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Immune deserts in head and neck squamous cell carcinoma: A review of challenges and opportunities for modulating the tumor immune microenvironment

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Abstract

Immunotherapy revolutionized cancer treatment but has yet to elicit durable responses in the majority of patients with head and neck squamous cell carcinoma (HNSCC). HNSCC is generally characterized by a high tumor mutational burden, which has translated to a large neoantigen load that could prime the immune system to recognize and eliminate malignant cells. Studies are increasingly showing, however, that HNSCC is an “immune desert” tumor that can hijack multiple parts of the tumor immunity cycle in order to evade immune recognition and suppress immune system activation. Herein we will review how HNSCC tumors modulate their architecture, cellular composition, and cytokine milieu to maximize immunosuppression; as well as relevant therapeutic opportunities and emerging issues facing the field of HNSCC immuno-oncology.

Keywords

Head and neck cancer; squamous cell carcinoma; cancer immunology; tumor microenvironment; antigenicity; immunogenicity; immunotherapy; immune desert; immune evasion; immunosuppression

Introduction

The field of oncology was transformed with the discovery of immunotherapy, which leverages the body’s immune system to recognize malignant cells as foreign. Immunosurveillance involves the presentation of tumor proteins to antigen presenting cells (APCs), whose subsequent activation leads to immune cell killing of malignant cells and the attraction of T and B cells primed to the tumor’s specific antigens [1]. Head and neck squamous cell carcinomas (HNSCC) have a large number of mutations harbored by each tumor [2], which has in turn been associated with immunotherapy responsiveness in other malignancies [3]. Additionally, HNSCC tumors tend to have high tumor immune

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CONFLICTS OF INTEREST

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cell infiltrate, which has been linked to prognosis in various HNSCC subtypes [2]. While there have been some responses to immunotherapy, there is an overall low response rate in HNSCC [4, 5], with specific HNSCC subtypes that appear particularly resistant [5–7]. These tumors are thus considered poorly immunogenic or "immune deserts," which is thought to result from either decreased detection by the immune system or suppression of the immune system's response to the tumor. In this review, we will discuss how tumor microenvironment (TME) in HNSCC leads to immunosuppression; as well as opportunities and challenges for targeted immunotherapeutics.

Tumor architecture enhances immune evasion

Solid tumors tend to create an architecture that protects them from immune detection, as well as infiltration by and elimination from immune cells (Figure 1). For instance, tumors typically are surrounded by a dense extracellular matrix, limiting immune cell infiltration and through exclusion, their anti-tumor effect [8]. As solid tumors grow, their centers become increasingly hypoxic and potentially necrotic [9]. Hypoxia in the TME can lead to activation of angiogenesis, which can result in recruitment of immunosuppressive cells, tumor progression, and enhanced metastatic potential [10, 11]. Pro-angiogenesis molecules such as prostaglandin E_2 and vascular endothelial growth factor (VEGF) are also overexpressed in HNSCC [10]. The abnormal and disorganized vasculature created are inherently leaky and contribute to increasing hypoxia, thus furthering the angiogenic-immunosuppressive cycle. Additionally, solid tumors lack normal lymph vessels, and the resultant increase in interstitial fluid pressure prevents lymphocyte extravasation [8]. Researchers have thus investigated ways to prevent or reverse hypoxic and vascular abnormalities, including using agents targeting VEGF. Recent evidence has demonstrated VEGF inhibition is a potent immunomodulatory agent that limits the immunosuppressive mechanisms of Treg mobilization and proliferation, decreases immunosuppressive cytokine release, and allows dendritic cell maturation and increased antigen presentation [12]. In fact, a phase II trial of the VEGF-inhibitor axitinib showed correlation with improved survival in unresectable recurrent or metastatic HNSCC [13]. Understanding the physical barriers imposed by the tumor is also vital for localizing drug delivery, which holds promise in limiting systemic effects of immunotherapies that currently have a narrow therapeutic window between anti-tumor effects and induction of autoimmune responses.

Furthermore, angiogenesis and TME hypoxia are critical mediators of cancer stem cell (CSC) survival, with recent evidence linking CSC activity with direct and indirect immune avoidance. CSCs are a rare subset of cancer cells that are believed to initiate tumor growth, promote metastases, and allow for therapeutic resistance [14]. Part of their ability to survive and allow for long latency lies in their ability for immune escape. CD44+ CSCs have been shown to downregulate antigen presentation through depressed HLA-A2 and class II expression and limit T cell activity through altered immunomodulatory cytokine levels, specifically IL-8 and IL-4 [15, 16]. Overexpression of PD-L1 in CSCs has been shown to further enhance immune evasion through the endothelial to mesenchymal transition/β-catenin/STT3/PD-L1 signaling pathway [17]. This interaction of immune cells and mesenchymal cells creates a symbiotic relationship for immune evasion and maintenance of CSC. This mesenchymal support system has been well characterized in

the role of cancer associated fibroblasts (CAFs) as critical mediators of CSC maintenance in immune-replete niches. Finally, a major component of CSC-associated immune escape likely arises from evolutionary selective pressures and CSC capacity for editing neoantigens, further enhancing immune evasion. While this work has been well-characterized in breast and lung cancer, CSCs as a mechanism for immune desert cancers represents a novel area of research in HNSCC.

