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Immune Escape and Immune Checkpoint-associated Therapies in the Tumour Microenvironment of Head and Neck Squamous Cell Carcinoma

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Abstract. Head and neck squamous cell carcinoma (HNSCC) comprises a prevalent category of malignant neoplasms that present as oropharyngeal, oral cavity, laryngopharyngeal, hypopharyngeal, and laryngeal cancers. Each year, close to a million people around the globe find themselves grappling with these fierce and relentless cancers. Addressing HNSCC often requires a multifaceted approach, ranging from surgical intervention and radiation to chemotherapy, immunotherapy, or a blend of these treatments. Nonetheless, the five-year survival rate for HNSCC persists at fifty percent overall and has not exhibited substantial improvement in recent years. Prior research has demonstrated that the tumor microenvironment (TME) significantly influences recurrence, metastasis, and drug resistancein individuals with HNSCC. This review outlines the roles of both anti-tumor and pro-tumor immune cells, as well as the extracellular components of the tumor microenvironment (TME) in head and neck squamous cell carcinoma (HNSCC).The discussion encompasses classical immunotherapies for HNSCC, the molecular pathogenesis of HNSCC, the tumor microenvironment in HNSCC, and the mechanisms through which HNSCC cells evade immune surveillance. The paper highlights several clinical trials that focus on using CTLA-4 inhibitors alongside combination therapies involving programmed cell death protein 1 (PD-1) and its ligand, PD-L1. As well as looking forward to some potential therapeutic approaches in clinical care that are expected to provide new strategies for clinical treatment.

Keywords: Head and Neck Squamous Cell Carcinoma (HNSCC); Immune Checkpoints; Immune Escape; PD-1/PD-L1; Cytotoxic T Lymphocyte Antigen 4 (CTLA-4).

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) stands as the sixth most common cancer worldwide, with approximately 600,000 new diagnoses each year. This cancer predominantly develops in the mucosal linings of the mouth, throat, and voice box. Key risk factors linked to HNSCC include highexposure to tobacco-related carcinogens and excessive alcohol use. Additionally, oncogenic viruses, particularly high-risk strains of human papillomavirus (HPV), with HPV-16 being notably significant, are increasingly recognized as common causes of head and neck squamous cell carcinoma (HNSCC) in younger patients. Treatment options for HNSCC include surgery, radiotherapy, chemotherapy, and targeted therapy, either alone or in combination, with the appropriate approach depending on the tumor's location, stage, as well as the patient's age and overall health. Poor prognosis in HNSCC patients is due to high rates of recurrence and metastases that occur within the lymph nodes. Generally, the overall five-year survival for patients with HNSCC is approximately 50 to 60%. As many as 30% develop recurrent cancer and eventual failures in treatment [1].

The TME encompasses a highly interwoven cellular and non-cellular compartment that performs various key functions in tumor growth and development. Cellular components include diverse populations of stromal cells, such as CAFs, ECs, and vascular elements, but also immune cells like TAMs, MDSCs, T cells, B cells, and NK cells. These cells are interactively close in the TME in promoting tumor development. On the other hand, at the non-cellular level, the main composition

will be made of extracellular matrix proteins such as collagen, fibronectin, and laminin that provide structural supports and biochemical cues that drive cell functions [2].

These tumor cells highly rely on the TME for their supplementary resources, which are nutrients, intermediary metabolites, hormones, cytokines, chemokines, and growth factors important in tumor growth, proliferation, and survival. It also contributes to immune evasion by building a protective niche that enables a tumor to escape elimination by the host immune system and maintains an inflammatory environment that promotes the development of cancer. Moreover, the metabolic changes within the rapidly proliferating tumor cells can remodel the TME to alter its cellular composition and functionality toward creating an environment that further favors the invasion, metastasis, and treatment resistance of cancer cells. These dynamic interactions give a basis for targeting the TME in therapeutic approaches with the aim of halting tumor progression.

