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The Genetics of Wound Healing and Oral Cancer

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ABSTRACT
The most frequent cancer in India is oral cancer, which has been epidemiologically associated to chewing betel nut and other carcinogens. But the p53 and p15 genes showed a number of point mutations. In order to determine hereditary risks as well as indicators for oral cancer and wound healing, this review was undertaken. In terms of genotype frequencies and cigarette smoking dose, polymorphisms of the CYP1A1 and GSTM1 genes are linked to malignancies caused by tobacco use. Additionally, E6/E7 expression was discovered in malignancies, the majority of which originated in the oropharynx. p53 is approximately seven times more sensitive to E6-mediated proteolytic degradation when homozygous arginine is present at codon 72. As one of the main mitogens involved in cutaneous wound healing, erythropoietin, vascular permeability factor (VPF, commonly known as vascular endothelial growth factor or VEGF), and PDGF have all been identified. Cell survival is improved when NF-kB is activated. In tonsilar cancer, the presence of the human papilloma virus is a markedly positive prognostic feature that can be employed as a marker to optimise patient care.

Keywords: Genetics, genetic screening, oral cancer, wound healing, gene therapy.

INTRODUCTION
The sixth most prevalent cancer in the world, head and neck squamous cell cancer (HNSCC), has a significant negative influence on patients' and survivors' quality of life. Up to 40% of all cancer cases in South East Asia and India are oral squamous cell carcinomas (OSCC). [1] In order to lessen the burden of HNSCC, early detection of high risk premalignant lesions and early malignancies is of utmost importance. Data support the concept that there are at least two progression paths to malignancy, each with a different prognosis, in contrast to the prevalent understanding of HNSCC as a single progression mechanism. New classification schemes for this tumour type in regard to prognosis may result from this new understanding on the mechanism of mouth cancer development. The fact that it is currently impossible to predict in advance which 2-5% of the more common leukoplakias will develop into cancer is a severe clinical issue. In order to determine the hereditary risk as well as the indicators for both oral cancer and wound healing, this review was undertaken. A thorough search of the literature turned up 56 publications, of which 38 were found to be pertinent.

GENOMICS OF ORAL CANCER AND WOUND HEALING
The many kinds of oral cancer and their connections to premalignancies as well as the consequences for prognosis have been identified using gene expression profiling. First, figuring out the molecular pathways may help us comprehend why cancer spreads, and

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second, we might pinpoint specific biological sites that call for effective preventive measures. One of the traits of normal cells is their restricted proliferative potential, which means that after roughly 50 population doublings, they permanently stop reproducing (or "senesce"). The "end replication problem" is a condition that occurs during normal cell growth and causes the ends of chromosomes (telomeres) to gradually shorten. The signals produced when one or more telomeres reach a certain length are thought to be what cause senescence. Senescence occurs in around 60% of dysplasias and about 40% of primary oral cancers (SCCs). The expression of the novel p53 target gene, DRAM, as well as Rb/E2F target genes varies between mortal and immortal SCCs [2].

Different groups have been found to be more or less susceptible to the risk of alcohol consumption depending on the availability of particular alcohol dehydrogenase gene variants. The risk of developing tobacco-related behaviours is raised by genetic polymorphisms in numerous xenobiotic metabolising enzymes, including the glucathione S transferase genes (GSTMI), glucosyltransferase 1A7 (UGT1A7), and cytochrome P4501A1. [3]

When specific genes, such as p15, the p65 subunit of the transcription factor (NF-kappa B), and I kappa B kinase, are expressed at extremely high levels, malignancy may result not having a tumour suppressor gene The expression of the hepatocyte growth factor oncogene is involved in the invasive metastatic transformation of HNSSCs, and PTEN may be a significant prognostic factor for tongue SCC [4]. Epithelial growth factor (EGFR) and proactive cell nuclear antigen (PCNA) expression levels that are high are associated with poor prognosis and short patient survival. The crucial cell cycle control is modulated by components regulated by cyclin D 1 (CCND1). In a sizeable part of HNSSC with aggressiveness, early recurrence, and prognosis, CCND1 is overproduced. The overexpression of CCND1 has been linked to radiosensitivity and may be a predictor of how well radiation therapy will work on the HNSSC. In the treatment of HNSSC, antisense CCND1 may be beneficial, especially in combination therapy, such as with cisplatin [5, 6, 7]

Recently, a link has been found between the development of HNSSC and the presence of the human papilloma virus (HPV). [8-11] The production of the E6 and E7 oncogenes along with the inactivation of pRB and p53 is a crucial molecular factor supporting a causative involvement for HPV-16 in HNSCC. As evidence of E7 action, it has been demonstrated that pRB protein levels are downregulated in HNSCC that are HPV-16 positive. [12, 13]

The HPV-16-positive tumours may be divided into two categories based on E6 and p53 expression. The tumours either expressed the E6 gene and had p53 mutations, or they did not express the E6 gene and had p53 mutations. [14] Tobacco use and alcohol use, two additional prominent risk factors for HNSCC, may represent alternate paths in the emergence of these tumours. [15] Early disease identification and the use of biomarkers to identify people who are at high risk are crucial due to the link of HNSCC with clinically substantial morbidity and disfigurement. The development of a sensitive, validated laboratory test to detect HPV in oral exfoliated cells that would reflect HPV high risk types in head and neck tumours was one of the recommendations from a recent National Cancer Institute (NCI) workshop convened to assess viruses associated with human cancers [16]. Small oncogenic viruses called HPVs have been linked to the development of epithelial cancer, and the tumour suppressor gene p53 is essential for preventing genomic damage. Oral verrucous carcinomas exhibit H-ras gene activation and HPV infection. These findings support the multihit model of carcinogenesis and imply that HPV infection and H-ras gene mutation may account for at least two of these events in some cases of mouth cancer [17].

