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SATELLITE DNA AS A BIOMARKER IN ORAL CANCER DETECTION

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ABSTRACT

Oral cancer has emerged as an increasing public health problem with high incidence and mortality rates all over the world. Therefore, the implementation of early detection of oral cancer approaches are importance which could reduce the morbidity and mortality rate. Sensitive and specific biomarkers for oral cancer are likely to be most effective for screening, diagnosis, staging and follow-up for this dreaded malignancy. Unlike other deep cancers, oral cancer is located in oral cavity. Hence, the oral cancer lesion makes the measurement of tumor markers in gene as an attractive alternative for tissue testing. The DNA molecules derived from the living cancer cells can be conveniently obtained from tissue. Thus DNA biomarkers, a non-invasive tissue-based biomarkers may be an effective modality for early diagnosis of disease, prognostication and monitoring post therapy status. The emerging field of DNA biomarkers has great potentials to prove its clinical significance to combat oral cancer. Hence, we have reviewed importance of DNA as biomarkers for oral cancer detection.

KEYWORDS: screening, diagnosis, staging, prognostication and monitoring.

INTRODUCTION

Oral cancer is among the leading cancer type in South Central Asian men [1], including India**.** Oral precancerous lesions (PCLs), a benign morphologically altered tissue that has a greater than normal risk of malignant transformation, such as leukoplakia etc., is also very common. Precancerous condition is a condition that does not necessarily alter the clinical appearance of local tissue but is associated with a greater than normal risk of precancerous lesion or cancer development in that tissue such as sub mucous fibrosis etc. Leukoplakia and sub mucous

fibrosis are early indicators of damage to the oral mucosa with a transformation rate of 2–12% to frank malignancies.[2]

Oral cancer affects approximately 0.5% (5 million people) of the population in the Indian subcontinent and is now a public health issue in many parts of the world, including the United Kingdom,[3] South Africa, and many southeastern Asian countries.[4] As a result of transmigration of populations, an increasing number of OSMF cases are being found in other countries.[5] It constitutes one of the major oral health problems in countries like India. Oral lesions and cancers are now affecting even young individuals.

Oral leukoplakia is a common precancerous lesion, characterized by morphologically altered tissue, in which cancer is more likely to occur than its apparently normal counterpart**.** Leukoplakia is defined as a predominantly white lesion of the oral mucosa that cannot be removed by scraping and cannot be characterized clinically or microscopically as any other definable lesion. There is a wide range in the malignant transformation rates (0.3-17.5) of leukoplakia. The frequency of malignant transformation for oral leukoplakia varies between 0-20percent in an observation period of 1-30 years. In general, it is more or less accepted that approximately 3% of leukoplakia will be transformed into cancer in an average period of 5 years**.** Leukoplakia occurs commonly in the age group of 35-45 years. Clinically various forms of leukoplakia have been reported such as homogenous, ulcerated, nodular (speckled), verrucous and candidal**.** Males are more affected than females (because most of the smokers are male). Interestingly it has also been reported that the Leukoplakia on the oral floor or ventral tongue shows malignant transformation of 16% to 19% but those occurring in females are high (47%).[6]

Oral sub mucous fibrosis (OSF) is a pre-cancerous condition characterized by the accumulation of collagen in the lamina propria of oral mucosa. It is characterized by a juxtra-epithelial inflammatory reaction followed by fibroelastic changes in the lamina propria and associated epithelial atrophy.[7] The disease affects most part of the oral cavity as well as the upper third of the esophagus. The incidence of OSMF has increased manifold in various parts of the Indian subcontinent, including Allahabad from South India suggested that tobacco chewing was the most important risk factor for multiple oral premalignant lesions and may be a major etiological factor for cancers on the oral epithelium in the Indian population. In Taiwan, over two million people have the habit of chewing areca nut, and more and more

youngsters do**.** Similarly, oral cancer is associated with tobacco chewing in various forms in several other countries of the world.

Although the available epidemiological evidence indicates that the chewing of the tobacco/pan masala/areca nut is an important risk factor for OSMF, not all chewers develop the disease indicating the importance of genetic predisposition. Genetic predisposition might explain such an individual variabil. Metabolic enzymes that are potentially involved in either the activation (Phase I) or detoxification (Phase II) of chemical carcinogens in tobacco smoke/pan masala have received a great deal of attention recently as possible genetic susceptibility factors for a variety of cancers.

