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Review Article

SALIVARY TUMOR MARKERS - A REVIEW

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ABSTRACT

Saliva is an emerging body fluid for detection of clinical diseases with several advantages for disease diagnosis and prognosis. Oral and systemic diseases may affect salivary glands directly or indirectly and influence the quantity and composition of saliva that is produced. Although, the presence of oral cancer markers is normal, the discovery of systemic markers in saliva has offered renewed interest in the potential use of saliva as a diagnostic fluid. Several serum circulatory tumor markers are known to be expressed in saliva with significant correlation to that of the levels in the serum which makes it an attractive fluid for diagnosis of systemic tumors. Various studies have been reported on specific cancer markers such as c-erbB-2, CA 15-3, CA 125, AFP, PSA, CA19-9, Interleukins, kallikreins, ß glucuronidase, osteopontin, immunoglobulins, leptin, VEGF-A which help in the diagnosis of tissue specific benign and malignant tumors. With the development of several new technologies investigations on cancer markers in saliva has been easier and rapid. The two important technologies being developed are salivary proteome and salivary transcriptome analysis with the principle of various proteins and transcriptomes. Several pathways enable the transport of these markers into the saliva. Recent advances in proteomics have put forth a platform for fingerprint profiling of multiple biomarkers in saliva with improved characterization of these salivary markers. The purpose of the review is to look for the potential systemic tumor markers in saliva detected with the modern sophisticated technology which makes it a non interventional and effective diagnostic fluid.

Keywords: Biomarkers, Tumor markers, Salivary Markers, Oral Cancer, Systemic Cancer.

INTRODUCTION

Human saliva is a biological fluid of varying diagnostic potential with several advantages for disease diagnosis and prognosis, such as low invasiveness, minimum cost and easy sample collection with minimum discomfort to the patient/subject. Also handling of saliva during the diagnostic procedures is easier than blood as it does not clot and there is no risk of exposure of the laboratory technician to blood borne diseases. Hence processing and analysis of this biological fluid is the most important criteria and if tests could be easily conducted in clinics with saliva, for early detection of diseases, the quality of life for patients would be greatly improved.[1, 2] Saliva is a product of multiple salivary glands lying beneath the oral mucosa. Salivary glands produce both serous and mucinous saliva containing minerals, electrolytes, enzymes, growth factors, immunoglobulins, mucin and other glycoproteins. It has also been stated that the blood concentrations of many metabolites are reflected in saliva such as urea, uric acid, and albumin.[2, 3, 4] Saliva contains a wide range of altered levels of

proteins in disease too, which may provide information for detection of the same. Profiling the proteins in saliva as the disease progresses could probably reveal a relationship with potential biomarkers to understand different stages of diseases that may be useful in medical diagnostics.[3] For example, Interleukin-6 (IL- 6) and IL-8 are involved in the pathogenesis of oral squamous cell carcinoma (OSCC) and have been linked with increased tumor growth and metastasis; hence its levels could serve as informative biomarkers for OSCC in saliva.[5] This review is an attempt to study the already established tissue specific systemic tumor markers in serum, those systemic tumor markers which have been already established in saliva and to conclude with systemic markers which have not yet been probed in saliva.