Given that TME displays potent properties in HNSCC that determine the fate of tumour cells, grasping the complex communication between cancer cells and the host's immune system is crucial for successfully treating HNSCC. Cancer cells have evolved various strategies to escape immune detection, enabling their continued growth, survival, and spread [3]. Uncovering the cellular and molecular signaling pathways tied to immune checkpoint inhibition could pave the way for new immunotherapies designed to counteract these evasive tactics. This review contributes to the understanding of emerging research on the current state of TME, summarises the molecular mechanisms by which tumour cells interact with TME and discusses therapeutic strategies to target microenvironmental components. Given that TME plays a key role in regulating tumourigenesis, progression and response to anticancer therapies, a deeper understanding of the bidirectional communication between tumour cells and TME will inspire innovative combination therapies targeting both tumour cells and microenvironmental components.

This review examines the role of TME in HNSCC through antitumour and pro-tumour immune cells and extracellular components. It discusses TME in classical HNSCC, mechanisms of cell-cell immune escape in HNSCC, and relevant immunotherapies for HNSCC. Clinical trials of immune blockade therapies for HNSCC, and combined immune checkpoint inhibition are also presented, with a focus on illustrations of clinical trials include those exploring the use of CTLA-4 inhibitors alongside combination treatments targeting the PD-1/PD-L1 pathway. And, some potential immunosuppressive therapies in clinical treatment are also envisioned, which are expected to provide new strategies for clinical treatment.

2. TME in HNSCC

The concept that the tumor microenvironment (TME) plays a critical role in cancer progression is far from new. As early as 1863, Rudolf Virchow observed that white blood cells surrounded cancer cells, which led him to propose that chronic inflammation could be a precursor to cancer. However, Virchow's work focused on immune cells only, not taking into consideration the broader components comprising the TME. Later, in 1889, Paget extended this concept in his "seed and soil" hypothesis, which suggested that all elements of the TME, not just immune cells, play a role in the development of cancer. Further building on this, Bissell and co-authors later established that the involvement of the TME is just as critical as genetic factors in tumor initiation and progression. In the last decade, comprehensive investigations have established the crucial role of the TME in controlling the growth and spread of HNSCC, further strengthening its status as one of the most important concepts in tumor biology. The roles played by the main cellular constituents of the TME and their communication via the secretion of growth factors, cytokines, and chemokines in a complex network with their malignant cellular counterparts have become of growing interest. Complete characterization of the tumour microenvironment is indeed a pre-requisite for the development of reliable prognostic markers and novel advanced therapies in head and neck squamous cell carcinoma [4].

In HNSCC, the tumor microenvironment (TME) is composed of diverse, non-cancerous cells embedded within a complex extracellular matrix (ECM), collectively forming the tumor stroma. A

constant exchange of signals between the cancer cells and their surrounding stroma occurs, enabling the tumor to manipulate the microenvironment through paracrine signaling, which enhances tumor growth and metastasis. The key cellular elements of the tumor microenvironment (TME) consist of immune cells, fibroblasts, mesenchymal stromal cells, cells originating from the hematopoietic and bone marrow lineages, vascular endothelial cells, and nerve cells.These non-cancerous cells are estimated to constitute about 90% of the total tumor mass. While some of these cells may initially act to limit tumor progression, growing evidence suggests they also significantly contribute to cancer growth and dissemination.

Cancer was once viewed merely as a mass of undifferentiated tumor cells, with little attention given to the stromal cells present in its microenvironment. In the case of HNSCC, however, the tumor microenvironment is now understood to be a complex ecosystem made up of both cellular and non-cellular components. The cellular elements include altered stromal cells such as cancer-associated fibroblasts (CAFs), endothelial cells (ECs), adipocytes, neuroendocrine cells, blood and lymphatic vessels, as well as a variety of infiltrating immune cells like T-cells, B-cells, and natural killer cells. The non-cellular elements of the tumor microenvironment (TME) include extracellular matrix (ECM) proteins such as collagen, fibronectin, and elastin, alongside a range of physical and chemical factors like pH, oxygen concentration, interstitial pressure, and fluid flow [5]. Recent studies show that stromal cells provide tumor cells with vital substances, including metabolites, nutrients, hormones, cytokines, and chemokines, as well as growth factors, all of which are essential for tumor growth, invasion, metastasis, and survival. Moreover, these stromal cells play a role in recruiting cancer-associated fibroblasts (CAFs), tumor-supporting immune cells, and inflammatory cells, and help tumor cells escape immune detection. This interaction fosters an environment conducive to tumor growth, metastasis, and resistance to therapies. These findings highlight the critical role of the TME in influencing abnormal tissue behavior and advancing the progression of more aggressive malignancies. The involvement of TME in HNSCC is illustrated in Figure 1.

