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Tumor Immune Microenvironment in Head and Neck Cancers

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Abstract

Head and neck cancers are a heterogeneous group of tumors that are highly aggressive and collectively represent the sixth most common cancer worldwide. 90% of head and neck cancers are squamous cell carcinomas (HNSCCs). The tumor microenvironment (TME) of HNSCCs consists of many different subsets of cells that infiltrate the tumors and interact with the tumor cells or with each other through various networks. Both innate and adaptive immune cells play a crucial role in mediating immune surveillance and controlling tumor growth. Here, we discuss the different subsets of immune cells and how they contribute to an immunosuppressive TME of HNSCCs. We also briefly summarize recent advances in immunotherapeutic approaches for HNSCC treatment. A better understanding of the multiple factors that play pivotal roles in HNSCC tumorigenesis and tumor progression may help define novel targets in order to develop more effective immunotherapies for HNSCC patients.

Keywords

cancer immunotherapy; head and neck cancers; tumor microenvironment; tumor infiltrating lymphocytes

Overview of head and neck squamous cell carcinoma (HNSCCs)

Head and neck cancers (HNC) are a heterogeneous group of tumors arising from the mucosal surfaces of the upper aerodigestive tract which includes the sinonasal and oral cavities, nasopharynx, oropharynx, hypopharynx, and larynx. Collectively, HNC is the sixth most prevalent cancer worldwide with over 880,000 new cases diagnosed and more than 450,000 patients die each year[1]. 90% of all HNCs are head and neck squamous cell carcinomas (HNSCCs) and roughly 75% of these cases are associated with alcohol and tobacco use. However, emergences of new studies have shown that oncogenic human papillomavirus (HPV) infection may be a risk factor associated with 22% of oropharyngeal squamous cell carcinoma (OSCC) and 47% of tonsillar squamous cell carcinomas (TSCC)[2–5]. HNSCCs can severely impact the quality of life of patients while have poor prognosis, low responsiveness to treatment and drug resistance. HNSCC malignancy has a high morbidity and mortality rate since only 50%–60% of patients have a survival rate of 5

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years after diagnosis of HNSCC, and up to 30% of patients develop cancer relapse and treatment failure[6]. It has been found that one of the most imperative prognostic determinants of the survival rate from HNSCC is the presence of lymph node metastases[7].

Immune cells in HNSCCs

A major deterrent of HNSCC treatment is the high rate of recurrence and/or metastases in patients, which not only stresses the difficulty in treating HNSCCs but also conveys the complex molecular conditions. The rationale behind the high rate of metastatic HNSCC and recurrence is likely due to the interactions of the surrounding tissue matrix and immune cells that make up the tumor microenvironment (TME). The host immune system is capable of recognizing and eliminating neoplastic cells; however, evasion of immunosurveillance generates an environment that accommodates the progression and survival of tumor cells[6,8–10]. Interestingly, HNSCCs have the ability to not only avoid recognition by immune cells, but they are also immune-suppressive[6,10]. This immune evasion is achieved by downregulating human leucocyte antigen (HLA) expression, which in turn impairs cancer cell recognition by T cells[11]. In addition, the HNSCC TME has also been shown to impair tumor-infiltrating lymphocyte (TIL) function[10,12,13]. TME is composed of different subsets of cells, such as cancer-associated stromal fibroblasts, T cells, B cells, neutrophils, macrophages, myeloid-derived suppressor cells (MDSC), natural killer (NK) cells and mast cells[9,10,14–18]. These different subsets of cells infiltrate the tumors and interact with the tumor cells as well as with each other through various networks (Figure 1). Both innate (e.g., NK cells) and adaptive (e.g., $CD8^+$ T cells) immune cells play a crucial role in immune surveillance and controlling tumor growth; on the other hand, some subsets of immune cells (e.g., MDSCs and macrophages) can also promote tumor growth[19]. Thus, tumors progress if they can escape and/or suppress anti-tumor immune responses. In this regard, tumors often evade host's immune surveillance by suppressing cytotoxic T cell function or by activating and expanding immunosuppressive cell populations. The mechanisms by which HNSCC TME may regulate and impair host's immunity are discussed in the following sections.

T cells

T cells are lymphocytes that are a crucial component of the adaptive immune system and are categorized into $CD4^+$ and $CD8^+$ T cells. While CD8 TILs can directly kill tumor cells via producing perforin/granzymes, activated CD4 and CD8 TILs can also secrete cytokines (e.g., IFN-γ, TNFα) which have tumor cell killing activity or can recruit other immune cells that mediate cytotoxic anti-tumor immune responses[12] (Figure 1).

In one study using OSCC patient samples, it was observed that the majority of intratumoral TILs were $CD8^+$ T cells, while 67% of those patients had intratumoral $CD4^+$ TILs[20]. They found that a higher frequency of surrounding peritumoral $CD8^+$ TILs correlated with better clinical parameters in HNSCC patients (e.g. smaller tumor size and lower probability of lymph node metastasis); however, it did not correlate with patient survival[20]. The ratio of CD4:CD8 TILs was 0.745, and this ratio was found to be higher in large tumors and advanced stage tumors[20]. While the density of peritumoral $CD8^+$ TILs in OSCCs was associated with some clinical parameters, neither the frequency of intratumoral $CD8^+$ TILs

nor the ratio of CD4:CD8 TILs was shown to have any relationship with clinical parameters[20]. In contrast, another study reported that higher CD4 and CD8 TIL levels were correlated with improved overall survival (OS), and relapse-free survival (RFS)[21]. Furthermore, after controlling for other prognostic factors, higher CD4 levels predicted improved OS and disease-specific survival[21]. Consistently, another systematic review and meta-analysis confirmed that $CD3^+$ and $CD8^+$ TILs have a favorable and prognostic role in HNSCC clinical outcomes and found that $FoxP3^+$ TILs also correlate with improved OS[22].

