REVIEW ARTICLE OPEN

# Tumor microenvironment: an evil nexus promoting aggressive head and neck squamous cell carcinoma and avenue for targeted therapy

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Head and neck squamous cell carcinoma (HNSCC) is a very aggressive disease with a poor prognosis for advanced-stage tumors. Recent clinical, genomic, and cellular studies have revealed the highly heterogeneous and immunosuppressive nature of HNSCC. Despite significant advances in multimodal therapeutic interventions, failure to cure and recurrence are common and account for most deaths. It is becoming increasingly apparent that tumor microenvironment (TME) plays a critical role in HNSCC tumorigenesis, promotes the evolution of aggressive tumors and resistance to therapy, and thereby adversely affects the prognosis. A complete understanding of the TME factors, together with the highly complex tumor–stromal interactions, can lead to new therapeutic interventions in HNSCC. Interestingly, different molecular and immune landscapes between $HPV^{+ve}$ and $HPV^{-ve}$ (human papillomavirus) HNSCC tumors offer new opportunities for developing individualized, targeted chemoimmunotherapy (CIT) regimen. This review highlights the current understanding of the complexity between $HPV^{+ve}$ and $HPV^{-ve}$ HNSCC TME and various tumor–stromal cross-talk modulating processes, including epithelial–mesenchymal transition (EMT), anoikis resistance, angiogenesis, immune surveillance, metastatic niche, therapeutic resistance, and development of an aggressive tumor phenotype. Furthermore, we summarize the recent developments and the rationale behind CIT strategies and their clinical applications in $HPV^{+ve}$ and $HPV^{-ve}$ HNSCC.

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## INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the 6th most common cancer worldwide, with an annual incidence of more than 800,000 new cases and 350,000 deaths.[1–3] Clinically, pathologically, phenotypically, and biologically, HNSCC is a heterogeneous disease of the oral cavity, oropharynx, hypopharynx, larynx, and paranasal sinuses.[4,5] Oral squamous cell carcinoma (OSCC) is the major subtypes of HNSCC and accounts for two-thirds of the cases in developing countries. While tobacco and alcohol consumption are responsible for ~75% of HNSCC cases, recently, a substantial increase in human papillomavirus (HPV)-associated oropharynx cancers (OPC)[6] in the Western world has been observed which is expected to surpass cervical cancers by 2020 in the USA.[7] In contrast to the etiological role of tobacco smoking in Western countries,[8] the use of smokeless tobacco (ST) products like pan masala, gutkha, and betel quid are the major risk factors in Asian countries, including India.[9–12] Other etiological factors such as exposure to radiation,[13] wood dust,[14] asbestos,[15] salted foods,[14] poor oral hygiene,[16] and Epstein–Barr virus (EBV) infection[17] also increase the risk of HNSCC.

HNSCCs are mostly diagnosed at an advanced stage with locally advanced (LA) or distant metastasis (DM). Despite multimodality therapeutic interventions which include surgery, radiotherapy (RT), chemotherapy (CT), and/or immunotherapy (IT), a majority (40–60%) of the LA tumors ultimately display recurrence/local progression. Treatment of metastatic and recurrent (R/M) HNSCC tumors with palliative CT also displays poor prognosis. The complete understanding of the HNSCC tumor biology might help us overcome the low therapeutic response of HNSCCs and aid in developing therapeutic strategies with minimal inherent or acquired resistance. Therefore, understanding the HNSCC biology and identifying novel therapeutic targets for effective management of this malignancy is the dire need.[18]

Most of the previous studies were focused on targeting only cancer cells. However, recent studies have shown that noncancerous cells surrounding the tumor and extracellular matrix (ECM) proteins, which together form the TME, play a critical role in

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