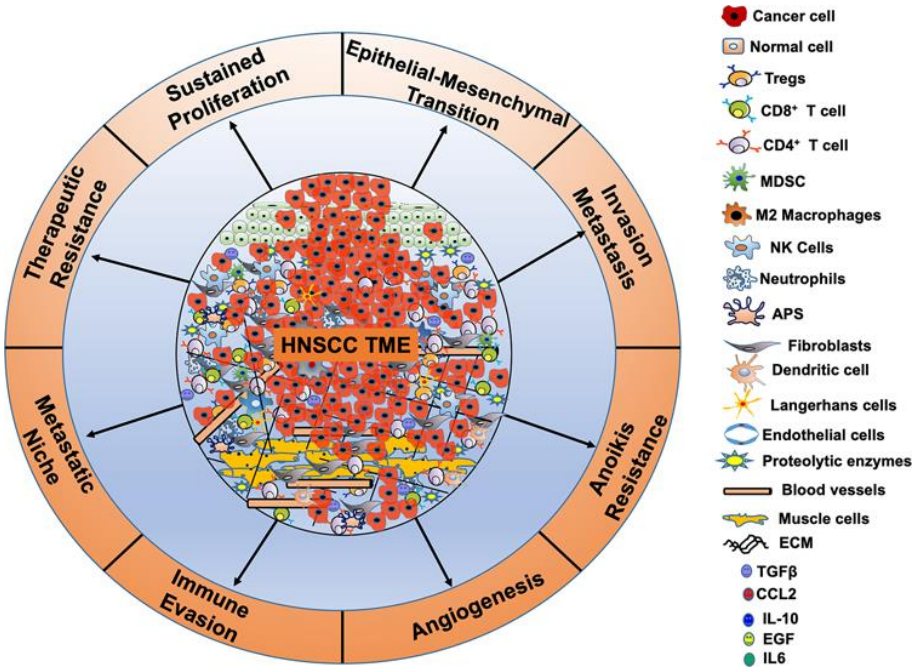

Fig. 1 Role of TME in HNSCC [1].

By downregulating critical anti-tumour immunity signalling steps, HNSCC can elude immune surveillance and cause unchecked tumour growth. Some of the immunosuppressive mechanisms in TIME include a decrease in chemokines that attract immune effector cells, an increase in immunosuppressive Th2-type cytokines, a decrease in chemokines that attract M2 macrophages or MDSCs, and a reduction in T-cell receptor (TCR) activity, along with impaired interaction between HLA peptide antigens due to the disruption of antigen processing mechanisms, ultimately hindering the processing and presentation of tumor-associated antigens.Furthermore, tumor cells undergo a

dynamic process termed immunoediting, in which fewer immunogenic tumor cells that can evade the immune response proliferate under selection pressure, giving them a survival advantage.

3. Immune Escape Mechanism

It was shown that by evaluating data from preclinical and translational studies,one way to categorize tumors is according to their immunological phenotype. These can be inflammatory (hot form), immune exclusion (exclusion), or immune desert (cold form).

The initial characteristic is the occurrence of tumour-infiltrating lymphocytes, accompanied by myeloid cells and monocytes; these infiltrating immune cells, and at times the tumor cells themselves, show activation of immune checkpoints, especially PD-1 and its ligand, PD-L1. mRNA analysis of tumor specimens can detect numerous pro-inflammatory and effector cytokines.This immune profile may be responsive to immune checkpoint inhibitors, suggesting that an anti-tumor immune response, though currently suppressed, is already present.