MARKERS OF ORAL AND SYSTEMIC CANCER

The presence of oral cancer biomarkers in saliva is a known fact due to direct contact between saliva and the oral cancer lesion and detection of these alterations/markers may be useful in diagnosis of the disease. The presence of mitochondrial DNA mutation and aberrant promoter hypermethylation of cancer related genes is natural in oral cancer.[6, 7] Saliva (oral fluids) is an emerging biofluid for detection of clinical diseases. Seven salivary mRNAs have been identified that discriminate the OSCC patients from the healthy matched subjects. A multicentre trial on a large set of patient population is being carried out to validate this set of signatures for oral cancer.[7] Aberrant hypermethylation of atleast one of these 3 genes -the tumor suppressor gene p16 (CDKN2A), the DNA repair gene O^6-methylguanine-DNA-methyltransferase (MGMT) and gene death associated protein kinase (Dap-K) were detected in the saliva sample of primary stage head and neck carcinoma patients whereas abnormal methylation of DNA was seen in all stages of the cancer.[8] Elevated levels of salivary carcinoembryonic antigen (CEA), defensin-1, tumor necrosis factor alpha (TNF-α), IL-1, IL-6, IL-8, osteopontin and cluster determinant-44 (CD44) were detected in patients of oral cancer. CEA is a protein found in many types of cells but is associated with tumor cells and the developing fetus. TNF-α, IL-1, IL-6 and IL-8 when produced in abnormal fashion are said to be involved in cell growth, invasion and interruption of tumor suppression, immune status and survival of the patients with oropharyngeal carcinoma. Soluble TNF receptor 1 was also found to be higher in OSCC and could likely be used as an additional tumor marker.[9, 10, 11] Several serum circulatory epithelial tumor markers such as cytokeratin fragment 19.21 and 19.1 (Cyfra 21-1), tissue polypeptide specific antigen (TPS), squamous cell carcinoma (SCC) antigen, carbohydrate antigen 125 (CA125), and CA19-9 were found to be significantly increased (by 400%) in the saliva of oral cancer patients.[12] p53 gene mutations are the most frequent alterations seen in human cancer. These mutations lead to the accumulation of p53 proteins in the nucleus of the tumor cells. p53 gene alterations, an early event occurring several years before the clinical manifestations of the disease, are seen in the case of OSCC. The presence of p53 antibodies in saliva was found to be in correlation to the antibodies present in the serum and its detection in saliva also offers a specific method to diagnose OSCC with p53 aberrations.[13] In a study conducted on p53 gene mutations recovered from head and neck SCC's, the genes were sequenced retrospectively and the altered DNA sequences were used as tumor-specific genetic markers for head and neck cancer cells in patient saliva.[14] In more recent times five new protein biomarkers have been discovered and validated by immunoassays for oral cancer detection-Cancer Mac-2 binding protein (M2BP), Myeloid related protein-14 (MRP14), CD59, profilin and catalase. [7] However, the measurement of markers related to systemic tumors in saliva makes it an attractive, non invasive and an alternative to serum testing.[15]

SYSTEMIC TUMOR MARKERS IN SALIVA

Estrogen Receptor-α

In a study conducted by a team from University of Texas Health Science Center, Houston, reported that specific protein markers in saliva can easily identify people with breast cancer cells, benign tumor cells and healthy cells. The researchers have claimed that a person with breast cancer secretes a different profile of proteins compared to a normal healthy individual.[15] Research studies have suggested that the expression pattern of proteins in breast and salivary gland tumors may be common in these two tissues. Several mechanisms have been hypothesized to explain the novel biomarkers of breast cancer in saliva. The most likely mechanism is speculated to be estrogen receptor-alpha (ER-α) dependant for expression. This finding provides a clue to study the mechanism and expression of these proteins of multiple disease states at distant tissues. [16, 17] Estrogen receptors are found to be over expressed

in cases of breast cancer. Binding of the estrogen to the estrogen receptor (ER) stimulates the proliferation of mammary cells leading to increased cell division and DNA replication leading to mutations. At the same time, genotoxic wastes are produced during the metabolism. Both these factors are said to be associated with the disruption of cell cycle, apoptosis and DNA repair leading to the formation of tumor. [18] The discovery of this marker for breast cancer in saliva, has therefore offered renewed interest in the potential use of saliva as a diagnostic fluid for other cancers as well.

