REVIEW ARTICLE

IL6 Gene Polymorphism and Oral Cancer: A Review

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ABSTRACT

Oral cancer is labeled as one of the most common human malignancy worldwide. Regardless of the advancements made in its treatment it has a very low 5 years survival rate. This is due to late diagnoses and poor responses to treatment because of advanced/late stage at the time of presentation. Specific early biomarkers are required that can predict severity and stage of the disease. Inflammatory cytokines especially, IL-6 plays a central role in cancer. IL-6, a pro-inflammatory cytokine, secreted by various cells of the body, has been thoroughly investigated in oral cancer development and progression by various studies. An electronic article search was done through PubMed, Google Scholar and Medscape, using the following keywords: oral cancer, Interleukin-6 and IL6 gene polymorphism. All types of articles were included to discuss the role of IL 6 gene polymorphism in the development of oral cancer.

KEY WORDS: *IL 6 Gene Polymorphism, Oral cancer.*

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INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) occupies the sixth rank among the most prevalent cancers worldwide[1], and 80-90% of these cancers are of Oral Squamous Cell Carcinoma (OSCC) type [2, 3].The overall 5 year survival rate of head and neck cancer has been low (over 50%) in the last two decades regardless of the advancement in detection and treatment[4]. Oral carcinogenesis is a multiple step process, influenced by various environmental factors and genetic modifications in oncogenes and tumor suppressor genes[5]. These genetic alternations can be recognized before the disease is physically established. Since these changes arise specially in cancer cells, so they can be used as potential biomarkers[6]. Recent advancements have been made in research field to understand the HNSCC progression at molecular level, and this has helped to identify various biomarkers, which help in detection of not only primary cancers but also recognition of recurrent tumors (or relapses) at a very early stage[7].

A number of medical and epidemiological researches have observed that chronic inflammation plays a role in predisposing a subject at risk of developing various types of cancer and the malignant cells proliferates under the influence of mediators released by the inflammatory cells[8, 9].Several mechanisms like, genetic and epigenetic changes creates an inflammatory microenvironment which further supports the development of cancer, demonstrating a connection between inflammation and cancer[10]. And polymorphism of these inflammatory cytokine genes is thought to be linked with cancer vulnerability[11]. Interleukin 6 is a multifunctional cytokine that enhances the activity of cancer cells[12]. It is thought to be involved in malignant transformation and growth of the tumor cells[13]. These properties results from neo-angiogenesis and inhibition of apoptosis of cancer cells[14]. These changes are mediated by different pathways including transcription activator 3 and the signal tranducer[15,16,17]. Different stages of tumor development including initiation, promotion, malignant transformation, invasion and metastasis are thought to be due to markedly raised levels of IL6 and its major effectors like signal transducer and activator of transcription 3 (STAT 3)[18-21]. Furthermore IL 6 levels in vitro and vivo are reported to be influenced by genetic variants of IL 6 which is a G-to-C substitution at position -174 upstream of the transcription start site[22]. An electronic article search was done through PubMed, Google Scholar and Medscape, using the following keywords: oral cancer, Interleukin-6 and IL6 gene polymorphism. All types of articles including (randomized controlled trials, clinical observational cohort studies, review articles, case reports) were included.

DISCUSSION

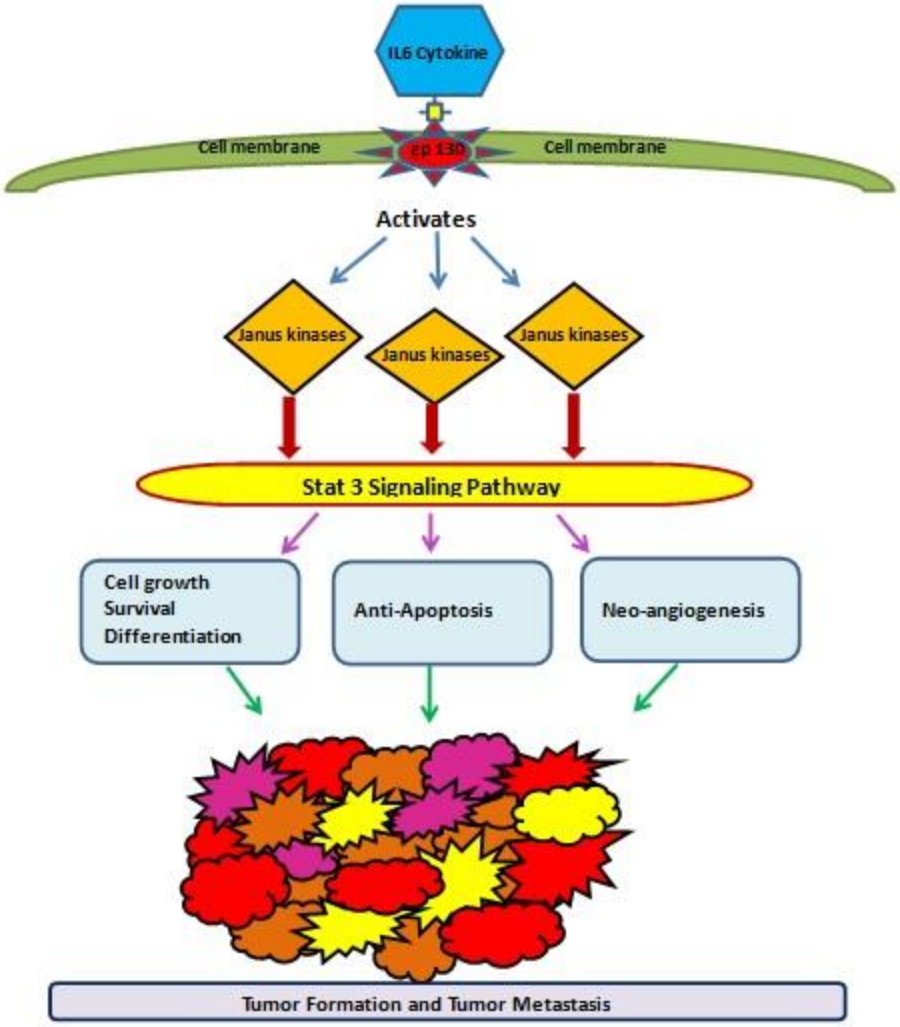
For detection of cancer at an early stage various biomarkers have been investigated so far, A reliable biomarker must meet the following criteria: (a) the alteration in its level can be accurately measured (b) it must be assessable in small specimens(c) it must be transformed in high-risk tissues, but not in normal tissues and (d) changes in its levels must be detected at early stages of cancer development. So in the present article we will review the recent discoveries for IL6 cytokine as potential biomarker for the early detection of OSCC.