Solid tumors can also create a metabolically inhospitable TME, as rapidly-dividing malignant cells quickly deplete the local nutrients available for infiltrating immune cells. Without adequate substrate, metabolic checkpoints and subsequent dysfunction of immune cells are triggered [18–20]. The growing tumor, meanwhile, can continue to thrive by switching from oxidative phosphorylation to a glycolytic pathway that leads to a more tumor-favorable TME via acidification [9, 21]. Metabolic reprogramming is thus thought to be a likely cancer treatment both for limiting cancer glycolysis and optimizing immune metabolism. Along these pathways, multiple studies have focused on epacadostat, an inhibitor of indoleamine 2,3-dioxygenase (IDO-1), an enzyme that depletes the essential nutrient tryptophan from the TME. In phase I/II trials of epacadostat administered in combination with pembrolizumab or nivolumab for advanced solid tumors, durable antitumor response was seen in the HNSCC subsets [22, 23]. Recent results from a phase III trial of epacadostat plus pembrolizumab in melanoma patients did not meet its primary end point of improving progression-free survival compared to pembrolizumab monotherapy, however [24]. Future studies may attempt subject selection based on IDO-1 tumor expression, use of other IDO-1 inhibitors, or combinatorial therapy with immunotherapies targeting other pathways.

Malignant cells can directly impair immune recognition of tumors

T cells

Cytotoxic CD8+ T lymphocytes (CTLs) are an important part of the body’s cancer-fighting immunological machinery. Reflecting a trend seen in other malignancies, higher numbers of CTLs have been correlated with improved HNSCC outcome [25–28]. Multiple oncogenic pathways have been implicated in impairing the T cell priming, activation, and infiltration required for a robust immune response however. Thus, the T cells that are present in immune desert tumors are often dysfunctional or “exhausted,” or T cells may be excluded from the TME altogether.

Immune checkpoints, or inhibitory receptors present on immune effector cells, normally prevent overreaction to self antigens. Tumors can hijack this system by upregulating immune checkpoint receptors and their ligands, thus hindering CTL activity. For example, binding of the immune checkpoint receptor PD-1 expressed on T cells to PD-L1 on malignant cells leads to T cell dysfunction via reduced T cell receptor (TCR) signaling, cytokine production, cell mobility, and differentiation into T regulatory (Treg) cells [29]. Importantly, PD-L1 is upregulated in some HNSCC tumors, and thus anti-PD-1 immune checkpoint inhibitors such as nivolumab and pembrolizumab are immunotherapies currently employed for HNSCC [30, 31]. Additional studies are underway to test other inhibitory receptors considered potential markers of T cell dysfunction, such as CTLA-4, LAG-3, and TIM-3 [6, 32] (Figure 2).

Preliminary studies have identified TCR pathways involving the transcription factors NFAT and TOX for mediating T cell dysfunction, but much work remains to identify robust markers for exhaustion and to ascertain whether immunotherapy reinvigorates dysfunctional lymphocytes or primarily acts upon new effector cells [33]. T cell exhaustion is likely the major limitation to the long-term efficacy of treatments that activate the body's immune system, and thus understanding its development is critical for advancing immunotherapy.

Immune escape can also occur via endogenous mutations in oncogenic pathways. In HNSCC, the WNT-β-catenin pathway appears to affect both T cell priming and trafficking into the TME via decreased recruitment of dendritic cells necessary for tumor antigen presentation to CTLs [34, 35]. Similarly, gain-of-function mutations in the MYC pathway, which are present in HPV-negative HNSCC [36], lead to decreased CTL recruitment and antigen-presenting cell (APC) activation through decreased PD-L1 and CD47 expression [35]. T cell activation is further limited by tumors with downregulation of co-stimulatory molecules like OX40 and CD137 required for T cell activation [37]. Thus, agonists to these receptors, as well as other co-stimulatory receptors such as CD27 and GITR, are now being tested as adjunctive treatments for a variety of malignancies [38].

B cells

B cell phenotypes in HNSCC vary between HPV and non-HPV-mediated cancers and stage of disease, likely reflecting why studies thus far have shown both positive and negative associations of B lymphocyte numbers and prognosis [39]. Similar to their T cell counterparts, B cells can participate in adaptive immunity or regulatory cells dampening the immune response. In comparison to tumor infiltrating T cells, HNSCC studies have not been as consistent in reporting B cell numbers or phenotypes, and thus future studies will be required to determine the impact of certain B cell profiles [40].

Of recent interest to the cancer immunology community more broadly, aggregates of B cells surrounded by T cells and specialized vasculature known as tertiary lymphoid structures have been identified in both autoimmune disease and across multiple cancers [41]. These formations lack capsules and thus experience direct antigenic stimulation and have been associated with a robust immune response and more favorable prognosis in multiple malignancies [42, 43]. In HNSCC, B cells and tertiary lymphoid structures have been identified [29, 40, 44], and HPV-specific antibody secreting cells in the TME were found to correlate with plasma IgG titers [44]. Additional research is needed to understand the mechanistic contribution of B cells to tumor immunity.

NK cells and NKT cells

Natural killer (NK) cells, potent mediators of innate immunity, can also be suppressed by HNSCC. While a recent systematic review in HNSCC revealed that generally numbers of NK cells are positively correlated with improved patient outcomes, tumors can escape NK cell-mediated killing with downregulation of downstream effectors of NK cell ligands [45]. Additionally, tumor-induced downregulation of Toll-like receptors (TLRs) on NK cells has been linked to a decreased innate immune response to HNSCC [46], and HLA mutations on tumor cells may also decrease NK-mediated elimination of HNSCC cells in the setting of

resistance to cetuximab [47]. Meanwhile, a subpopulation of lymphoid cells called natural killer T cells (NKT cells) have also been implicated in adaptive immunity [48]. Preliminary evidence suggests that low numbers of peripheral NKT cells are associated with poor prognosis in HNSCC patients [49].

