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Genetics and Oral Cancer: A Review

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Introduction

Head and neck cancer (HNSCC) is the sixth most common cancer worldwide and has a severe impact on quality of life for patients and survivors. OSCC incidence accounts for up-to 40% of all malignancies in India and South East Asia. Therefore, early diagnosis of high risk pre-malignant lesions and early cancers are high priorities for reducing the burden of HNSCC. In contrast to the current perception of head and neck cancer as a single progression mechanism, but data support the idea that at least two progression routes to malignancy exist, with different prognosis. This new information on the mechanisms of oral cancer development may lead to new ways of classifying this tumour type in relation to prognosis. A serious clinical problem is that, by current methods, it is impossible to identify in advance the 2-5% of the more common leukoplakias that will progress to cancer. Gene expression profiling has tried to identify different types of oral cancer and to investigate their relationships to premalignancies and the implications for prognosis. First understanding the molecular progress may help to understand why cancer progresses and identify specific biological points appropriate for prevention strategies.

Normal Keratinocyte Senescence

One of the characteristics of normal cells is their limited proliferative potential, i.e. they permanently cease proliferating ('senesce') after about 50 population doublings. During normal cell proliferation the ends of chromosomes (telomeres) become progressively shortened due to a phenomenon known as the end replication problem. Senescence is thought to be triggered by signals generated by one or more telomeres reaching a critical length. The about 40% of primary oral cancers (SCCs) and about 60% of dysplasias are mortal and undergo senescence Mortal and immortal SCCs also differ in the expression of *p53* and *Rb/E2F* target genes, including the novel *p53* target [1-3].

The presence of specific alcohol dehydrogenase gene polymorphism has been determined to confer differential susceptibility to the alcohol risk in certain populations. Genetic polymorphisms of several xenobiotic metabolizing agents including the cytochrome P450IA1, glucathione S transferase genes (*GSTMI*). Glucosyltranserase IA7 (*UGT1A7*) genes have increased risk for tobacco related habits [4].

In the cases, very high levels of expression of certain genes, *p15* the *p65* subunit of the transcription factor (NF-kappa B) and I kappa B kinase, may lead to malignancy. Lack of tumor suppressor gene *PTEN* may be an important prognostic factor of the squamous cell carcinoma of tongue, expression of hepatocyte growth factor

oncogene is involved in invasive metastatic change of head and neck squamous cell cancer (HNSCC). High expression of epithelial growth factor (EGFR) and the proactive cell nuclear antigen (PCNA) have been related with short patient survival and are thus of poor prognosis. Cyclin D I (CCNDI) regulatory factors modulates the critical cell cycle control. CCNDI is over produced, in a significant proportion of head and neck squamous cell cancer (HNSCC) with aggressiveness, early recurrence and prognosis. Over expression of cyclin D1 (CCNDI) has been related to radiosensitiity and may be a prognostic factor of the effectiveness of radiation therapy on head and neck squamous cell cancer (HNSCC). Antisense cyclin DI may be useful, particularly in combination therapy, for instance with cisplatin, in treatment of head and neck squamous cell cancer (HNSCC) [5].

An association between the presence of HPV and the development of head and neck cancer has been established recently. A critical molecular parameter supporting a causal role of HPV 16 in head and neck squamous cell carcinoma (HNSCC) is the expression of the *E6* and *E7* oncogenes coupled with inactivation of pRB and *p53*. Indeed, it has been shown that pRB protein levels are down-regulated in HPV 16-positive head and neck squamous cell carcinoma (HNSCC), a clear indication of E7 activity. Concerning *E6* and *p53*, the HPV 16-positive tumors could be divided into two groups. The tumors exhibited *E6* gene expression and lacked *p53* mutations or, alternatively, they lacked *E6* expression and carried *p53* mutations. Infection with oncogenic HPV types and the other major risk factors for head and neck cancer, tobacco and alcohol, may represent alternative pathways in the development of these cancers. The association of head and neck cancers with clinically significant morbidity and disfiguration makes the early detection of the diseases and biomarkers to identify individuals at high risk of great importance. One of the conclusions from a recent National Cancer Institute (NCI) workshop convened to assess viruses associated with human cancers was that future HPV research needs to focus on developing a sensitive, validated laboratory test to detect HPV in oral exfoliated cells that could reflect HPV high risk types in head and neck tumors. HPVs are small oncogenic viruses, which are implicated, in epithelial carcinogenesis, and *p53* is a tumor suppressor gene with a central role in the prevention of genomic injury. HPV infection and activation of the *H-ras* gene is seen in oral verrucous carcinomas. These results continue to confirm the multihit hypothesis of tumorigenesis and suggest that in some cases of oral cancer at least two of these events are *H-ras* gene mutation and HPV infection. Betel quid probably causes additional mutagenic steps in the carcinogenic process. The *E6* oncoproteins of these high risk HPVs are known to bind and induce degradation of *p53* tumor suppressor protein [6-9].