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The carcinogenic process is likely to undergo extra mutagenesis steps as a result of betel quid [18].It is known that the E6 oncoproteins of these high risk HPVs bind to and cause the p53 tumour suppressor protein to degrade via ubiquitin pathways. A frequent polymorphism in exon 4 of the p53 gene, which codes for either a proline or an arginine at codon 72, regulates this degradation [19]. In the majority of populations, polymorphisms in genes implicated in the metabolism of numerous endogenous and exogenous carcinogens are rather prevalent. P450 cytochromes (CYP), which are enzymes, catalyse the insertion of one molecular oxygen atom into a substrate. This is an example of a phase I activation reaction, which turns indirect carcinogens into active electrophiles that can interact with the biological macromolecules DNA, RNA, and proteins. The CYP super family of genes codes for CYPs.

[21] One of the most important subgroups of detoxifying enzymes is glutathione S-transferases. A number of growth-promoting cytokines are expressed under the direction of NFjB, and the G0-G1 transition induces the DNA-binding activity of NFjB. The expression of genes necessary for invasion and metastasis is also activated by NFjB. [22] In tumour cells, IjBa expression lowers the incidence of metastasis. [5] Hodgkin's lymphoma has IjBa gene mutations that are thought to make NFjB constitutively active in Hodgkin's cells, supporting IjB's function as a tumour suppressor [23]. Knowledge of the targeted gene function and enzyme activity provides insights into methods by which dietary variables affect the process of carcinogenesis. The ability to focus diet interventions at people and subgroups who are genetically vulnerable and responsive to the impacts of nutritional variables will be made possible by increased information in this field [24].

There are subpopulations with higher genetic instability. These people are more likely to acquire head and neck cancer and accumulate DNA mutations, and various aberrations of chromosome 3p have been found in premalignant lesions of the mouth. [25] Individual differences in the susceptibility to chemical carcinogens is one of the most crucial factors in the risk assessment of oral cancers. People with certain polymorphisms in the CYP1A1, GSTM1, and zinc finger protein 217 have a genetically high risk of OSCC. [6]

A complicated combination of cells, mediators, growth factors, and cytokines plays a role in the wound-healing process. [26] Clotting and the recruitment of inflammatory cells are the first steps in the chain of events, which subsequently leads to a highly proliferative state. In this proliferative stage, keratinocytes expand over the wound to create a new epithelial layer, angiogenesis takes place, and fibroblasts are engaged in the manufacture and remodelling of the collagen matrix. The healing process depends on this final stage. [27] Endothelial cells undergo a genetic programme change during neovascularization, expressing an angiogenic phenotype that includes protease production, cell migration, and proliferation, followed by dedifferentiation, leading in the development of new blood vessels. [28] The growth of new blood vessels creates a pathway for the transport of nutrients and oxygen, as well as a pathway for inflammatory response factors. Its impairment causes a delay in skin restoration. Healing is accompanied by an increase in the release of angiogenic growth factors from macrophages and keratinocytes, such as vascular endothelial growth factor (VEGF), fibroblast growth factor, and platelet-derived growth factor.

EPO, in dose-dependent inhibition, prevented the development of granulation tissue. By promoting the production of granulation tissue, neovascularization, and dermal regeneration, the RHuEPO gene can accelerate wound healing. This may be especially important in the clinical setting of disrupted and slow wound healing. Smad3, a nuclear transcriptional

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activator, and Smad2, a closely similar homologue, are both intracellular mediators of TGF-activity.

The intracellular signalling from TGF-s 1, 2, and 3 as well as activin is mediated by Smad2 and Smad3, each of which has been identified as a critical element in the cellular proliferation, differentiation, and migration essential to the healing of cutaneous wounds. Exogenous TGF signalling through intact alternative pathways combined with in vivo Smad3 pathway disruption may be therapeutically beneficial in speeding all facets of poor wound healing.

CONCLUSION

The discovery of genes is only the first step toward a fundamental knowledge of human disease. Cancer genetic counsellors work with patients who have the disease or have a family history of it. These genetic targets can be used in gene therapy to treat oral tumours, bone restoration, and wound healing. Suicide gene therapy, also known as genetic prodrug activation therapy, gene replacement therapy, adenovirus E1 region gene therapy, and immunological gene therapy, are all gene therapy options for head and neck cancers. Tissue engineering for soft tissues and bone is also now a reality thanks to significant advances in genetics, proteomics, and molecular biology. In the near future, mouth cancer patients may have a new future.

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