There has been increasing interest in therapies targeting NK cells. Shin et al identified that NK cells anti-tumor activity could be potentiated with multiple molecules through the aryl hydrocarbon receptor [50]. For instance, there are currently studies focused on combining PD-1/PD-L1:CTLA-4 axis inhibition with lirilumab, a monoclonal antibody targeting killer-cell immunoglobulin-like receptors (KIRs), which is thought to be a major inhibitory signal for NK-mediated cytotoxic cell immunity [6]. Additionally, NK cell checkpoint inhibitors have entered clinical trials [45]. Studies are still too premature, however, to determine the efficacy of these strategies.

Other cells within the tumor microenvironment can exert immunosuppressive effects

Stromal cells

CAFs, the predominant cell type in tumor stroma, secrete cytokines that often act on multiple immune cells simultaneously or otherwise alter the TME to influence immune cell infiltration. CAFs produce soluble factors such as IL-6 that exert influence on T-cells, NK cells, dendritic cells (DCs), macrophages, and neutrophils; in HNSCC, this mechanism correlates with worsened survival [51–54]. CAFs also secrete other growth factors, chemokines, and matrix-metalloproteinases (MMPs) that together induce tumor progression through TME remodeling [21, 55, 56]. In preclinical models, both CAFs and HNSCC tumor cells secrete paracrine factors that promote the proliferation of both cell types and overall tumor growth and invasion [56, 57]. Thus inhibitors of factors like fibroblast growth factor can be considered as a potential oncologic treatment [57].

MDSCs

Myeloid-derived suppressor cells (MDSCs) are immature myeloid cells that are found in almost all individuals with cancer and have been shown to inhibit antitumor immunity while promoting cancer progression [58, 59]. Previous studies identified levels of MDSCs as well as granulocyte-macrophage colony-stimulating factor (GM-CSF) correlated with HNSCC advanced stages, recurrence, or metastasis [60]. Recently, Tsai et al used *in vitro, in vivo,* and clinical data to explore the positive correlation of IL-6 with recruitment of MDSCs and expression of PD-L1 in the induction of an immunosuppressive TME [51]. Furthermore, MDSCs encourage an antitumor environment through production of neoangiogenesis factors, MMPs, reactive oxygen species that prevent lymphocyte activation, sequestration of metabolites needed by effector cells, chemokine secretion, and cell-to-cell inhibitory contact with immune infiltrating cells [58]. A double-blinded placebo-controlled trial showed decreased MDSC numbers and improved CTL function with administration of tadalafil, an inhibitor of phosphodiesterase 5 that diminishes the immunosuppressive effects of MDSCs [61]. Preclinical studies also show promise in disrupting the MDSC trafficking mechanism through CXCR1/2, a chemokine that is often overexpressed in HNSCC [62–64].

Antigen-presenting cells

Professional APCs such as DCs, macrophages, and B cells are also affected by HNSCC cells. Tumor-associated macrophages (TAMs) can take an M1-like (antitumor) or M2-like (pro-tumor) phenotype. Polarization to “anti-inflammatory” M2-like macrophages can be induced in the acidic hypoxic TME [65]. In HNSCC, this is associated with production of pro-tumor factors like IL-6 and IL-10, leading to poorer patient outcomes [66–68]. Furthermore, TAMs also consume local nutrients needed by CTLs, express PD-L1, and recruit Tregs [59]. Use of an inhibitor of colony-stimulatory factor 1 receptor (CSF1R), which is necessary for TAM recruitment, is currently under study [59].

Malignant cells also can reduce their own antigenicity, or the ability for the body’s immune system to recognize tumor proteins as foreign to incite an immune response. Antigen processing and presentation is a complex pathway, and disruption of critical proteins can interfere with immune detection of the tumor. These disruptions can take the form of germline or somatic alterations, although they generally seem to be caused by transcriptional changes [69]. Mutations and differential expression of human leukocyte antigen (HLA) alleles [70, 71], β-2 microglobulin [72], antigen processing machinery (APM) [69, 73], and STAT1 signaling, as well as altered regulation of HLA expression [74, 75], have been found in the HNSCC TME.

Recent compelling evidence, including ours, suggests that type I interferon (IFN-I) signaling in the TME promotes CD8+ CTL production in melanomas and other cancer types. The induction of IFN-I is mediated by pattern recognition receptors, including DNA sensors such as cyclic GMP-AMP synthase (cGAS). DNA-bound cGAS generates a second messenger cyclic GMP-AMP to activate the adaptor protein stimulator of IFN genes (STING1), which promotes IFN-I. IFN-I targets genes including a number of Th1 chemokines, such as CXCL9 and CXCL10, which are critical for the tumor-homing of APCs, as well as cross-presentation and expansion of effectors, but STING signaling is often inhibited in cancers. SOX2 in HPV-negative HNSCC and HPV16 E7 can both dampen STING1-mediated immune activation, suppressing cancer immunogenicity [76].

Immunoediting has also been identified in some cancers, where the immune system eliminates malignant cells with “stronger” antigens early on in tumor development, thus selecting for fewer antigens that may inherently lead to weaker immune responses [77, 78]. These “weak” antigens can provide the tumor time to develop immune escape mechanisms or to benefit from immune effector cell dysfunction from chronic antigen signaling. Treatment approaches for correcting antigen presentation defects might include the use of co-stimulatory molecules for antigen presentation, modulation of epigenetic regulation for antigen processing genes, and even directly replacing mutated genes [79], as well as adoptive T cell transfer as discussed later.

