



A REVIEW ON REGULATORY PROTEINS AS POTENTIAL SALIVARY BIOMARKERS IN ORAL CANCER DETECTION

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Abstract: The Preventive measures and therapeutic strategies are attaining timely with a great efforts of clinicians and scientists of the same on oral cancer. Mere improvement in therapeutic strategies is not enough to decrease the mortality and morbidity rate of oral cancer. However the recent studies have proved that delay in diagnosis remains one of the major causes of the high morbidity and mortality rate. Therefore the aim of this review is to cover the most recent data on salivary biomarkers in the detection of oral cancer.

Salivary biomarkers serve as the diagnostic tool in oral cancer namely increased salivary fluid levels of cell cycle regulatory proteins such as Cyclin D1, Ki67, glycolytic enzymes like Lactate Dehydrogenase (LDH) and Matrix Metallo Proteinase (MMP) as diagnostic tools in oral cancer is reviewed.

Key words: Saliva, Oral Cancer, Cyclin D1, LDH, MMP\

I Introduction:

Saliva, a biological fluid serves as the diagnostic tools as it possess several biomarkers. Bio monitoring of these biomarkers like proteins, nucleic acids, circulating tumor cells, or disease drivers related to infections proved their usefulness in the diagnosis of human diseases including oral cancer [1]. Oral cancer reported as one of the serious health problem globally [2]. The morbidity and the mortality rate of oral cancer has been increased day by day it is because of the late diagnosis in an advanced stage [3]. Screening and an early detection of oral cancer have however increases the survival rate, the reason is pre- malignant tumors even can be detected in saliva unlike that of the biopsy procedures that are available [4].

Hence, salivary biomarkers have been used widely to elucidate the clinical behavior of oral cancer [5, 6], specifically Cyclin D1, Ki-67 proteins and glycolytic enzymes (LDH and MMP) [7, 8 and 9]. To consider a molecule as a biomarker it should have to satisfy the following criteria: 1. the altered can be objectively measured; 2. must be measurable in small specimens; 3. must be altered in the high-risk tissues, but not in the normal tissues; and 4. must be altered in the early stages of cancer development [10]. This review article aims to covers the recent data on regulatory protein biomarkers with particular attention on Cyclin D1, Ki67, glycolytic enzymes like Lactate Dehydrogenase (LDH), Matrix Metallo Proteinase (MMP) role in the early detection of oral cancer.

II THE SALIVA AS A PERFECT DIAGNOSTIC TOOL:

The saliva has gain an utmost importance in early detection of cancer especially in high risk patients, patients with premalignant lesions and patients with a previous history of cancer [11]. The human saliva is a clear, slightly acidic (pH= 6.0-7.0) biological and informative body fluid rich in bio molecules like protein, mRNA, and DNA that are used as biomarkers for translation and clinical applications [12]. Because of having many advantages over the serum and tissues the saliva has proved as a perfect diagnostic tool, in clinical diagnosis of pathogenic diseases. The advantages include simple collection; storing and transportation procedures, cost-effectiveness, an adequate volume of sample obtain easily, and repeated sampling for a longer period [13].

Saliva detection is essential in oral cancer among other type of cancers because of its direct contact with oral cancer lesions or tumour. The saliva of the oral cancer patient contains the altered dead cells in their oral cavity this allow us to detect the saliva for the presence of those fallen cells or altered cells commonly called as salivary biomarkers. Hence the saliva is used as the primary choice in screening and identification of salivary biomarkers in the oral cancer [14].In light of the above, the saliva has been considered as a perfect diagnostic tool in oral cancer detection.

III SALIVARY BIOMARKERS:

The Bio markers are formed only in the tumour cells. They may be genes or gene products that are not found in the normal cells, but are highly expressed in the malignant or abnormal cells [15].

The advantages of biomarkers in oral cancer detection have summarized by Chan and Sell Table: 1 [16].