The second distinguishing characteristic is the immune exclusion phenotype, characterized by a substantial presence of immune cells outside the tumor nests, restricted to the surrounding stromal tissue. Following treatment with immune checkpoint inhibitors (ICIs), CD8 and CD4 T cells may display activation and proliferation but are unable to penetrate the tumor, indicating a problem with effective tumor homing.This tumor type does not respond to checkpoint inhibitors, indicating that its mechanism of immune evasion is independent of the inhibitory effects of the PD-L1 pathway.

The immune desert phenotype is characterized by a lack of T cells in the tumor microenvironment or stroma, coupled with immunosuppressive alterations in the tumor immune environment, vascular structures, or stromal components. These tumors infrequently exhibit responsiveness to anti-PD-L1/PD-1 therapy. This phenotype may indicate a lack of pre-existing anti-tumor immunity, implying a critical barrier in the generation of tumor-specific T cells. Both the "cold" and "excluded" phenotypes may be classified as non-inflammatory tumors [6]. Data is current as of October 2023. As illustrated in Figure 2.

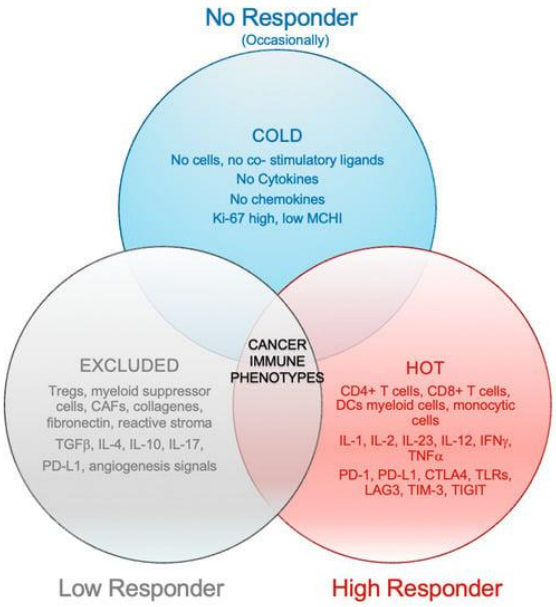

Fig. 2 Types of immune escape [2].

4. Application of Immune Checkpoint Therapy

immunological checkpoints modulate self-tolerance and immunological activity through regulatory signals. It plays an essential role in protecting host tissues from immune-mediated indirect damage

and avoiding autoimmune diseases. To keep self-tolerance and protect neighboring organs from immune reactions, immunological checkpoints control T cell activity.

Recently, immunotherapy has emerged as a key strategy for treating tumors. One prominent method is immune checkpoint blockade (ICB), which uses monoclonal antibodies to interfere with the interactions between checkpoint proteins on immune cells and their ligands on tumor cells. The main focus of ICB involves targeting CTLA-4 and the PD-1/PD-L1 pathways, which have been extensively researched and are of great interest. In the tumor microenvironment (TME), the PD-1/PD-L1 axis is essential for regulating communication between immune cells and tumor cells [4].

5. Cytotoxic T Lymphocyte Antigen 4 (CTLA-4)

Activated by CD28, CTLA-4—the first immune checkpoint receptor to be clinically targeted—generates the immunosuppressive molecule transforming growth factor-β (TGF-β). It is mainly expressed in T cells. Receptors that span cell membranes are CTLA-4 and CD28, respectively.In its role as a negative regulator of immune responses, CTLA-4 binds to B7 proteins that cause T-cell dysfunction. To efficiently stimulate the immune response without causing excessive damage to normal tissues is the normal function of CTLA-4's immunosuppressive effect under normal conditions. Nevertheless, when cancer cells release TGF-β, it can trigger the expression of CTLA-4, which in turn causes a decrease in the number of functional T-cells, a condition that could potentially suppress the immune system. On T-cell surfaces, CD28 binds CTLA-4 more strongly than it does to CD80 and CD86, which are co-stimulatory molecules. The outcome is that T cells can't multiply and do their job [7].

CTLA-4 and CD28 interact with the ligands CD80 and CD86 present on the surface of antigen-presenting cells (APCs). When T cells become activated, they express CTLA-4, which accumulates at the junction between the T cell and the APC, thereby blocking co-stimulatory signals and suppressing the response of the activated T cells.

