others while expression of MEG-3 was downregulated. **HOTAIR** is significantly increased

in tumours especially in lymph node metastasis, but it required tissues in large quantities.[4] This gene is required for epigenetic differentiation of skin over the surface of the body.

MALAT-1 was then used but it did not differentiate between metastatic and non metastatictumours. NEAT-1 is found abundant in metastatic tissue, but since it is highly unstable, it is not much expressed in saliva.[4]

Nowadays, **micro RNA(miRNA)** have also used for various salivary diagnostics.[5] The miRNAs are endogenous, small, noncoding, regulatory RNAs (18-25 nucleotides long)that negatively regulate gene expression at the translational level. According to the study by Heravi et al, **miRNA-27b** levels were significantly increased OSCC patients. The gene is required for the progression of the lesion rather than the initiation. It also identifies malignancy from precancerous lesion.[6] Similarly miRNA-200 and miRNA125 was expressed in supernatant saliva of patients with OSCC.[7] These miRNA regulates epithelial to mesenchymal transition-related gene expression and determines prognosis of cancer.

Similarly miRNA-136 was under expressed and miRNA-191 is also a stable salivary marker for OSCC as it showed minimum intra group and intergroup variability.[6]

Salivary **mRNA** is an easy method of screening for oral cancer. Since mRNA is very labile, it has to be detected by micro array and PCR. It is a highly sensitive and specific biomarker.[7] *IL8, IL1B,* and ferritin polypeptide mRNAs were found to be significantly elevated in the saliva of oral cancer patients and are also significantly elevated in oral cancer tissues.[8] Five other cancerassociated genes as being up-regulated in saliva from oral cancer patients, such as *DUSP, H3F3A, OAZ1, SAT, S100P*. *DUSP1* gene encodes a dual specificity phosphatase andhas been implicated as a mediator of tumor suppressor PTEN signaling pathway[9] and H3F3A identified as a proliferative marker.[8]

PROTEOMIC MARKERS

Proteins coded by IL8 and IL1B genes are I8 and IL1beta which are significantly higher in cases of OSCC. Any immunological disease can increase the level of cytokines but even thenit is not as high as seen in OSCC patients.[10] p-53 is a protein that is accumulated in the nuclei in various cancer cells. They are coded by p 53 tumour suppressor genes. These are not seen in normal human cells. In heavy smokers, it is seen even before the clinical signs of tumour are noticed. Anibodies to p53 are detected easily.[11]

SALIVARY GLAND TUMOURS

Salivary glands are responsible for production of a large portion of saliva, so the composition and content of saliva can directly reflect the pathological change of salivary glands. In a study, quantitative measurement of the levels of FGF2/fibroblastic growth factor receptor 1 (FGFR1) in the saliva and serum from patients with salivary gland tumors, using an enzyme-linked immunosorbent assay (ELISA) were taken. The saliva levels of FGF2 in patients with salivary gland tumor were significantly associated with the presence of tumor and showed good sensitivity and specificity. Their results suggested that salivary FGF2 and FGFR1 can be used as potential biomarkers in the diagnosis of salivary gland tumors.[12]

BREAST CANCER

Screening mammographyis considered the gold standard for detection of breast cancer; however, the sensitivity of this test is between 54% and 77% dependingon the type of mammographic procedure. To confirm the diagnosis of breast cancer, mammotomy are followed bya histopathological and immunohistochemistry analysis, which are invasive and associated with patient morbidity.[13]

CA15-3 is a large transmembrane glycoprotein, which is fre-quently overexpressed, aberrantly glycosylated in cancer. It is the most widely used serum marker to detect recurrent breast cancerand monitor treatment of patients with advanced disease. It was found that the salivary andserum levels of CA15-3 were significantly higher in cancer patientsand in stage 2 breast cancer, with a significant positive correlation between serum and saliva CA15-3 concentrations, allowing apotential use of salivary CA15-3 in the initial detection of breastcancer in women.[14]

It was proven in a study that the salivary levels of c-erbB-2, CA15-3 and p53 in the breast cancer patients were notably higher thanthe salivary levels of control group subjects, suggesting that these biomarkers have potential use in initial diagnosis and/or follow-up for the detection of breast cancer.[15]

Mucin1 (MUC1) is a transmembrane glycoprotein formed by two subunits that is glycosylated and overexpressed in breast tumor in over 90% and plays a pivotal role in progres-sion of the disease. It is con-sidered one of the most specific and validated antigens in Breast cancer patients.[16] The combination of salivary IgG anti-HER2 and salivary IgG anti-MUC1, were significantly higher in patients with breast cancer compared to the

controls.[17] Metabolites like proline, valine and taurine were increased in patients with higher risk of breast cancer and a useful diagnostic tool for this disease.[18] Thepanel of 9 combined biomarkers with 8 mRNA biomarkers andone protein (CSTA + TPT1 + IGF2BP1 + GRM1 + GRIK1 + H6PD + MDM4-+ S100A8 + CA6) exhibited excellent diagnostic test accuracy (DTA) for breast cancer diagnosis.[13]

LUNG CANCER

Lung cancer is the leading cause of cancer death for both men and women worldwide as it is mostly diagnosed at late and progressed stage with the consecutive poor therapy outcome. EGFR, a frequently mutated molecular target in lung cancer [40–42], is a discriminatory biomarker in saliva. EGFR was more abundantly expressed in lung carcinoma tissue than in adjacent normal lung. Indeed, EGFR mRNA was elevated in the saliva of lung cancer patients.[19]

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