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| <ul style="list-style-type: none"> ➤ Biomarker is a prognostic indicator in disease diagnosis. ➤ Tumor Volume can be estimated. ➤ Detection of oral cancer at early stages. ➤ Monitoring responses to therapy. ➤ Detecting the cancer recurrence. ➤ Direct the immunotherapy. ➤ Radio immune localization of tumor masses. ➤ Treatment success rate can be evaluated |
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Table - 1 Advantage of Biomarkers:

IVCYCLIN D1 GENE MARKER:

Cyclin D1 is a cell cycle regulator that binds to cyclin-dependent kinase (CDK) 4 and CDK6. These cyclin-CDK complexes induce DNA synthesis and transition of cells between G1/S phases and make the cyclin D1 as a potential target in cancer detection [17, 18]. In various studies it has been reported that cyclin D1 level is increased in 30% of Head and neck SCC [19]. Indirectly the level of Cyclin D1 is increased during cancer it depends on the over expression of NF- κ B. Consonantly, NF- κ B levels increase gradually from pre-malignant lesions to invasive head and neck SCC via NF- κ B signalling pathway at the early stages of carcinogenesis and activate the growth promoting genes such as c-myc and Cyclin D1 [20-23].

Moreover, an elevated Cyclin D1 expression has been associated with higher tumor size, lymph node commitment and poor prognosis [24-26].; interestingly, one of the recent study reported an increased levels of cyclin D1 was seen in invasive clones of a tongue SCC cell line when compared to its non-invasive counterpart and is correlates with the expression of Ki- 67 [27]. The studies proved that cyclin D1 is often a target in oral cancer detection [28]. A higher level of dysplasia in oral SCCs and pre-malignant lesions was also previously related to Cyclin D1 over expression [24, 29-30]. Suitably, in of the study it was reported that 80% of T3/T4 cases had significantly higher Cyclin D1 and Ki-67 expression [31]. Ki67:

Ki-67 is present throughout the cell cycle. It is a current nuclear antigen in S, G2, and M phase, helps in the outcome of a neoplastic human cell growth rate [32]. Studies proved that in cancer cells Ki 67 expressed at low to moderate levels where as Ki 67 in oral normal epithelium, expressed at low levels [33]. Several studies reported the possible association between highly expressed Ki-67 cell and normal cell [34, 35] and in a recent study it was proved that over expression of CD147 and Ki-67 is linked to a worse prognosis of tongue SCC [36].

V Glycolytic Enzymes:

Matrix Metallo Proteinase and Lactate Dehydrogenase:

Matrix Metallo Proteinase has been studied in various studies during cancer detection [37]. MMPs prevent apoptosis by reducing natural killer cells count it shows gelatinases and collagenases activity.

These are stromelysins, and membrane-type MMPs [38] and have the capacity to cleave FAS receptors. They plays a dual role in angiogenesis, increase the bioavailability of vascular endothelial growth factor receptor [39] active role in the cell to cell adhesion, cell to extracellular matrix adhesion, breakdown of collagen (type IV, V, VII, X), fibronectin and elastin, [40]. It regulates cell growth and inflammation by altering several protein receptors such as chemokines and cytokines [41]. In a recent study MMP-9 has applied clinically as an early detection diagnostic tool in the future [42]. The studies on MMP reported that Future studies on large populations should evaluate the possibility as an adjunct for diagnosis, during the treatment and follow-up of oral cancer.

Lactate Dehydrogenase:

LDH is present in all most in every cell but it is present within the cell, the extracellular presence of LDH has been seen only in necrosis or tissues break down case. The dysplastic changes in cancer cell formation are associated with high glycolytic activity as a result breakdown of glucose to pyruvate occurs resulting in a rapid increase of lactate dehydrogenase (LDH) enzyme activity [43]. Due to high glucolytic activity the amount of lactic acid rate is increased ultimately this leads to the production of LDH because as it is consider as a key enzyme to breakdown lactic acid in glycolysis. Several studies reported the correlation between LDH with the histopathological grade of tumour [44]. The LDH level is high in tumor cell whereas the normal cell shows low rate of LDH [45, 46]. The studies on LDH all reported that it can be used as salivary biomarker for diagnosis of oral cancer.

VI Conclusion: Saliva has been analyzed for diagnostic purposes. Salivary biomarkers are useful in the diagnosis of variety of diseases. It is a noninvasive, 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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