T regulatory cells

Activated Tregs appear to suppress effector cells with inhibitory cytokines, metabolic competition, or direct inhibitory action on effector T cells and DCs [6, 80]. Frequency of circulating Tregs is higher in HNSCC patients than controls and generally are associated

with lower numbers of CTLs [81]. Studies in HNSCC have revealed mixed results on the influence of Tregs on prognosis, perhaps based on the subtype of HNSCC studied, as well as the activation status and localization of Tregs in relation to the tumor [20, 29, 82, 83]. Targeting CCR4, a surface molecule predominantly seen on activated Tregs; TCR signaling; immune checkpoint receptors; and GITR, which modulates Treg immunosuppression; are some of the Treg-related treatment options currently being explored [84].

Cytokine milieu

As described above, HNSCC consists of malignant cells, host stromal cells sabotaged by tumor paracrine signaling, immune cells with suppressive phenotypes activated by the tumor, and immune effector cells either excluded from the tumor or rendered dysfunctional in the TME. The cytokines involved in creating this pro-tumor environment are multifold. For instance, malignant cells may directly secrete immunosuppressive and anti-inflammatory cytokines like IL-10 and TGF-β that negatively affect APCs and T cells [77, 85, 86]. Malignant cells can also secrete other cytokines that can polarize immune effector cells toward adopting an anti-inflammatory phenotype that leads to tumor progression [77], or they can produce chemokines that attract immunosuppressive cells into the tumor [87]. Meanwhile, HPV, a viral mediator of the majority of oropharyngeal HNSCC, is known to evade immune detection by interfering with normal immunostimulatory pathways of interferon production [76].

Thus, treatments focused on the TME cytokine milieu can either introduce pro-inflammatory cytokines or inhibit pro-tumor cytokines. In fact, administering pro-inflammatory cytokines such as IL-2, TNF-α, and IFN-α was the earliest form of immunotherapy in oncology [88, 89]. More recently, a phase II trial has found that a combination of immunostimulatory cytokines can increase tumor-infiltrating CTLs when administered as a neoadjuvant treatment [90], and a phase I/II study of an agonist for IL-15 with cetuximab in HNSCC is currently underway (NCT04136756). Other forms of immunotherapy in clinical trials include monoclonal antibodies targeted against pro-tumor cytokines [6]. Further studies are warranted to determine the appropriate manipulation of local cytokines to modulate the TME, particularly if other therapies are prescribed concurrently.

Emerging issues in immuno-oncology

Delineation of the myriad of mechanisms for immunosuppression induced by the HNSCC TME have led to creation of many novel immunotherapy approaches [6, 91]. At the time of writing this manuscript, there were 219 recruiting trials for HNSCC in the United States, of which 173 included inhibitors of the immunosuppressive TME (Table 1) or immunostimulatory agents (Table 2). Regardless of the type of immunotherapy utilized, additional research is required for understanding how to efficiently target, monitor, time, and combine these strategies.

Using signatures to target therapy

Precision immuno-oncology demands a reliable method for ascertaining the particular deficits of a patient’s anti-tumor immune response in order to deliver an efficacious therapy.

Given the early predominance of PD-L1 inhibitors as HNSCC immunotherapy, PD-L1 expression by tumors was considered a predictive marker, although this has not been validated likely due to its poor specificity and association with immune infiltrate [7]. More recently, immunogenomic signatures show promise as a method for clustering cancers, allowing for rationalized decisions of what combination of immunotherapies to use for that particular tumor grouping [2, 47, 92–96]. Moving towards tumor-specific therapy is critical given that only a subset of patients respond to a given immunotherapy, subjecting the remaining treated patients to the financial burden, opportunity cost, and side effect profile of the chosen therapy. While immunogenomic signatures may prevent these consequences, prospective studies are needed to validate these strategies.

There has been recent recognition that even dysbiosis, or disruption to the gut microbiome, can lead to resistance to immune checkpoint inhibitor therapy [97]. Thus, microbiome signatures may also one day have implications for HNSCC treatment selection. Much work remains to understand the potential implications for the known microbiome diversity between anatomic subsites and patients [98].

Tumor-specific and tumor-associated antigen therapies

Advances in immunogenomics also hold promise in identifying antigens that may be tumor-specific (TSA) or tumor-associated (TAA). This is most immediately applicable to virally-mediated disease, with active investigations into targeting HPV proteins [6, 99]. For non-virally-mediated tumors, however, there is no consensus on a high-throughput reliable and specific methodology for antigen prediction, particularly for non-missense antigens such as structural variants [96, 100]. It is also unclear how to select which antigens are the most biologically relevant. What is evident is that antigens will vary between cancer subtypes, and may differ between patients or across time in the same patient [96]. There is also evidence that HPV-positive HNSCC may employ distinct immune evasion strategies as compared to HPV-negative disease [101]. Currently, there are trials studying vaccines involving HPV-specific peptides; p53, which is mutated in most HNSCC; and even patient specific antigens [91].

Another innovation has been the development of adoptive cell transfer, where a patient's immune cells are removed and reintroduced after modification *ex vivo* to enhance their activity or specificity to a tumor [77]. Early success of these therapies in hematologic malignancies [102] have led to interest in extending this therapy to HNSCC (Table 2). The earliest adoptive cell transfer in HNSCC included expansion and activation of harvested tumor-associated TILs [103, 104]. More recently, chimeric antigen receptor (CAR) cells, which do not rely on major histocompatibility complex-mediated antigen presentation, have been applied to HSNCC for T cell [105–110] and NK cell [111] based therapies. Adoptive cell transfer will likely require combinatorial treatment to be efficacious in HNSCC, however, given the less robust responses seen in solid tumors, poor persistence of the transferred cells, and antigen modulation seen *in vivo* [112, 113].