HER2/neu and CA 15-3

Appearance of breast cancer changes the set of proteins secreted by the salivary glands and the profile of salivary proteins is different compared to that of the healthy subjects. In a study done to compare the protein expression in benign and malignant breast cancer using isotope tagging, about 49 of the 130 proteins were differentially expressed. Studies also suggest that, additionally, there may be protein profiles that are unique to ductal carcinoma and fibroadenoma cancers. The protein, (c-erbB-2), also known as HER2/neu, is a prognostic breast cancer marker assayed in tissue biopsies from women diagnosed with malignant tumors. An elevated level of this marker indicates aggressiveness and poor prognosis for patient survival. Recent studies suggest that soluble fragments of the c-erbB-2 oncogene may be released from the cell surface and become detectable in patients with carcinoma of the breast. CA 15-3 was set as a standard to measure the diagnostic effectiveness of c-erbB-2 protein. The salivary and serological levels of c-erbB-2 and CA15-3 were significantly higher in the cancer patients, than the salivary and serum levels of healthy controls and benign tumor patients and also it was found that this protein showed high efficiency than the standard CA 15-3 protein. Pilot studies have indicated that the saliva test for this oncogene c-erbB-2 is both sensitive and reliable and is potentially useful not only in initial detection but also of the follow-up screening for breast cancer. [19]

CA125

CA125 is a widely used tumor marker measured most often in women with cancers of the reproductive tissues including the uterus, fallopian tubes and ovaries. Other cancers that may cause abnormal CA125 levels include cancer of the pancreas, lungs, breast and colon. [20] Tumor markers with high sensitivity and high specificity for endometrial cancer are not known at present, although CA-125 is often used in clinical practice. CA-125 values may also be elevated in a number of gynecologic (eg, endometrium, fallopian tube) and nongynecologic (eg, pancreas, breast, colon, lung) cancers. However, the most marked elevations (>1500 U/mL) are generally seen with ovarian cancer. [21] In a study conducted in ovarian cancer patients to compare the CA125 levels in saliva and serum, a linear correlation was observed with respect to the sensitivity of serum and saliva CA125 level. However, there was a drastic difference in the false positive rate of serum CA125 (72.7%) as against salivary CA125 (13.6%). Therefore salivary CA 125 had a better diagnostic value than the serum CA 125. [22]

Prostate specific antigen

Prostate specific antigen (PSA) is a protein produced by the normal prostate cells. It is normally present in low levels in the serum of all adult men. The normal range is 0 to 4 ng/ml. Rising levels of PSA are associated with the prostate cancer. Also in women the greatest concentrations of this antigen is present in breast milk and amniotic fluid. [23] However, it has been clear that PSA is detectable not only in prostrate tissue but also in cancer tissues away from the prostate and normal tissues as well. Hence, it cannot be entirely relied on PSA for diagnosis of metastatic prostate cancer. PSA is detectable in normal man and often is elevated in benign prostatic hypertrophy, which may limit its value as a screening tool for prostate cancer. [24] In an investigation done to determine the free and total PSA levels, and free to total (f/t) ratio in the fasting saliva, in comparison with the serum levels in normal as well as cancer patients, a significant difference between free and total PSA levels in both the saliva and serum samples was noticed, but the salivary f/t ratio was in correlation to that of the normal subjects which indicated that PSA in saliva cannot be efficiently used as an alternate to serum PSA. [25]

An increasing number of systemic diseases and conditions have been shown to be reflected diagnostically in saliva. Efforts are also being made to apply salivary proteomics for disease-specific biomarker discovery, such as lung, gastric and pancreatic cancer. In a study involving detection of salivary biomarkers in pancreatic cancer, revealed eleven mRNA biomarkers with high specificity and sensitivity that differentiated the pancreatic cancer patients from healthy

individuals. The altered gene expression in saliva supernatant was discovered using Affymetrix Human Genome U133+2.0 array. The validation for pancreatic cancer detection was done by logistic regression model in combination with three mRNA biomarkers, yielding a high sensitivity and specific method of distinguishing cancer patients from healthy subjects. This is a proof that salivary biomarkers may be a novel diagnostic tool for the non invasive detection of a systemic cancer. [26] Salivary mRNA and bacterial biomarkers would therefore emerge as highly specific and sensitive tools for lung cancer detection as well. [27]

