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REVIEW ARTICLE

Interleukin-6 role in head and neck squamous cell carcinoma progression

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Abstract Interleukin-6 (IL-6) is a pleiotropic cytokine which plays an important role in a number of cellular processes including proliferation, survival, differentiation, migration and invasion. IL-6 mediates its downstream effects by activating a number of signaling cascades including JAK/STAT, PI3K/AKT and MAPK pathways. In addition to its effects on tumor cells, IL-6 also regulates tumor progression and tumor metastasis by modulating tumor angiogenesis and tumor lymphangiogenesis. A number of studies have shown that IL-6 levels are markedly upregulated in cancer patients. We and others have shown that high IL-6 expression independently predicts tumor recurrence, tumor metastasis and poor survival in head and neck cancer patients. Therefore targeting IL-6 signaling is a potential therapeutic strategy for the treatment of head and neck squamous cell carcinoma (HNSCC). In this review, we discuss the current understanding of the role of IL-6 in HNSCC progression and potential therapeutic strategies to target IL-6 signaling for the treatment of head and neck cancer patients.

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Introduction

Head and neck squamous cell carcinoma (HNSCC) remains a major health care problem worldwide, comprising almost 50% of all malignancies in some developing nations.[1–3] Although advancements in the anti-cancer treatments including surgery, radiation and chemotherapy have increased the local control of HNSCC, the overall survival rates have not improved significantly over the last three decades.[3,4] Five year survival rates for patients with early stage localized head and neck cancers are more than 80% but drops to 40% when the disease has spread to the neck nodes, and to below 20% for patients with distant metastatic disease.[4] Acquisition of chemoresistance and metastatic phenotype are the major causes of treatment failure and mortality in these patients.[1,5] It is therefore imperative that we gain a better understanding of the molecular mechanisms that contribute to the aggressive tumor phenotype in order to develop novel and effective strategies for the treatment of head and neck cancer patients.

Interleukin-6 (IL-6) is one of the key molecules that has been widely studied and implicated in poor clinical outcomes in HNSCC patients.[6–10] IL-6 was initially identified and cloned as B-cell stimulatory factor-2.[11–13] At the same time a number of other molecules (IFN-β2, plasmacytoma growth factor and hepatocyte-stimulating factor) were independently cloned and found to be identical to IL-6.[14–16] Accumulating evidence has shown that IL-6 plays an important role in a number of biological process including immune regulation, hematopoiesis, inflammation and oncogenesis.[17–19] IL-6 is produced by a wide variety of cell types including immune cells (macrophages, dendritic cells and B-cells), endothelial cells and tumor cells.[20–23] We and others have shown that IL-6 levels are markedly elevated in the blood samples from cancer patients including HNSCC and independently predict tumor recurrence, poor survival and tumor metastasis.[6–8] A number of mechanistic studies have corroborated these clinical observations. Using our *in vitro* and *in vivo* head and neck cancer models, we were able to demonstrate that IL-6 is a potent inducer of epithelial to mesenchymal transition (EMT) in head and neck cancer cell lines thereby promoting regional (lymph node) and distant (lung) metastasis.[20] Similarly, Lederle et al[24] demonstrated that IL-6 promotes malignant growth of squamous cell carcinoma by regulating a complex cytokine and protease network. Recent studies have also highlighted the role of IL-6 in the acquisition of chemoresistance and stem cell phenotype in cancer cells.[25–28] We hereby present a review of recent studies that demonstrate the role of IL-6 in head and neck cancer progression.

Clinical significance of IL-6 in HNSCC

The association of IL-6 with clinical parameters (clinicopathological factors) and oncological outcomes in HNSCC has been largely studied over the past two decades. Several studies have shown elevated levels of IL-6 in HNSCC.[6,8,26,29] In a study of 65 untreated HNSCC patients and 20 healthy volunteers, Mojtahedi et al[29] found that serum levels of IL-6 and IL-18 were significantly increased in HNSCC patients compared to healthy individuals, however only the difference of IL-6 levels was found to be statistically significant. In addition, they showed that IL-6 concentration increased as tumor stage progressed and a significant difference was observed between stage IV vs stage I/II/III disease. These results suggest the activation of the Th2 arm of the immune response in HNSCC patients. However, Lathers et al[30] found elevated levels of IL-2 and GM-CSF in addition to IL-4, IL-6 and IL-10, thereby suggesting that HNSCC patients might have incomplete Th2 skewing. This theory of incomplete Th2 immune switch was further supported by the work of Sparano et al[31] where they examined blood samples from 58 patients of histologically proven HNSCC and showed that there were significantly higher levels of IL-6 and IL-10 as compared to IL-12. In addition, they showed that T3 and T4 patients had a positive relationship between tumor size and serum IL-6 levels. Similarly, in a case—control study of 90 HNSCC patients and 39 controls, Riedel et al[8] showed higher levels of IL-6 in serum of HNSCC compared to healthy controls. They also showed a statistically significant correlation between serum IL-6 concentrations and with higher tumor stage and positive lymph nodes. In a prospective study of 85 patients with primary HNSCC, Tartour et al[32] showed a significant association between higher lymph node (N) classification and elevated serum IL-6 levels.

In addition to serum levels of IL-6, tumor IL-6 expression both at mRNA and protein levels are also directly correlated with higher tumor stage and positive lymph nodes.[9,33] Wang et al[33] examined IL-6R and IL-6 mRNA expression in 86 oral squamous cell carcinoma tumor specimens and showed significantly higher IL-6R and IL-6 mRNA expression in tumor samples as compared to normal mucosa. IL-6 and IL-6R mRNA levels were also associated with larger tumors and more advanced histological grade. We have recently examined IL-6 expression in HNSCC by immunohistochemistry and our results show a direct correlation between IL-6 expression and tumor stage, tumor recurrence, perineural invasion, extracapsular spread and inversely associated with HPV status.[9]

Considering the direct correlation between elevated IL-6 levels and high risk clinicopathological features in HNSCC, it does not come as a surprise that increased IL-6 levels are also associated with poor oncological outcomes in HNSCC and are reflective of a high burden of disease. This concept is further strengthened by the reduction of IL-6 levels after treatment in HNSCC patients. Several reports have studied IL-6's association with oncological outcomes in HNSCC. Allen et al[34] studied numerous cytokines (IL-6, IL-8, growth-related oncogene-1 [GRO-1], VEGF and hepatocyte growth factors) longitudinally in a small prospective study of 30 patients with advanced oropharyngeal HNSCC receiving chemoradiation treatment by measuring serum levels at baseline and every 3 months. They showed a significant decrease in disease specific survival with longitudinal increase in levels of IL-6, suggesting that IL-6 could be a biomarker of treatment response and survival. Similarly, De Schutter et al[35] did a retrospective study of 34 patient samples showing that pre-treatment IL-6 serum level is an independent predictor of local control, disease free survival and overall survival. These concepts where further strengthened by our large prospective, longitudinal cohort study of 444 patients, where we have shown that serum IL-6