Combination therapy

Promising preliminary results have been seen for combining immune checkpoint inhibitors, biologics, metabolic agents, chemotherapy, and radiotherapy [6, 7, 99]. Since immunological dysfunction can develop over time and during treatment [114], further work remains to determine optimal timing of immunotherapeutic intervention, including as neoadjuvant therapy [115], window of opportunity trials [116] for surgically resectable HNSCC, concurrently with traditional definitive treatment, or as adjuvant or salvage therapy. Regardless of which therapies are combined, caution and thoughtful studies are required to understand the effects of each added therapy on the original treatment, as well as the resultant adverse effects. Caution is warranted when targeting multiple points of the tumor immunity cycle (Figure 3) given serious potential adverse effects of even single agent immunotherapies that range from common reactions of fatigue or rash to severe, potentially life-threatening complications [117]. Beyond immediate complications of treatment, HNSCC survivors face significant quality of life effects from multimodality treatments [118] that must be balanced with the potential oncologic benefit for added therapies.

Radiation, for instance, increases the antigenicity of tumors due to direct mutagenesis and induction of inflammatory cascades, thus multiplying immunotherapy's potential effects [119, 120]. Chemotherapy, meanwhile, likely has synergistic effects with immunotherapy given its known disruption to tumor architecture with subsequent antigen presentation [4]. In recent years, there have been many trials of immunotherapy given before, with, or after radiation alone or chemoradiation in HNSCC, which are nicely summarized elsewhere [121]. These investigations have utilized neoadjuvant, concurrent, and adjuvant immunotherapy to take advantage of immune priming with intact lymphatic structures, synergism from chemoradiation-induced tumor architecture disruption and neoantigen production, and immune surveillance mechanisms for residual or recurrent disease [122].

Further potentiation of the immune response to tumors has focused on dual modality therapy with targeted therapies. Immune checkpoint inhibitors are being studied in combination with cetuximab, an anti-EGFR monoclonal antibody that remains the only targeted therapy approved for HNSCC to date. Cetuximab has been found to induce both innate and adaptive immune responses, as well as to alter expression of immune checkpoint receptors on TILs [6]. Additional targeted therapies acting upon the EGFR pathway are under investigation [123]. DNA Damage Repair (DDR) pathways have also been therapeutic targets. For instance, PARP and ATM inhibitors have shown a capability to increase antigenicity in several tumor types, thus priming an immune response when given in conjunction with PD-1/PD-L1 and CTLA-4 inhibitors [124–128]. Recent evidence in HNSCC suggests similar susceptibility to immune modulation through DDR-inhibition [129–131]. Whether other targeted therapies, reviewed elsewhere [132], potentiate tumor response to immunotherapy has yet to be seen.

Finally, simultaneously targeting multiple immune checkpoints, such as PD-1/PD-L1 and CTLA-4, has also shown some hopeful results in melanoma [133] and thus is now being investigated in HNSCC [134]. Combination therapy with newer strategies such as adoptive

T cell transfer, cancer vaccines, and genetically-modified viruses are potential approaches as well [91, 110, 135].

Immune Modulation

In a recent phase II trial, neoadjuvant pembrolizumab was found to induce a partial response (>10%) in nearly half of treated patients (16/36) with a favorable response seen in those with specific pre-treatment immune profiles (i.e. PD-L1 overexpression, elevated TIL counts and IFNγ activity) [136]. This suggests that immune profiles may serve as a predictive biomarker for determination for immunotherapy. In immunosuppressed tumors, immune modulation to manipulate the TME to be more accommodating for immune infiltration is a novel approach. Only one trial in HNSCC has been done to assess the ability to immunomodulate immune desert malignancies. IRX-2, a primary tumor cell-derived biologic made up of Th 1 cytokines (IL-2, IL-1β, IFN-γ, and TNF-α) was shown in vitro to modulate and overcome tumor-mediated immunosuppression. In a phase II trial, IRX-2 was subsequently found to increase tumor infiltrating lymphocytes and reduce tumor size [137]. This is being further studied in a multicenter, randomized, phase IIB trial, INSPIRE (IRX-2 Neoadjuvant Therapy in HNSCC to Provide Immune Response Enhancement) trial (NCT02609386), but offers a novel way to improve immunotherapy efficacy.

Conclusion

The advent of immunotherapy has indelibly changed the landscape of oncology. Notable responses to immunotherapy have been seen in some; however, the vast majority of patients fail treatment. While HNSCC was initially considered ripe for immunotherapy due to high tumor mutational burden, a subset are “immune deserts” characterized by a failure of tumor detection or mounted response by the immune system. As the field understands more about the immunosuppressive TME of HNSCC and how the patient and malignancy’s underlying immunogenomics set the stage for immune evasion, tumor-specific therapeutics that promote tumor antigencity and immunogenicity can be chosen. Continuous assessment of a malignancy’s evolution and combination therapies will likely be required in the ongoing battle against a tumor’s immune evasion strategies.