Alpha fetoprotein

Alpha fetoprotein (AFP) is a protein that has been encoded by the AFP gene. AFP is normally produced during fetal and neonatal development, by the liver, yolk sac and in small concentrations by the gastrointestinal tract. By the second year of life, AFP concentrations decrease rapidly and thereafter, normally, only trace amounts are detected in serum. Normal adults have serum AFP concentrations of less than 10ng/ml. AFP has also been demonstrated in various tumours such as hepatoma, hepatoblastoma, acute and chronic liver cirrhosis and so on. However, it has been implicated that salivary glands are not involved in the synthesis of these proteins. [28] In a preliminary investigation carried to detect the presence of AFP in the human saliva in patients with hepatocellular carcinoma, significant increase in the levels of AFP was observed with respect to the normal subjects. Also a significant correlation was noticed between saliva and serum levels of AFP. It is highly probable that the salivary AFP appears in saliva from plasma by passive seepage. AFP is a useful marker in hepatocellular carcinoma and germ cell tumors associated with extreme elevations >500ng/ml. Hence salivary AFP detection may prove to be a promising technique for detection of hepatocellular carcinoma with saliva as the diagnostic fluid. [29]

CA 19-9

CA 19-9 is not sensitive or specific enough to be used as a screening marker for cancer, and it is not of diagnostic value to any specific type of cancer. Yet, it is mainly used as a general tumor marker. CA 19-9 can only be used as a tumor marker if the cancer is producing elevated amounts of it. Since CA 19-9 is elevated in about 65% of those with bile duct (hepatobiliary) cancer, it may be used to help evaluate and monitor people with this type of cancer. CA 19-9 might be a valuable new diagnostic tool in the preoperative differentiation between malignant and benign parotid tumors but further investigation in a larger number of patients is required to confirm its use as an efficient biomarker to detect specific tumors. [30]

Immunoglobulins

Immunoglobulins are not classic tumor markers but are antibodies/blood proteins which are normally synthesized by the immune system cells to fight against the foreign substances/antigens. There is an elevated level of immunoglobulin in blood in certain bone marrow cancers such as multiple myeloma and Waldenstrom macroglobulinemia. Therefore the presence of high levels of specific monoclonal immunoglobulins is a sign of patients with myeloma or macroglobulinemia. These paraproteins are usually complete antibody molecules but may be isolated light chains or, rarely, heavy chains. They may be lambda or kappa light chains and of any immunoglobulin subtype. The levels of these immunoglobulins can be followed to see the prognosis of the related tumor, i.e., the amount of paraprotein serves as the index for tumor volume which can be used to know the response to the treatment. [31] A study in OSCC patients to detect the levels of IgA, IgG and haptoglobulin reported the significant increase of these markers in untreated OSCC patients compared to the control group. Also a significant increase in IgG and IgA was noticed in the OSCC treated patients compared to the level of salivary haptoglobulin. The IgG and IgA levels were also found to be increased in patients with precancerous lesions. The possible appearance of these immunoglobulins in saliva may be because of direct transudation from the blood or as a local defense mechanism against the tumor development. These salivary parameters evaluated from OSCC patients indicated the presence of IgG and secretory IgA which may prove as a significant prognostic value in early detection of OSCC. [32]

Research studies have also reported the presence of β (2)-microglobulin in the saliva of patients with malignant tumors in the case of head and neck tumors. The malignant tumor cells are likely to excrete β (2)-microglobulin in higher amounts resulting in the infiltration of these proteins into saliva making this a possible method of diagnosing tumors. [33]

ß Glucuronidase

ß glucuronidase is an acid hydrolase that deconjugates glucuronides, however little is known about human β glucuronidase.[34] The salivary ß glucuronidase is said to have application in the detection of head and neck tumors. The subsequent changes in the enzyme level can be used as a diagnostic index to detect the high risk group for malignancy and also to determine the prognosis during the course of the disease.[35]