Moreover, CTLA-4 is expressed on regulatory T cells (Tregs). CTLA-4 possesses characteristics that occasionally result in its localization to the plasma membrane. Approximately 90% of CTLA-4 is situated intracellularly. Around 90% of CTLA-4 is located inside the cell rather than on the cell surface. Unlike CD28, which remains primarily on the cell surface, CTLA-4 is notable for its ability to undergo rapid endocytosis. This process causes more than 80% of CTLA-4 molecules present on the cell surface to be internalized within just five minutes. Interestingly, once CTLA-4 is internalized, it is not necessarily degraded; instead, it can be transported back to the cell surface. This recycling occurs through the release of CTLA-4 from endosomes, allowing it to return to the plasma membrane and continue regulating immune responses. This dynamic cycling between the cell surface and intracellular compartments is a key mechanism by which CTLA-4 modulates the immune system, ensuring tight control over T cell activation and maintaining immune homeostasis. Figure 1 shows that while labeling experiments revealed only weak co-localization of CTLA-4 with lysosomes, other experiments demonstrated that lysosomal blockade could inhibit CTLA-4 degradation. [1] As shown in Table 1.

Table 1. Available clinical trials of CTLA-4 inhibitors for the treatment of HNSCC.

Clinical trials of CTLA-4 inhibitors for the treatment of HNSCC	status	phase	NCT Number
Ipilimumab	recruiting	1	NCT02812524
Nivolumab Ipilimumab	not recruiting	2	NCT02919683
Nivolumab Ipilimumab Cetuximab, cisplatin, carboplatin, fluorouracil	not recruiting	3	NCT02741570
anti-CTLA-4 antibody	recruiting	1	NCT03058289

6. PD-1/PD-L1

PD-1 is a member of the CD28 receptor family and is primarily expressed on activated T and B lymphocytesPD-L1 and PD-L2 are the ligands for PD-1, and they are found on endothelial and epithelial antigen-presenting cells, as well as on activated lymphocytes. PD-L1 typically shows limited expression in normal tissues but can be both inducible and constitutively expressed in various solid tumors and hematological cancers. When overexpressed in tumor cells, PD-L1 can promote tumorigenesis. In cancers like non-small cell lung cancer (NSCLC) and melanoma, high levels of PD-L1 expression on tumor cells are closely associated with higher tumor grades and poorer patient outcomes. In head and neck squamous cell carcinoma (HNSCC), PD-L1 is produced due to a malfunction in the PD-1 signaling pathway, leading to immunosuppression within the tumor.

The PD-1/PD-L1 pathway may also be activated during chronic inflammatory conditions. The development of HPV-related HNSCC is largely driven by the activation of this pathway. HPV-positive HNSCC tissues tend to have a higher lymphocyte density and greater PD-L1 expression than HPV-negative tissues, with infiltrating cytotoxic T lymphocytes (CTLs) also showing increased PD-1 levels.PD-L1 can also convey additional immunosuppressive signals by binding to CD80 receptors on T cells. Consequently, the success of blocking the PD-1/PD-L1 axis may differ based on the unique immune environment within various HNSCC tumors. Blocking PD-1 interferes with its interactions with both PD-L1 and PD-L2, whereas targeting PD-L1 prevents it from binding to both PD-1 and CD80 [7].

The PD-L1 and PD-1 interaction plays a vital role in defining the tumor microenvironment (TME) by affecting the activity of various immune cells, including T cells, dendritic cells (DCs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs). Blocking PD-1 on Tregs reduces their capacity to support immune tolerance, although this does not mean that PD-1 itself directly augments Treg function.For effector T cells, the presence of PD-1 is often seen as an indicator of cell exhaustion, which also heightens their susceptibility to the apoptotic effects induced by the PD-L1 pathway. Additionally, the PD-L1 pathway suppresses the function of anti-tumor T cells and alters the interactions among cells involved in both innate and adaptive immunity, including DCs, MDSCs, and Tregs, as shown in Table 2 [8].

Table 2. Status of PD-1/PD-L1-related combination therapy clinical trials.

