

INTERLEUKINS WITH A NOTE ON IL6 IN ORAL MALIGNANCY

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ABSTRACT

Interleukins are the most ubiquitous cytokines found in inflammatory conditions. They have varied role in physiological and pathological conditions. Their action is orchestrated by interaction between different cytokines/ receptors and tissue microenvironment. The present article briefs about Interleukin 6 and its role in Oral squamous cell carcinoma (OSCC).

KEYWORDS: Interleukins, IL6, Oral ssquamous cell carcinoma.

INTRODUCTION

Interleukins belong to the family of cytokines which regulate immunological, inflammatory and reparative host responses. The term interleukin refers to the products of leucocytes that exert a regulatory influence on other cells. They are highly potent hormone-like substances which are active even at femtomolar (10^{-15} M) concentrations. They exert paracrine effect on the cells of the microenvironment. Sometimes, they act on the cells that produce them (autocrine effect).^[1] Interleukins have pleotropic effects on various cell types. Interleukins have been categorized and subcategorized as IL 1 to IL 38 based on the source of cells that produce them and their major functions.^[2] (Table 1).

Table 1: Biologically important Interleukins.^[1]

Interlukins	Main Sources	Major Function
IL1 (α and β)	Macrophages and other cell types	Proliferation and differentiation of T, B and other cells; pyrogenic; induce acute phase proteins; bone marrow cell proliferation
IL2	T cells	Promote growth and differentiation of T and B cells, cytotoxicity of T and NK cells, secretion of other lymphokines
IL3	T cells	Multi-CSF
IL4	T _H cells	Proliferation of B and cytotoxic T cells; increase IgG1 and IgE production; enhances MHC class II and IgE receptors
IL5	T _H cells	Proliferation of eosinophils, stimulate IgA and IgM production
IL6	T _H , macrophages, fibroblasts	Promote B cell differentiation; IgG production, acute phase proteins
IL7	Spleen, bone marrow stromal cells	B and T cell growth factor
IL8	Macrophages, others	Neutrophil chemotactic factor
IL9	T cells	T cell growth and proliferation
IL10	T, B cells, macrophages	Inhibit IFN production and mononuclear cell functions
IL11	Bone marrow stromal cells	Induce acute phase proteins
IL12	T cells	Activate NK cells
IL13	T cells	Inhibit mononuclear cell functions
IL17	T _H 17 cells	Proinflammatory marker

Cytokines mediate their actions by JAK-STAT and NF- κ B pathway.^[3] The net effect of the pathways depends on the cytokines involved. IL 12 activation of JAK- STAT pathway causes upregulation of proinflammatory cascade whereas IL-10 has an inhibitory effect.^[4]

Interleukin 6

Interleukin 6 is a pleiotropic cytokine secreted by T lymphocytes, B lymphocytes, fibroblasts, endothelial cells, keratinocytes and cancer cells. It is a 26 kD glycoprotein involved in differentiation of B cells to plasma cells and also proliferation of T cells.^[5] IL6 is a biologically active cytokine which has role in immune regulation, hematopoiesis, inflammation, and oncogenesis. IL 6 mediates its action largely through JAK-STAT pathway.^[6]

JAK-STAT pathway

The Janus kinase/signal transducer and activator of transcription (Jak/Stat) pathway were discovered 20 years ago as a mediator of cytokine signaling. There are four Jaks, and seven Stat involved in the pathway. There are Jaks Jak1, Jak2, Jak 3 and Tyk2 which selectively

bind different receptor chain.^[7] Seven mammalian Stat family members involved are STAT 1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. Different cytokine activate a particular STAT.^[8]

IL6 signals by binding to a soluble circulating receptor, which then binds to a cell-surface receptor called gp130. Binding of the ligand dimerizes the receptors and induces a conformational change allowing JAK proteins to bind to their intracellular domains and phosphorylate tyrosine residues, converting the receptor into a tyrosine kinase. The activated receptors now phosphorylate STAT3 proteins, allowing them to form homo- and heterodimers and move rapidly into the nucleus, where they associate with other proteins to form transcriptional complexes (Figure 1). Positive regulators of JAK- STAT pathway include cytokines, receptors, tyrosinases. Negative regulators include tyrosine phosphates, protein inhibitors of activated STAT, suppressor of cytokine signalling proteins.^[6]

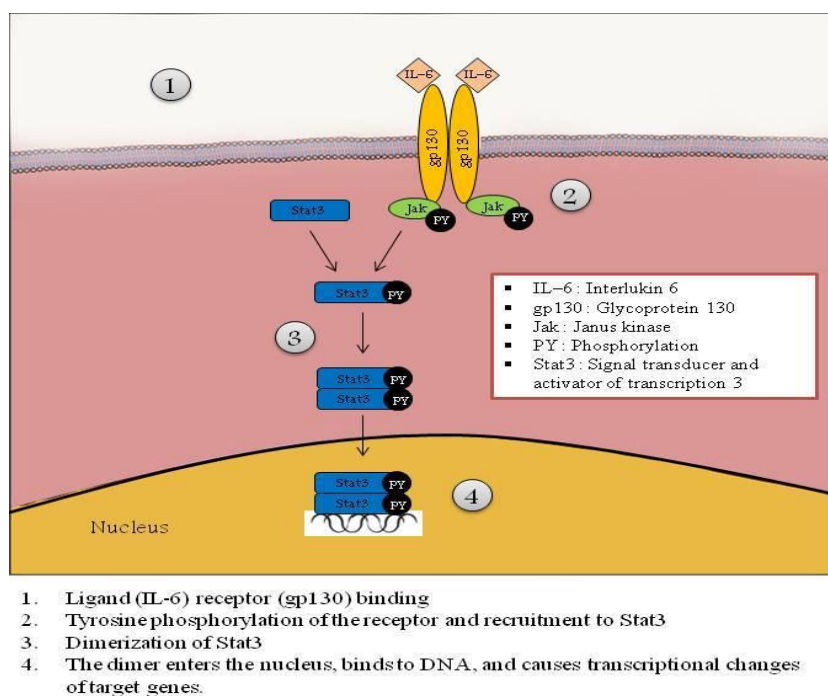


Figure 1: IL6 mechanism through JAK/STAT pathway.

Interleukin 6 and oral cancer

Interleukin 6 has been implicated in many physiological and pathological conditions like trauma, infections, immune disorders, malignancies. In many malignancies it is seen that IL6 activates STAT3 transcriptional mediators which are found continuously tyrosine phosphorylated which in turn is because of increased binding of IL6 and its receptor.

The expression of interleukins in oral squamous cell carcinoma (OSCC) has been shown consistently associated with poor prognosis in many studies. Jinno et al, Chen MF have shown positive correlation of IL6 with tumor progression. Sato J et al, Duffy in their study have found that IL6 expression was associated with locoregional recurrence of OSCC. Tawara K showed that IL6 was associated with cancer metastasis to bone. Shinriki showed in their study that IL6 promotes OSCC by increasing endothelial growth factor C synthesis and lymphangiogenesis. Yadav A in their study showed that IL6 caused metastases of tumor by Epithelial Mesenchymal Transition.

CONCLUSION

Interleukin 6 has been found to be the most abundant cytokine found in inflammatory conditions. Drug designed as antagonist to IL6 receptors (Tocilizimab) has been proved to be active in cases of Rheumatoid arthritis. Although positive correlation between IL6 and severity of OSCC has been established by many studies, therapeutic intervention using IL6 inhibition at receptor level, JAK-STAT pathway is still at experimental level. Hence more research is required in this direction.

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