This degradation is controlled by a common polymorphism of the *p53* gene encoding either a praline or an arginine at its condon 72 in exon 4. A polymorphism of genes involved in metabolism of various endogenous and exogenous carcinogens are relatively common in most population. P 450 cytochromes (CYP) are enzymes, which catalyse the insertion of one atom of molecular oxygen into a substrate. This is a typical reaction of activation (Phase I), which converts indirect carcinogens into active electrophiles capable of interacting with the biological macromolecules DNA, RNA and protein. CYPs are coded by genes of the CYP super family. Glutathione S-transferases are one of the major groups of detoxifying enzymes. NFjB controls the expression of a number of growth promoting cytokines and the DNA binding activity of NFjB is induced during the G0-G1 transition. NFjB also activates the expression of genes important

for invasion and metastasis, *LjBa* expression in tumor cell decreases the frequency of metastases. Mutations in the *LJBa* gene have been detected in Hodgkin's lymphoma and are suggested to render NFjB constitutively active in Hodgkin's cells, consistent with a role for LjB as a tumor suppressor. Insights into mechanisms by which nutritional factors affect the process of carcinogenesis are provided by knowledge of the targeted gene function and enzyme activity. Increased knowledge in this area will allow a more refined approach to reducing risk for caner, with diet interventions targeted toward individuals and subgroups that are genetically susceptible and responsive to the effects of nutritional factors [10-13].

Subpopulations exist who have increased genomic instability. These individuals are at an increased risk for the accumulation of DNA mutations and the development of head and neck cancer. Individuals with specific polymorphisms in the *CYP1A1*, *GSTM1* genes and finger protein 217 have a genetically high risk of oral squamous cell carcinoma suggesting that an individual difference in susceptibility to chemical carcinogens is one of the most important considerations in the risk assessment of oral cancers [14,15].

The wound-healing process involves a complex interplay of cells, mediators, growth, and cytokine. The cascade of events begins with clotting and recruitment of inflammatory cells and then proceeds to a highly proliferative state. During this proliferative phase, fibroblasts are involved in synthesis and remodelling of the collagen matrix, keratinocyte spread across the wound to form a new epithelial layer, and angiogenesis occurs. This latter step is crucial in the healing process. During neovascularisation, endothelial cells change their genetic program and express an angiogenic phenotype that includes the production of protease, cell migration, and proliferation, followed by dedifferentiation, thus resulting in the formation of new blood vessels. The formation of new blood vessels provides a route for oxygen and nutrient delivery, as well as a conduit for components of the inflammatory response. Healing is concomitant with an increasing release of angiogenic growth factors from macrophages and keratinocytes, such as vascular endothelial growth factor (VEGF), fibroblast growth factor, and platelet-derived growth factor, and its impairment leads to a delay in skin repair. EPO, dose-dependently inhibited granulation tissue formation. *RHuEPO* gene is able to improve wound healing by stimulating granulation tissue formation, neovascularisation and dermal regeneration. This might be of particular relevance in the clinical situation of disturbed and delayed wound repair [16,17].

Both Smad3 and its closely related homologue, Smad2, are intracellular mediators of TGF-b function, acting as nuclear transcriptional activators. Smad2 and Smad3 mediate intracellular signalling from TGF-bs 1-3 and activin, each of which has been implicated as an important factor in the cellular proliferation, differentiation and migration pivotal to cutaneous wound healing. Disruption of the Smad3 pathway *in vivo*, coupled with exogenous TGF signalling through intact alternate pathways, may be of therapeutic benefit in accelerating all aspects of impaired wound healing [18,19].

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