PD-1/PD-L1-related combination therapy	Status	Phase	NCT Number
PD-1 + surgery	recruiting	2	NCT03355560
PD-1 + chemotherapy (phase 3 and 4 only)	not recruiting	2/3	NCT04129320
PD-1 + radiotherapy (phase 3 and 4 only)	recruiting	3	NCT03765918
PD-1 + CTLA-4	recruiting	1/2	NCT03019003
PD-L1 + MDSCs	not recruiting	2	NCT 04262388
PD-L1 + Treg cells	recruiting	1/2	NCT 03844763

7. Clinic Analysis of PD1 Inhibitors

Monoclonal antibodies designed to target humanized PD-1 and PD-L1 are being tested in clinical trials for patients with advanced solid tumors and have gained FDA approval. These immune checkpoint inhibitors (ICIs), which focus on the PD-1/PD-L1 pathway, have been authorized for treating various cancers, such as non-small cell lung cancer, uroepithelial carcinoma, renal cell carcinoma, and hepatocellular carcinoma.Four mAbs have been approved targeting PD-1/PD-L1: navulizumab, pabolizumab, afolizumab, and atilizumab. The anti-PD-1 agents include navulizumab and pabolizumab, and afolizumab and atilizumab bind to PD-L1. Currently, FDA licensure has been granted only to navulizumab and pabolizumab for the treatment of refractory HNSCC to cisplatin, recurrent, or metastatic.

It is a monoclonal IgG4 antibody, which achieves its action through the inhibition of co-inhibitory signals via the PD-1/PD-L1 pathway. Indeed, for HNSCC patients, it is the first approval of any immunotherapy from the FDA, and that was based on the results of Phase III clinical trial Checkmate 141 [NCT02105636]. In the study, patients with recurrent HNSCC were randomized for their disease six months after platinum-based chemotherapy. Patients will be randomized in a 2:1 fashion to either navulizumab or the standard single-agent systemic therapy administered biweekly, such as methotrexate, docetaxel, or cetuximab. The key end point of this study design is overall survival. Other end points may include objective remission rates, PFS, safety, and patient-reported quality of life. The findings indicated a median survival of 7.5 months for the nabulizumab-treated cohort and 5.1 months for the standard treatment cohort (95% CI, P=0.01). The estimated 1-year survival rates were approximately 36.0% for the nabulizumab group and 16.6% for the standard treatment group. The progression-free survival rate for nabulizumab at six months was 19.7%, in contrast to 9.9% for the standard treatment group [9].

Patients treated with nabulizumab showed a longer overall survival than those receiving standard therapy, regardless of the cancer's PD-L1 expression levels or p16 status. There was no notable association between PD-L1 levels (whether high or low) and p16 status (positive or negative) in the tumor, independent of the type of treatment administered. Pabolizumab, a humanized IgG4-κ monoclonal antibody with strong affinity for PD-1, received FDA approval in 2017 following results from the Phase Ib KEYNOTE 012 cohort expansion trial. In 2019, the Phase III trial (KEYNOTE 048) evaluating pabolizumab for relapsed or metastatic HNSCC confirmed its superior efficacy. Interim data revealed that combining pabolizumab with chemotherapy significantly extended overall survival (OS) compared to cetuximab with chemotherapy (13.0 months vs. 10.7 months, P = 0.003). Given these positive efficacy and safety outcomes, pabolizumab with chemotherapy is now established as the first-line treatment for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), while pabolizumab alone is the recommended first-line option for patients with recurrent or metastatic PD-L1-positive HNSCC [9].

Clinical trials have yielded incongruous outcomes. Patients with PD-L1 exhibit clinical responses to cancer treatment, although some PD-L1-expressing individuals demonstrate resistance to immunotherapy. Consequently, it is essential to ascertain the correlation between PD-L1 status and disease prognosis, as well as to establish the appropriate threshold for PD-L1 expression. PD-L1 immunohistochemical staining alone is not always a reliable predictor of immunotherapy response, highlighting the need for other biomarkers to be considered. Employing both qualitative and quantitative multiparametric analyses can provide a more comprehensive assessment. Although PD-L1 expression remains a key indicator, it should be evaluated in conjunction with other factors, such as the density, makeup, and activation state of inflammatory cells within the tumor microenvironment (TME). In HNSCC, the combined presence of PD-L1 expression and cytotoxic T lymphocytes (CTLs) within tumor cells offers a more accurate prediction of therapeutic response than PD-L1 expression alone.