The assessment of cytokines / hormones in saliva has gained wide acceptance but little is known about its presence in saliva. Salivary peptide hormones such as EGF and transforming growth factor α (TGF-α) are likely to be involved in the promotion of cell proliferation. There has been evidence proving the role of salivary cytokines such as IL-8 and leptin in tumorigenesis in the oral cavity and salivary glands.[36] The expression of the cytokine leptin in saliva was found to be increasing significantly compared to the healthy parotid tissues in the salivary gland tumors. This cytokine was known to be produced directly by the salivary gland tumors and not imported from the blood. The assessment of these salivary hormones provides new ways for the detection of promising tumor markers.[37]

A study aimed at the early detection of OSCC of the tongue using quantitative ELISA revealed five cytokines that were elevated in the treatment group when compared to the healthy subjects, which correlated with the decreased survival rate. IL-1α, IL-6, IL-8, vascular endothelial growth factor A (VEGF-A) and TNF-α were the five cytokines that could serve as potential biomarkers in screening and early detection of cancer.[38]

Kallikreins

Kallikreins are a group of 15 secreted serine proteases possessing numerous physiological roles which are encoded by the genes Tissue kallikrein (KLK_1) and Kallikrein related peptidase (KLK_{215}). The aberrant expression of these kallikreins using immunological assays makes them useful as a tool for screening and diagnosing malignancy.[39] Kallikreins are gaining increased attention as they play a role of biomarkers in screening, diagnosis, and prognosis and monitoring of various cancers such as breast, lung, ovarian and prostate. Recent studies have proved the involvement of kallikreins with the establishment and progression of malignancy. These secretor products from the salivary vesicles of parotid gland are known to function in the proteolytic cascade pathway leading to the cleavage of extracellular matrix components and also in the processing of peptide growth factors such as EGF which facilitates cancer cell invasiveness and metastasis.[40] Human kallikrein 6 (hK6), also known as protease M, is known to express in salivary gland tumors. However, further studies are required to assess whether it can be used as a specific biomarker in salivary gland tumors.[41] Assessment of the expression of hK14 in normal salivary glands and tumors including pleomorphic adenoma, adenoid cystic carcinoma and mucoepidermoid carcinoma, clearly show significantly increased levels of the protein in pleomorphic adenoma and adenoid cystic carcinoma than normal salivary glands and mucoepidermoid carcinoma which is suggestive of its use as a potential biomarker in differential diagnosis of the salivary gland tumors.[42] Picogram quantities of Human glandular kallikrein 2 (hK2) have been detected in saliva. hK2 is a prostate secreted protease known to activate the zymogen form of PSA suggesting its function in a combined form. hK2 functions as an activator molecule and PSA as an effector molecule in amniotic fluid, colostrums and seminal plasma but not in saliva. Only low concentrations of hK2 were detected in saliva.[43]

APPEARANCE OF TUMOR MARKERS IN SALIVA

Although it is inevitable that the markers of oral cancer will be reflected in the saliva, the relationship between systemic disease/ cancer and appearance of biomarkers in saliva is yet unclear. Several intracellular and extracellular pathways enable the biomolecules to move from blood capillaries to the saliva.[6] Many of the biomolecules enter into saliva from the blood by passing through the spaces between cells by transcellular (passive intracellular diffusion and active transport) or paracellular routes (extracellular ultrafiltration). These markers may be carried by the local capillaries of the salivary glands to the oral cavity through the flow of gingival crevicular fluid (GCF).[44] In a mouse model of melanoma and lung cancer conducted to check for the altered salivary biomarkers in systemic cancer revealed the production of growth factors at the tumor tissue site representing the Egr-1 signaling pathway, a mechanism in which nerve growth factor (NGF) produced by the tumor tissue alters the transcriptome of the salivary glands leading to altered gene expression reflecting in the salivary protein profiles. This study using mouse models of

melanoma and non small cell lung cancer has revealed that biomarkers specific for the lung cancer tumor were detectable in saliva of the mouse. This is suggestive that the salivary glands may be regulated by mediators released from remote tumors. The altered salivary protein pattern in the tumor bearing mice, confirmed the speculation of the researchers that the tumors secrete mediators which may affect the activity of transcription factor in salivary glands, thereby inducing either an up or down-regulation of protein transcript levels in saliva.[45]