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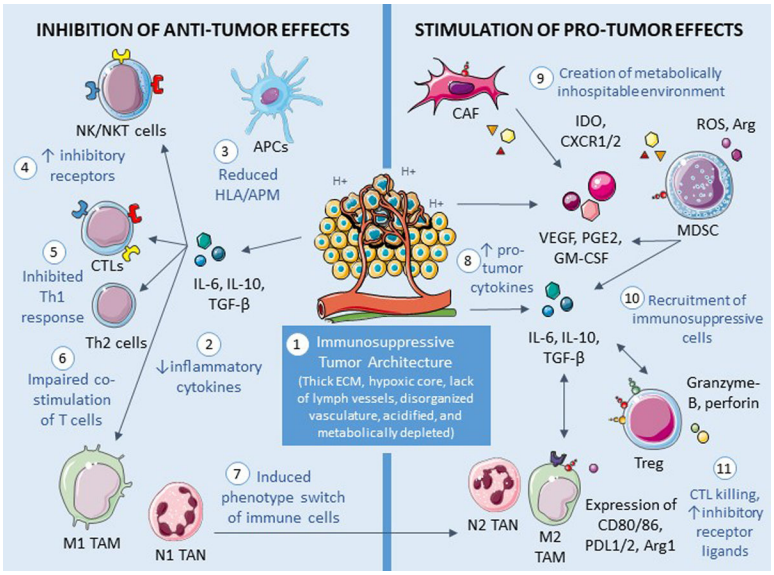

Figure 1. Immunosuppressive tumor microenvironment.

A variety of alterations in the tumor microenvironment have direct and indirect effects that suppress the innate and adaptive immune system. Anti-tumor effects begin with (1) an architecture that prevents entrance and subsequent function of effector immune cells. The tumor (2) secretes cytokines that further inhibit the immune system. Downstream effects include (3) suppressed antigen processing and presentation, (4) upregulated inhibitory receptors on effector cells, and (5) decreased Th1 response and (6) T cell co-stimulation. Furthermore, (7) multiple types of immune cells switch from a pro-inflammatory phenotype to a more pro-tumor state. The cancer also actively creates an environment that enhances tumor growth by (8) secreting pro-tumor cytokines. This ultimately leads to (9) metabolic depletion that hinders immune effector cells and (10) recruitment of immunosuppressive cells which subsequently (11) kill or inhibit immune effector cell functioning. NK=natural killer; NKT=natural killer-like; APC=antigen-presenting cell; HLA=human leukocyte antigen; APM=antigen processing machinery; CTL=cytotoxic T cell; IL=interleukin; TGF=transforming growth factor; TAM=tumor-associated macrophage; TAN=tumor-associated neutrophil; ECM=extracellular matrix; CAF=cancer-associated fibroblast; IDO=indoleamine-2,3-dioxygenase; CXCR="C-X-C" chemokine receptor; MDSC=myeloid-derived suppressor cell; ROS=reactive oxygen species; Arg=arginine; VEGF=vascular endothelial growth factor; PGE=prostaglandin E; GM-CSF=granulocyte-macrophage colony-stimulating factor; Treg=T regulatory cell; PDL1/2=programmed death ligand 1/2. Cellular images are modified from Servier Medical Art (https://smart.servier.com), used under the terms of Creative Commons License 3.0.

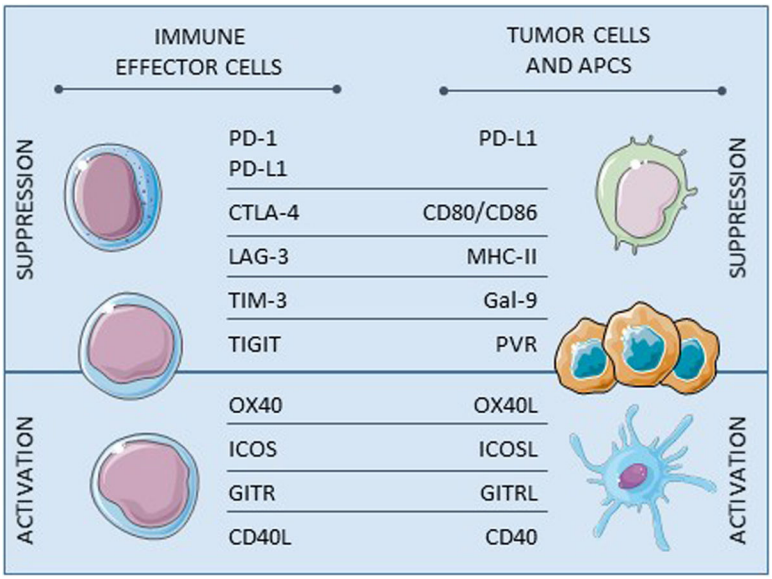

Figure 2. Major immunomodulatory T cell receptors and their ligands.

Tumor cells hijack T cell function by inducing inhibitory receptors or by suppressing stimulatory receptors, either directly or indirectly through antigen presenting cells. Thus these receptor:ligand axes represent therapeutic targets for immunosuppressive HNSCC. APC=antigen presenting cell; PD=programmed death; PD-L=programmed death-ligand; CTLA=cytotoxic T-lymphocyte-associated protein; LAG=lymphocyte activating gene; TIM=T cell immunoglobulin and mucin domain-containing; TIGIT=T cell immunoglobulin and ITIM domain; ICOS=inducible T cell co-stimulator; GITR=glucocorticoid-induced TNFR-related protein; CD40=cluster of differentiation; MHC-II=major histocompatibility complex 2; Gal=galectin; PVR=poliovirus receptor. Cellular images are modified from Servier Medical Art (https://smart.servier.com), used under the terms of Creative Commons License 3.0.