Patients exhibiting tumour cells with elevated levels of both PD-L1 and TILs may experience reduced disease-free survival compared to those with isolated expression of either marker. The data underscore that the overexpression of PD-1/PD-L1 in cancer may yield detrimental effects. The microenvironment of HNSCC requires further exploration and comprehension through a multiparametric approach [10].

8. Potential Therapeutic Molecular Pathways at Other Immunosuppressive Sites

In the battle against HNSCC, immunotherapy is poised to be a critical tool for medical oncologists moving forward. However, the currently approved immune checkpoint inhibitors (ICIs), such as pabolizumab and navulizumab, have demonstrated favorable clinical results in only a limited subset of patients. To address the primary resistance to ICIs and improve therapeutic outcomes, one strategy involves a detailed examination of the tumor microenvironment (TME) in HNSCC to identify novel targets or immune pathways that could be pharmacologically modulated. The TME differs significantly based on the cancer's etiology; for instance, HNSCC associated with carcinogens and HPV-positive cancers have distinct TMEs, resulting in varied mechanisms of immune evasion [11].

Recent research across clinical, genomic, and cellular fields has revealed that the tumor microenvironment (TME) in head and neck squamous cell carcinoma (HNSCC) is notably heterogeneous and exhibits significant immunosuppressive characteristics. While current clinical trials are investigating the combined use of immune checkpoint inhibitors with chemotherapy (CT) or radiotherapy (RT), gaining a more comprehensive understanding of the immune system's role in HNSCC is still essential [12], as shown in Table 3.

Table 3. Potential therapeutic molecules modulating HNSCC TME immunosuppressive cells.

Potential targets and mechanisms	Affect (usually adversely)
Blocking CD73	Downregulation of total PD-1 and CTLA-4 expression on T cells
Blocking TIM3	Enhancing anti-tumour immune responses by reducing tumour cytotoxicity
Anti-CD47 therapy	Stimulates cytotoxic T cells and reduces MDSCs
Targeting Notch1	Reduced numbers of MDSC and Treg cells, and expression of inhibitory immune checkpoint molecules (e.g. PD-1 and CTLA-4)
Blocking COX-2	Reduces MDSC induction and function and inhibits tumour growth
Activation of STAT4 pathway	Reduces T-cell immunosuppression and MDSC activity
Inhibition of JAK2/STAT3	Reduction of tumour-induced angiogenesis and MDSC

9. Conclusion

This review delves into the functions of both anti-tumor and pro-tumor immune cells, alongside the extracellular elements of the tumor microenvironment (TME) in head and neck squamous cell carcinoma (HNSCC). It further explores how HNSCC cells evade immune detection and examines therapies targeting immune checkpoint pathways, specifically focusing on clinical trials involving CTLA-4 inhibitors and PD-1/PD-L1 inhibitors. Insights from these studies, combined with the identification of new therapeutic targets, aim to guide the development of innovative immunosuppressive treatments to enhance the overall survival of HNSCC patients.

The primary objectives of treating HNSCC are to curb tumor growth and prevent metastasis. However, most preclinical studies, which primarily focused on genetic and epigenetic mutations—specifically altered gene expression in cancer cells—have not translated successfully in clinical trials. This failure is largely due to a limited understanding of HNSCC tumor biology and the critical role of the TME in shaping the progression of the disease and the development of effective immunotherapy strategies.

This review contends that researchers in HNSCC should investigate the tumor microenvironment in viral-associated and carcinogen-associated HNSCC independently. The distinction indicates that investigating immune cell infiltration, spatial interactions between tumor cells and immune cells, and the soluble factors involved in immune responses and evasion mechanisms (chemokines and cytokines) derived from extensive histological datasets will delineate new clinical subpopulations, thereby shifting the emphasis from the cancer itself to its microenvironment.

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