IL 6 mediated tumor genesis

According to Riedel et.al[23] study, environment that is rich in IL6 cytokine helps OSCC cells to more suitably attack and metastasize. While another study done by van Bokhorst-de et.al[24] reported that IL6 causes immune unresponsiveness and cachexia, which is observed in OSCC patients with poor outcomes. Yin et.al[25] and Kusaba et.al[26] observed that signal transduction and activator of transcription (STAT 3) phosphorylation are linked with various human cancers and predicts poor prognosis. The epigenetic switch from non-transformed epithelia to cancer cells is due to IL6 and its major effector (STAT 3),which is responsible for various process of tumor formation including, cell differentiation, proliferation, anti-apoptosis, neo-angiogenesis and metastasis[27] (Figure 1)

Figure 1: IL 6 mediated tumor genesis. IL 6 cytokine binds to gp130 on cell surface and causes activation of Janus kinases which further leads to activation of STAT 3 signaling pathway thus

leading to cell growth, survival, differentiation, angiogenesis, and anti-apoptotic properties which are responsible for tumor formation and metastasis



Raised levels of IL 6 produced by cancer cells

Studies have revealed that IL6 expression by autocrine and paracrine mechanisms lead to chronic inflammation, and also displays a very strong relation with cancer[28,29,30]. Squamous cell when stimulated by inflammatory cells, or when they are obtained from patients with lichen planus[31], radicular cyst[32], or psoriasis[33], produces cytokines in vitro, so it may be practical to consider that tumor cells in OSCC synthesize IL6. This pro-angiogenic and pro-inflammatory cytokine IL6 was considerably high in the saliva of OSCC patients when compared to patients having oral-premalignant lesions and control[34].Chen et.al[35] revealed that IL6 has been found in much higher concentrations in serum of Oral squamous cell carcinoma patients when compared with age matched control subjects. Regarding expression of OSCC using microarray significantly raised IL6 levels were observed[36], and high levels of this cytokine were found in the serum of OSCC patients when matched to that of the healthy controls[37,38]. Gallo et.al[39] did a study on patients with OSCC, which showed increase serum levels of IL6 that correlated with poor prognosis. Increased levels of IL6 in oral cancer is associated with the development of tumor cells, and when these levels were compared with IL 6 levels in patients with periodontal disease, they were much higher in oral cancer patients [40,41].An investigation done by Pak et.al [42]demonstrated a decline in the IL6 levels due to the effect of surgery, chemotherapy and radiotherapy in post-

treatment patients. While Ando et.al[43] found high IL6 levels in patients with cancer induced cachexia. Chang et.al[44] and Pine et.al[45] reported raised levels of IL6 linked with increased risk of cancer and also found high levels of IL 6 in advanced stage cancer. A research done by Vairaktaris et.al[46] validated IL6 gene polymorphism to be responsible for the development of OSCC, and Ujiie et.al[47] stated IL6 as a cancer disease predictive marker.

CONCLUSION

It is yet to be resolved that which cellular constituents produce this cytokine or whether the tissue levels of this cytokine is related with tumor size, lymph node invasion or histological grade of malignancy. This cytokine level is useful in determination of treatment possibility and may be a prognosticator, so information on this cytokine in Oral cancer is exceptionally vital. But since the expression of this cytokine can be influenced by many other factors, so studies should be carried out on large scale population before introducing it as a dependable discriminatory Oral Cancer biomarker.

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