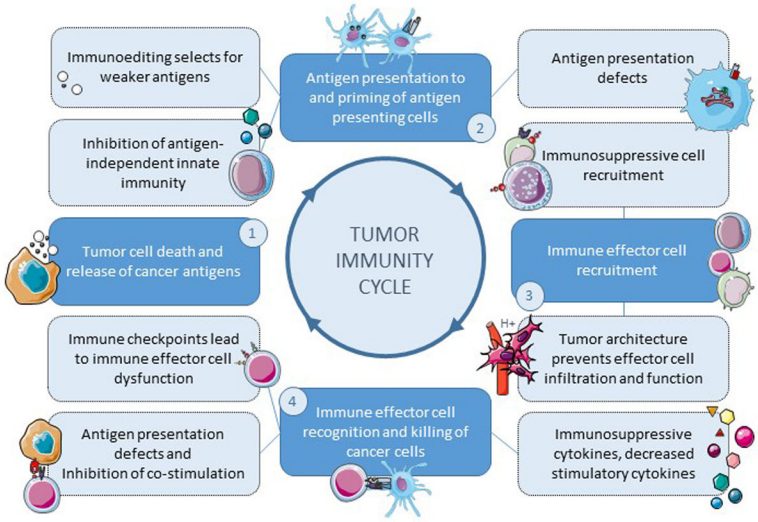

Figure 3. Immunosuppressive targets throughout the tumor immunity cycle.

Immunosurveillance involves (1) a process of released antigens from tumor cells, (2) presentation of tumor-associated antigens to antigen presenting cells, (3) chemotrafficking of immune effector cells into the tumor microenvironment, and (4) immune effector cell recognition and killing of the cancer cell. Tumors can evade the immune system throughout the tumor immunity cycle (dashed outlines).

Table 1.

Inhibitory immunotherapy agents included in recruiting clinical trials for head and neck cancer.

Drug Target	Drugs	Trials*
Anti-PD-1; Anti-PD-L1	ABBV151 (also targets TGF-β)	I-NCT03821935
	Abemaciclib	I/II-NCT03655444
	Alisertib	I/II-NCT04555837
	Atezolizumab	I-NCT03841110, I-NCT04096638, I/II-NCT03829501, I/II-NCT04471415, II-NCT03228667, II/III-NCT01810913, III-NCT03452137
	Avelumab	I-NCT03498378, II-NCT02554812, II-NCT03228667
	Bintrafusp Alpha / M7824 (also targets TGF-β)	I/II-NCT04220775, I/II-NCT04247282
	Cemiplimab	I/II-NCT03684785, II-NCT03565783, II-NCT03916627, II-NCT04242173
	GEN1046	I/II-NCT03917381
	Durvalumab	I-NCT03381183, I-NCT03618654, I-NCT03635164, I-NCT03739931, I/II-NCT03522584, I/II-NCT03618134, II-NCT02827838, II-NCT03174275, II-NCT03228667, II-NCT03529422, II-NCT03691714, I/II-NCT02643303, II/III-NCT03258554
	Nivolumab	I-NCT02636036, I-NCT03565445, I-NCT03690986, I-NCT03758781, I-NCT03829436, I-NCT03841110, I-NCT03906526, I/II-NCT02955290, I/II-NCT03247712, I/II-NCT03311334, I/II-NCT03370276, I/II-NCT03435640, I/II-NCT03655444, I/II-NCT03735628, I/II-NCT04180215, I/II-NCT04349267, II-NCT03228667, II-NCT03341936, II-NCT03355560, II-NCT03521570, II-NCT03646461, II-NCT03715946, II-NCT03799445, II-NCT03829722, II-NCT03854032, II-NCT03878979, II-NCT03944915, II-NCT04080804, II-NCT04326257
	PDR001	I-NCT01351103
	Pembrolizumab	I-NCT02376699, I-NCT02575404, I-NCT02783300, I-NCT03236935, I-NCT03245489, I-NCT03454451, I-NCT03565445, I-NCT03590054, I-NCT03647163, I-NCT03666273, I-NCT03799003, I-NCT03841110, I-NCT03849469, I-NCT04007744, I-NCT04187872, I-NCT04234113, I-NCT04344795, I-NCT04348916, I-NCT04429542, I-NCT04452214, I/II-NCT02799095, I/II-NCT02955290, I/II-NCT03138889, I/II-NCT03311334, I/II-NCT03474497, I/II-NCT03650764, I/II-NCT03674567, I/II-NCT03684785, I/II-NCT03684785, I/II-NCT03735290, I/II-NCT03789097, I/II-NCT04034225, I/II-NCT04060342, I/II-NCT04193293, I/II-NCT04555837, II-NCT02289209, II-NCT02641093, II-NCT02769520, II-NCT02777385, II-NCT02841748, II-NCT03049618, II-NCT03082534, II-NCT03085719, II-NCT03228667, II-NCT03383094, II-NCT03468218, II-NCT03546582, II-NCT03625323, II-NCT03645928, II-NCT03771820, II-NCT03823131, II-NCT03993353, II-NCT04144517, II-NCT04150900, II-NCT04220866, II-NCT04369937, II-NCT04414540, II-NCT04428151, III-NCT03765918, III-NCT04128696, III-NCT04199104, IV-NCT04489888
	Sintilimab	III-NCT03748134
	SL-279252	I-NCT03894618
	Tislelizumab	III-NCT03783442
	TPST-1120	I-NCT03829436, I-NCT04344795
	XmAb20717 (also targets CTLA-4)	I-NCT03517488
	XmAb23104 (also targets ICOS)	I-NCT03752398
Anti-CTLA-4	Ipilimumab	I-NCT02812524, I-NCT03690986, I-NCT04290546, II-NCT03799445, II-NCT04080804, II-NCT04326257
	Tremelimumab	I/II-NCT02643303, I/II-NCT03522584, I/II-NCT03618134, II-NCT03693612