Sat DNA

Satellite DNAs are tandemly repeated sequences that are present as long uninterrupted arrays in genetically silent heterochromatic regions.[8] Basic repeat units of satellite DNAs usually have distinct complex sequences, such as the 171-bplong monomer of the human satellite, which represents a main structural element of centromeric and pericentromeric regions. The most abundant mouse pericentromeric satellite also belongs to this group as it is composed of 234-bp monomers of specific sequence. However, other satellites are composed of short simple repeats, such as human satellite III with a 5 bp-long monomer, as well as many of the *Drosophila* satellites. Several different satellite DNAs are usually present in a species and are subject to the influence of gene conversion and unequal crossing over. These recombinational mechanisms are responsible for the rapid horizontal spread of mutations among monomers in a genome.

Most of the known satellites exhibit sequence change which seems to be constrained by selection in order to preserve some structural characteristics.[9] In addition to selection, the rate of sequence change depends on mutation rate, rates of recombinational processes that spread mutations horizontally through the repetitive family as well as on the rate of fixation within a population.[10]

Microsatellite DNA

Microsatellites (sometimes referred to as a variable number of tandem repeats or VNTRs) are short segments of DNA that have a repeated sequence such as CACACACA, and they tend to occur in non-coding DNA. In some microsatellites, the repeated unit (e.g. CA) may occur four times, in others it may be seven, or two, or thirty. In diploid organisms such as elephants,

each individual animal will have two copies of any particular microsatellite segment. For example, a father might have a genotype of 12 repeats and 19 repeats, a mother might have 18 repeats and 15 repeats while their first born might have repeats of 12 and 15. On rare occasions, microsatellites can cause the DNA polymerase to make an extra copy of CA similar to the way we find it difficult to say ≥toy boat≤ several times in a row with consistent accuracy. If an individuals DNA polymerase adds to the repeated sequence, then this slightly larger version can be passed on to offspring who will usually replicate it accurately. Over time, as animals in a population breed, they will recombine their microsatellites during sexual reproduction and the population will maintain a variety of microsatellites that is characteristic for that population and distinct from other populations which do not interbreed.

Biomarker

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In cancer, a biomarker refers to a substance or process that is indicative of the presence of cancer in the body. A biomarker might be either a molecule secreted by a tumor or it can be a specific response of the body to the presence of cancer. Genetic, epigenetic, proteomic, glycomic, and imaging biomarkers can be used for cancer diagnosis, prognosis and epidemiology.

According to the US National Institutes of Health's (NIH) Working Group and the Biomarkers Consortium, a biomarker is a characteristic that is objectively measured as an indicator of normal biological processes, pathogenic processes, or a pharmacological response to a therapeutic intervention The NIH's National Cancer Institute (NCI) describes biomarkers in its dictionary of cancer terms as "A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Biomarkers are also called molecular marker and signature molecules." Others define a biomarker as a measurable phenotypic parameter that characterizes an organism's state of health or disease, or a response to a particular therapeutic intervention. Biomarkers can also be defined as physical, chemical, or biological agents accessible in body matrices that can be measured in body fluid or cells. The United Nations' World Health Organization (WHO) defines a biomarker as any substance, structure or process that can be measured in the body or its products and influences or the incidence of outcome or disease

(Biomarkers in Risk Assessment: Validity and Validation, Environmental Health Criteria Series, No222, WHO). In the following sections we discuss different classifications of cancer biomarkers and their clinical implications and current challenges in the field.

Prognostic biomarkers

Prognostic biomarkers are based on the distinguishing features between benign and malignant tumors. These biomarkers may also be chosen based on the differentiation status of tumors which can influence clinicians' decisions related to treatment modalities. For example, the prognosis for human papillomavirus (HPV)-associated oral tumors is relatively good in terms of survival time because they manifest in a comparatively well differentiated state[11] Such markers are also important from the point of view of predicting relapse of oral cancer. Commercially available tests such as Oncotype DX (Genomic Health), Mamma Print (Agendia) and the H/I (AviaraDx) are popular in deciding the clinical outcome after surgery on the basis of genetic expression readout.

Predictive biomarkers

Predictive biomarkers, sometimes referred to as response markers, are utilized exclusively in the effect of administering a specific drug. These biomarkers allow clinicians to select a set of chemotherapeutic agents which will work best for an individual patient. For example, Herceptin is useful in breast cancer lesions showing only *Her2/Neu* overexpression, whereas tamoxifen is the preferred treatment for other breast cancer lesions. Thus *Her-2/Neu* is a predictive cancer biomarker for a subset of breast cancer therapies.[12] Likewise, drugs such as erlotinib or gefitinib work only in lung cancer patients with specific mutations in the epidermal growth factor receptor (EGFR) gene.[13]

Another cited example is the use of Gleevec, restricted to certain types of leukemia with Philadelphia chromosome.**[14]** Gleevec targets one cancer protein that causes Philadelphia chromosome positive chronic myeloid leukemia and another protein, Kit, which is the suspected cause of gastrointestinal stromal tumors.