DETECTION OF SALIVARY TUMOR MARKERS

Saliva sampling and processing is a simple procedure which requires only centrifugation and addition of protease inhibitors before storage. It is also an easily accessible fluid than tissue biopsies and blood sampling. Recently, there has been an appreciation of how saliva can reflect virtually the entire spectrum of health and disease status. But since every invention has its own limitations, it needs greater attention for the identification and development of salivary markers with validation in relation to biomarker panels that has to correlate with the disease onset and progression.[3, 44] The concern of low levels of analytes/diagnostic properties in saliva when compared to the serum has been overcome with the development of highly sensitive techniques. The development of these new techniques has expanded the salivary diagnostics from the oral cavity to the whole physiological system. Both the salivary proteomic and transcriptomic technology has increased the diagnostic potential of saliva.[46] Emerging technologies and discoveries from many fields are leading to saliva based high output, automated, portable, low cost, more efficient and rapid biochemical analysis. Different proteomic technologies such as two dimensional gel electrophoresis (2-DE/MS), shot gun proteome analysis based on mass spectroscopic technologies like Quadrupole Time of flow (TOF), Linear IT and LIT-Orbitrap have been used to analyze the protein composition of saliva qualitatively and quantitatively. Two dimensional gel electrophoresis (2-DE) coupled with either matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) or liquid chromatography-mass spectrometry (LC-MS/MS) has been used as a routine approach for salivary protein separation.[47] Surface Enhanced Laser Desorption-Ionization time-Mass spectrometry (SELDI-TOF-MS) may serve as a high output proteomic approach for profiling saliva. Using these novel technologies for detection, more than 300 different proteins have already been identified in saliva. The most acidic proteins identified were cathepsin L (p*I*, 4.36) and hyaluronan binding protein (p*I*, 4.38), and the most basic proteins identified were salivary proline-rich glycoprotein PRB2 (p*I*, 12.03) and a hypothetical protein (p*I*, 12.08). The smallest proteins identified using shotgun proteome analysis were T-cell receptor delta chain fragment (*M*r, 2.9 kDa) and defensin HNP-3, chain A (*M*r, 3.5 kDa), and the largest one was mucin 5B (*M*r, 590 kDa). Many small salivary proteins such as proline-rich proteins (PRPs), statherin, histatins and defensins were only identified by shotgun proteomics, whereas cystatins and immunoglobulin chains were the smallest proteins identified by 2-DE-MS methods. Salivary transcriptomic technology has become an added advantage to the existing techniques for the detection of numerous mRNA molecules as cancer biomarkers. Use of salivary transciptome in oral cancer patients has shown four salivary mRNAs with a power of 91% sensitivity and specificity for oral cancer detection.[2,47] Several technology groups are developing 'point-of-care-salivary' diagnostic technology to make it easier to read the salivary proteome. Miniaturized saliva based diagnostic technology may help in evaluating critical patient information using minute amounts of saliva that reflect patients health status and disease conditions.[46] Studies also suggest the presence of informative human mRNA in cell free saliva which acts as potential biomarkers for the detection of oral and systemic cancer. This was identified by microarray study using quantitative polymerase chain reaction (Q-PCR) analysis.[48]

Saliva being a complex mixture of proteins has to be processed by chemically labeling them in such a way, that, not only identification of the protein but also levels of the protein can be determined. The success rate of the oral fluid in cancer detection lies in serving these four important approaches: a) to screen healthy subjects for the presence / early detection of cancer; b) diagnosing specific type of cancer; c) to determine the prognosis of the cancer patients and d) to monitor the patient intermittently especially after surgery, receiving chemotherapy and other treatments associated with cancer.[46]