Drug Target	Drugs	Trials*
	XmAb20717 (also targets PD-1)	I-NCT03517488
	XmAb22841 (also targets LAG-3)	I-NCT03849469
Anti-LAG-3	Eftilagimod alpha	II-NCT03625323
	INCAGN02385	I-NCT03538028
	Relatlimab	II-NCT04326257, II-NCT04080804
	XmAb 22841 (also targets CTLA-4)	I-NCT03849469
Anti-TIM3	INCAGN02390	I-NCT03652077
Anti-Galectin	GR-MD-02	I-NCT02575404
Anti-CD39/HLA-G	TTX-080	I-NCT04485013
Anti-CD94/NKG 2A	Monalizumab	I/II-NCT02643550
Anti-ILDR2	BAY1905254	I-NCT03666273
Anti-NRP1	ASP1948	I-NCT03565445
Anti-KIR (NK cells)	Lirilumab	II-NCT03341936
Anti-S15 (M2 macrophages)	NC318	I/II-NCT03665285
Anti-Semaphorin 4D	VX15/2503	I-NCT03690986
Anti-inhibitor of apoptosis proteins	Debio 1143	III-NCT04459715
Nitric oxide synthase inhibitor	L-NMMA	I-NCT03236935
Anti-VEGF; Anti-PGE2	Cabozantinib	I-NCT03667482, II-NCT03468218
	Lenvatinib	I-NCT03524326, II-NCT04428151, III-NCT04199104
	Ramucirumab	I/II-NCT03650764
	TPST-1495	I-NCT04344795
Anti-IDO-1	Epacadostat	II-NCT03823131
	BAY2416964	I-NCT04069026
	BMS-986205	II-NCT03854032
Anti-TGF-β	ABBV151 (also targets PD-1)	I-NCT03821935
	BCA101	I-NCT04429542
	Bintrafusp Alpha (also targets PD-L1)	I/II-NCT04220775
	PF-06940434	I-NCT04152018
Colony-stimulating factor inhibitor	PD 0360324	II-NCT02554812

Drug Target	Drugs	Trials*
Anti-CCR4	FLX475	I/II-NCT03674567

* Phase of study (I-IV) and National Clinical Trial (NCT) numbers as registered with www.clinicaltrials.gov. Only trials that were actively recruiting at the time of manuscript writing are included.

Table 2.

Stimulatory immunotherapy agents included in recruiting clinical trials for head and neck cancer.

Drug Target	Drugs	Trials*
IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, TNF-α, IFN-γ, GM-CSF	ALKS4230	I/II-NCT02799095, II-NCT04144517
	Bempegaldesleukin	I/II-NCT03435640
	IRX-2	I-NCT03381183, I-NCT03758781
	IL-2	I/II-NCT03474497
IL-15 agonist	N-803	I-NCT04290546, I/II-NCT04247282, II-NCT03228667
	SO-C101	I-NCT04234113
INF-β	VSV-IFNβ-NIS oncolytic virus	I-NCT03647163
OX-40 agonist	ABBV-368	I-NCT03818542, I-NCT04196283
	MEDI0562	I-NCT03336606
	PF-04518600	II-NCT02554812
ICOS agonist	GSK3359609	II-NCT03693612, III-NCT04128696
	KY1044	I/II-NCT03829501
	XmAb23104 (also targets PD-1)	I-NCT03752398
GITR agonist	ASP1951	I-NCT03799003
CD3 agonist	GEN1044	I/II-NCT04424641
CD11b agonist	GB1275	I/II-NCT04060342
CD40 agonist	ABBV-927	I-NCT02988960, I-NCT03818542
CD73 agonist	CPI-006	I-NCT03454451
CD94/NKG 2A agonist	BMS-986315	I/II-NCT04349267
CD122 agonist	NKTR-214	I/II-NCT03138889, I/II-NCT03435640
CD137 agonist	Utomilumab	II-NCT02554812
TLR agonists	AST-008	I/II-NCT03684785
	CMP-001	II-NCT02554812
	NKTR-262	I/II-NCT03435640
	Poly ICLC	I/II-NCT02643303, I/II-NCT03789097
	Tilsotolimod	I-NCT04196283
	VTX-2337	I-NCT03906526
STAT3 agonist	NT219	I/II-NCT04474470
	TTI-101	I-NCT03195699
STING agonist	E7766	I-NCT04144140
	MK1454	II-NCT04220866

Drug Target	Drugs	Trials*
	SB11285	I-NCT04096638
Flt3L	Flt3L (dendritic cell growth factor)	I/II-NCT03789097
Antigenic challenge	Ad-p53 (p53 antigen)	II-NCT03544723
	CUE-101 (HPV E7 protein)	I-NCT03978689
	DSP-7888 (WT1 peptides)	I/II-NCT03311334
	HB201 (HPV E6 and E7 proteins)	I/II-NCT04180215
	PepCan (HPV E6 protein)	I/II-NCT03821272
	SNS-301 (human aspartyl/asparaginyl beta-hydroxylase HAAH; DNA cpG motifs)	I/II-NCT04034225
	YE-NEO-001 (patient-specific antigen)	I-NCT03552718
Antigen presenting cells	Ilixadencel (dendritic cells)	I/II-NCT03735290
Immune effector cells	IMA201 (Adoptive T cell transfer)	I-NCT03247309
	LN-145 (Adoptive T cell transfer)	II-NCT03083873, II-NCT03645928
	E6-specific T cell receptor T cells	I-NCT03578406
	KITE-439 (E7 T cell receptor T cells)	I-NCT03912831
	CIML NK cell infusion	I-NCT04290546
	FT500 (NK cell)	I-NCT03841110
Oncolytic virus	Enadenotucirev	I-NCT02636036
	ONCR-177	I-NCT04348916

*Phase of study (I-IV) and National Clinical Trial (NCT) numbers as registered with www.clinicaltrials.gov. Only trials that were actively recruiting at the time of manuscript writing are included.