Diagnostic markers may be present in any stage during cancer development.**[15]** Calcitonin in medullary thyroid cancer (MTC) is an example of a diagnostic marker present in the early stages of cancer. Moreover, a diagnostic cancer marker can be stage, tissue, relapse, follow-up and age specific.

HPV as a biomarker

HPV is considered to be a diagnostic cancer biomarker for uterine and cervical cancers as it is present in >90% cancer lesions. The use of HPV as a diagnostic biomarker has been a major step in the development of a cervical cancer screening program and in vaccine development. Recently, the US Food and Drug Administration (FDA) approved some diagnostic markers for bladder cancers based on urine analysis, such as bladder tumor antigen (BTA) and nuclear matrix protein-22 (NMP-22).[16] Survivin and calreticulin also have diagnostic potential for bladder cancer.[17]

SNP-biomarker

Single nucleotide polymorphisms (SNP) in many genes are major DNA markers, including *XRCC1*, *ATM*, *p53* (lung, head, and neck cancers); *CYP1A1*, *RAD1*, *BRCA1* and *BRCA2* (breast cancer); and *PGS2* (lung cancer). Other major DNA markers include loss of hetrozygosity (LOH); variation in copy number of genes; chromosomal aberrations at a gross cytogenetic level, such as translocation/fusion (BCR-ABL, PML-RARA translocation in leukemias), micro-satellite instability (MSI), and epigenetic modifications**.** Mutation(s) in DNA nucleotides in tumor promoters (*Ras*, *APC*), tumor suppressors (*p16*, *p53*, *p19*, *Rb*), cell cycles (cyclins), and DNA-repair related genes (*XRCC*) have been associated with prognosis and diagnosis of different cancers, although their clinical implications have yet to be established. The source of DNA may be from tissue, serum, sputum, saliva, bronchial tear, cerebrospinal fluid (CSF), and tumor cells circulating in the blood, bone marrow, and nipple aspirate.[18] Interestingly, besides nuclear aberrations, alterations in mitochondrial DNA (mtDNA) molecules are suggested strongly as biomarkers for numerous cancers.**[19]**

Epigenetic modification of nucleic acids and associated proteins (histones and non-histones) are important in carcinogenesis.[20] Histone deacetylation, lysine-specific histone-H3 methylation, and promoter region CpG methylation modulates transcription of tumor-suppressor genes (*CDKN2A*, *TP53*, *APC*, *BRCA1*); DNA mismatch-repair genes (*MLH1* or the *O6-methyl-guanine-DNA methyltransferase gene*, *MGMT*). Gene silencing by CpG methylation is one of best characterized epigenetic modifications to date.**[21]** The degree of methylation in prostate cancer tissue, sputum/serum from patients with lung cancer, and saliva in those with oral malignancies are directly implicated in the severity of the lesions. Repetitive DNA sequences, such as those belonging to the *Alu* family, are generally found in regions of DNA termed “satellite” DNA and are associated primarily with the pericentric

(next to the centromere and at the centromere/ juxtacentromeric and centromeric) heterochromatic region of metaphase chromosomes. In cells of normal postnatal somatic tissue, repetitive sequences are relatively enriched in 5-methyl cytosine (m5C) compared to the genome as a whole. However, in sperm cells, the normal methylation pattern of these repetitive regions of DNA is *Cancers* lower than that seen in most somatic cells. In virtually any other context, hypomethylation of repetitive sequences is generally indicative of malignancy. For example, hypomethylation of satellite DNA has been observed in ovarian tumors, and the degree of hypomethylation correlates with the malignant potential of the tumor based on histological criteria.

CONCLUSION

The transfer of scientific knowledge of biomarkers to clinical applications is a challenging process that has rarely resulted in clinical implementation. Understanding the sources of biomarkers (sat DNA) will be a significant objective in the development of diagnostics, as this will provide the rationale for the use of biomarkers for systemic diseases.

