



Review

# Chemokine-Cytokine Networks in the Head and Neck Tumor Microenvironment

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**Abstract:** Head and neck squamous cell carcinomas (HNSCCs) are aggressive diseases with a dismal patient prognosis. Despite significant advances in treatment modalities, the five-year survival rate in patients with HNSCC has improved marginally and therefore warrants a comprehensive understanding of the HNSCC biology. Alterations in the cellular and non-cellular components of the HNSCC tumor micro-environment (TME) play a critical role in regulating many hallmarks of cancer development including evasion of apoptosis, activation of invasion, metastasis, angiogenesis, response to therapy, immune escape mechanisms, deregulation of energetics, and therefore the development of an overall aggressive HNSCC phenotype. Cytokines and chemokines are small secretory proteins produced by neoplastic or stromal cells, controlling complex and dynamic cell–cell interactions in the TME to regulate many cancer hallmarks. This review summarizes the current understanding of the complex cytokine/chemokine networks in the HNSCC TME, their role in activating diverse signaling pathways and promoting tumor progression, metastasis, and therapeutic resistance development.

**Keywords:** head and neck squamous cell carcinomas; cytokines; chemokines; tumor microenvironment; apoptosis; invasion; metastasis; angiogenesis; response to therapy; immune evasion

## 1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is a very aggressive disease with a dismal prognosis. With an annual incidence of ~800,000 new cases and 350,000 deaths worldwide, HNSCC is the sixth most common cancer globally [1]. HNSCC includes tumors of the oral cavity, hypopharynx, oropharynx, larynx and, paranasal sinuses and is clinically, pathologically, phenotypically, and biologically a heterogeneous disease [2]. Oral squamous