Salivary proteomic analysis can be considered as an important approach towards the diagnosis and treatment of cancer, oral diseases and various other pathological conditions. Amylases, lipases, mucins, immunoglobulins, lysozyme, lactoferrin,

lactoperoxidase, cystatins, histatins, proline-rich glycoproteins, statherins, gustin, secretory leucocyte proteinase are the components present in normal saliva, the composition and flow rate of which determines the oral health. Compiling the salivary proteome is necessary to identify the peptide aberrations in the saliva which will pave the way to diagnose a number of novel biomarkers such as Matrix metallopeptidase 9 (MMP-9), Tissue Inhibitor metalloproteinase 1(TIMP-1), serpin B12, and kallikreins 1 and 11 for the detection of oral cancers.[49]

A syndicate of three research groups identified the subset of proteins in saliva by mass spectrometric approach which was validated by the immunoblot techniques. The saliva was collected as ductal secretions from the parotid and submandibular/sublingual glands. 1166 proteins were identified out of which 914 were from parotid and 917 were from submandibular/sublingual saliva. Comparison of salivary proteome with the plasma and tears were also done. The results stated 192 of 657 plasma proteins were present in saliva and 259 salivary proteins were observed in lacrimal secretions.[49]

The High Performance Liquid chromatography mass spectrometry (HPLC-MS) data from an investigation done on salivary statherin levels in patients with precancerous and cancerous lesions indicates a marked reduction in the salivary statherin levels compared to normal subjects.[50]

Saliva being the most easy of all biological fluids to collect and process, maybe a very good target for the search of new biomarkers of cancer. With data on the proteomics and transcriptomics of normal saliva getting upgraded by the extensive work carried out worldwide, studies on the altered scenario of the proteins in the saliva of cancer patients irrespective of whether the tumor is oral or systemic could be of utmost interest. Table 1 indicates that among the identified serum tumor markers most of them appear in saliva as well. A search for tissue specific markers in saliva therefore could facilitate an early, non interventional, less expensive, less stressful method of cancer detection leading to accurate diagnosis, appropriate treatment and the ensuing prognosis may give the patient a better quality of life.

Table 1. : Distribution of Tumor markers in serum, saliva and both body fluids

Tumor markers	In serum	In saliva	In both
p 53	+	+	+
EGFR	+	+	+
TGF-α	+	+	+
MMP-9	+	+	+
MMP-2	+	+	+
NF-κβ	+	+	+
CA 15-3	+	+	+
CA27-29	+	-	-
CEA	+	+	+
HER2	+	+	+
uPA ((urokinase plasminogen activator)	+	-	-
PAI (Plasminogen activating inhibitors)	+	-	-
Cathepsin D	+	-	-
Kallikrein 14	+	+	+
β (2)-microglobulin	+	+	+
Osteopontin	+	+	+
hK2 (human kallikerin peptidase 2)	+	+	+
EPCA (Early prostate cancer antigen)	+	-	-
AMACR (alpha methyl acyl Co-A racemose)	+	-	-
TGF-β1	+	-	-

AFP	+	+	+
SCC	+	+	+
CEA	+	+	+
CA125	+	+	+
RAB	+	-	-
Chromogranin A	+	-	-
α 1 antitrypsin	+	-	-
NSE	+	-	-
CD44	+	+	+
p 16	+	+	+
BRCA (Breastcancer susceptibility protein)	+	-	-
Defensin	+	+	+
IL-1, 6, 8	+	+	+
IgG, IgA	+	+	+
VEGF-A	+	+	+

'+' indicates Presence of the marker;'-' indicates absence of the marker

CONCLUSION

Although the origin of the disease-induced salivary biomarkers may be both systemic and local, stimulation of salivary gland by mediators released from remote tumors plays an important role in regulating the salivary biomarker profiles. With an attentive approach towards building novel techniques for the detection and validation of salivary markers for oral as well as systemic disease, saliva would serve as a very good diagnostic tool to improve the quality of life of the cancer patients. This review suggests that pursuing of saliva as a tool to detect the different types of cancer can pave the way for improved outcome of future non invasive investigation in the same field giving the patient a chance for a better quality of life.

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