REFERENCES

1. Parkinni,P.N. Global variation in cancer incidence and mortality. Curr. Sci., 2001; 81: 465–474.
2. Sankaranarayanan,R. et al. Chemoprevention of oral leukoplakia with vitamin A and beta carotene: an assessment. Oral Oncol. 1997; 33: 231– 236.
3. Canniff JP, Harvey W, Harris M. Oral sub mucous fibrosis: its pathogenesis and management. Br Dent J, 1986; 160: 429-434.
4. Maher R, Lee AJ, Warnakulasuriya KA, Lewis JA, Johnson NW 1994. Role of areca nut in the causation of oral submucous fibrosis: a case-control study in Pakistan. J Oral Pathol Med, 1994; 23: 65-69.
5. Reichart PA, Philipsen HP: Oral submucous fibrosis in a 31-yearold Indian women: first case report from Germany. Mund Kiefer Gesichtschir. 2006; 10(3): 192-196.
6. Hazarey VK, Erlewad DM, Mundhe KA, Ughade SN: Oral submucous fibrosis: study of 1000 cases from Central India. J Oral Pathol Med, 2006; 35: 1-6.
7. Tilakratne WM, Klinikowski MF, Saku T, Peters TJ, Warnakulasuriya S: Oral sub mucous fibrosis: Review on aetiology and pathogenesis. Oral Oncol 2005; 30: 30-32.
8. Charlesworth B, Sniegowski P, Stephan W (1994) The evolutionary dynamics of repetitive DNA in eukaryotes. *Nature*, 371**:** 215–220.

9. Ugarkovi,. Functional elements residing within satellite DNAs. *EMBO Rep*., 2005; *6*: 1035-1039.
10. Dover, G.A. Molecular drive in multigene families: how biological novelties arise, spread and are assimilated. *Trends Genet*., 1986; *2*: 159-165.
11. Mishra, A.; Bharti, A.C.; Varghese, P.; Saluja, D.; Das, B.C. Differential expression and activation of NF-kappaB family proteins during oral carcinogenesis: Role of high risk human papillomavirus infection. *Int. J. Cancer*. 2006; *119*: 2840–2850.
12. Roses, R.E.; Paulson, E.C.; Sharma, A.; Schueller, J.E.; Nisenbaum, H.; Weinstein, S.; Fox, K.R.; Zhang, P.J.; Czerniecki, B.J. HER-2/neu overexpression as a predictor for the transition from in situ to invasive breast cancer. *Cancer Epidemiol. Biomarker Prev*. 2009; *18*: 1386–1389.
13. Sharma, S.V.; Bell, D.W.; Settleman, J.; Haber, D.A. Epidermal growth factor receptor mutations In lung cancer. *Nat. Rev. Cancer*, 2007; *7*: 169–181.
14. Milone, J.H.; Enrico, A. Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. Leuk. *Lymphoma*, 2009; *50*: 9–15.
15. Habis, A.H.; Vernon,S.D.; Lee, D.R.; Verma, M.; Srivastava, S.; Unger, U. Molecular quality of exfoliated cervical cells: implications for molecular epidemiology and biomarker discovery. *Cancer Epidemiol. Biomarkers Pre.* 2004; *13*: 492–496.
16. Lau, P.; Chin, J.L.; Pautler, S.; Razvi, H.; Izawa, J.I. NMP22 is predictive of recurrence in highrisk
17. superficial bladder cancer patients. *Can. Urol. Assoc. J.* 2009; *3*: 454–458.
18. Kageyama, S.; Isono, T.; Matsuda, S.; Ushio, Y.; Satomura, S.; Terai, A.; Arai, Y.; Kawakita, M.; Okada, Y.; Yoshiki, T. Urinary calreticulin in the diagnosis of bladder urothelial carcinoma. *Int. J. Urol.* 2009; *6*: 481–486.
19. Sidransky, D. Emerging molecular markers of cancer. *Nat. Reviews. Cancer*. 2002; *2*: 210–219
20. Verma, M.; Srivastava, S. Epigenetics in Cancer: Implications for Early Detection and Prevention. *Lancet Oncol.* 2002; *3*: 755–763.
21. Enokida, H.; Shiina, H.; Igawa, M.; Ogishima, T.; Kawakami, T.; Bassett, W.W.; Anast, J.W.; Li, L.C.; Urakami, S.; Terashima, M.; Verma, M.; Kawahara, M.; Nakagawa, M.; Kane, C.J.; Carroll, P.R.; Dahiya, R. CpG hypermethylation of MDR1 gene contributes to the pathogenesis and progression of human prostate cancer. *Cancer Res.* 2004; *64*: 5956–5962.

22. Kaneuchi, M.; Sasaki, M.; Tanaka, Y.; Shiina, H.; Verma, M.; Ebina, Y.; Nomura, E.;Yamamoto, R.; Sakuragi, N.; Dahiya R. Expression and methylation status of 14-3-3 sigma gene can characterize the different histological features of ovarian cancer. *Biochem. Biophys. Res. Commun*. 2004; *316*: 1156–62.