By comparing the peripheral blood mononuclear cells (PBMC) of HNSCC patients and healthy controls, one study showed that there was no quantitative difference in the proportion of T cell subsets, but patient T cells had a qualitative difference from controls[23]. When these PBMC T cells were stimulated by peptide pools of viral antigens, T cells from the HNSCC patients produced a significantly weaker IFN-γ recall response compared to the controls[23], suggesting a systemic immunosuppressive condition in HNSCC patients. While peritumoral $CD8^+$ TILs may indicate an adaptive immune response, studies have shown that dysfunctional TILs are commonly present, which exhibit decreased cytokine production and proliferation ability and lack of cytotoxic functions[24,25]. Exhausted and dysfunctional TILs in HNSCC cases have been characterized by the upregulation of several checkpoint markers, such as programmed cell death 1 (PD-1), lymphocyte-activation gene 3 (LAG-3), T cell immunoglobulin mucin protein-3 (TIM-3), cytotoxic T lymphocyte–associated protein 4 (CTLA-4), and 2B4[26–29] (Figure 1). The cause and mechanisms by which the T cells become exhausted and dysfunctional in HNSCCs are discussed in detail below.

PD-1 is a co-inhibitory receptor expressed on activated $CD4^+$ or $CD8^+$ T cells, and PD-1 has two ligands, PD ligand 1 (PD-L1) and 2 (PD-L2)[30,31]. PD-1 is also considered a marker for exhausted T cells and is often upregulated in $CD4^+$ and $CD8^+$ TILs in various types of cancers[30,31]. $CD8^+$ TILs of human HNSCCs were found to express increased levels of PD-1 on their surface[32], and 66% to 79% of SCC patients had PD-L1-positive tumor cells[33–36]. In addition, we previously showed that $CD8^+$ TILs in a mouse SCC model highly expressed PD-1 and LAG-3[37]. Engaging PD-1 by binding to PD-L1 inhibits the functions of T cells or promotes their apoptosis[30,31]. Studies have shown that increased PD-L1 expression on tumor cells significantly decreased the level of $CD8^+$ T cells at the regional level in HNSCC TME through apoptotic mechanisms[38]. In addition, PD-L1 expression was detected in exosomes isolated from plasma samples of HNSCC patients, and circulating $PD\text{-}L1^{high}$ exosomes associated with disease progression in HNSCCs[39]. Of note, HNSCCs may also induce $CD8^+$ T cell apoptosis by producing $Fas\text{-}L^+$ microvesicles detected in serum samples of OSCC patients[40]. Altogether, these mechanisms may provide an explanation for a systemic immunosuppressive condition in HNSCC patients.

Another mechanism that causes the dysfunction of $CD8^+$ T cells in HNSCCs is the elevated levels of both circulating and tumor-infiltrating T regulatory (Treg) and Th17 cells[41,42]. Furthermore, Th17 cell proliferation is likely caused by the increased levels of IL-23 and IL-6 released by HNSCC cancer cells[42]. Tregs account for less than 5% of a subset of $CD4^+$ T cells in peripheral blood, which are characterized as $CD4^+CD25^+FOXP3^+$. Tregs regulate excessive immune reactivity toward other immune cells to prevent autoimmunity; however, this function also limits the immune system to target neoplastic cells[43,44]. Moreover,

peripheral Tregs can be recruited into the TME, where TGF-β causes them to differentiate and become more immunosuppressive[45] (Figure 1). Elevated level of TGF-β has been found during the latter phase of HNSCC progression, which seems to disrupt the ratio of Th17 vs. Tregs[46]. This disruption induced tumor-promoting Treg differentiation, and increased anti-inflammatory cytokine IL-10 production in HNSCCs[47,48]. On the other hand, a high level of FoxP3$^+$ Treg infiltration in HNSCCs was associated with longer RFS and OS[22,49]. This is probably because the presence of a high level of FoxP3$^+$ Treg in tumors indicates an on-going robust anti-tumor immune response, which contributes to inhibition of tumor growth.

In addition to dysfunctional T cells, decreased expression of major histocompatibility complexes (MHC), called HLA in humans, may also help the tumor cells evade adaptive immunity. MHC class I is essential for presenting peptides to CD8$^+$ T cells and for CD8$^+$ cytotoxic T lymphocytes (CTL) to recognize tumor cells expressing tumor-associated or tumor-specific antigens[50]. About 50% of HNSCC tumors might evade immune surveillance through the downregulation of MHC class I molecules[38]. While 12.7% of HNSCC cases showed no detectable expression of MHC class I, others had reduced MHC class I expression[38]. However, the mechanisms of MHC class I reduction in HNSCCs remain less well-understood. It has been found that during the early stages of HNSCC tumor development, the interaction of CD8$^+$ T cells and MHC class I in primary HNSCCs led to either tumor rejection or immune escape[13,51]. Decreased expression of MHC class I would allow tumor cells to escape the detection by CD8$^+$ T cells and avoid the activation of CD8$^+$ CTL-mediated anti-tumor immune responses[52].

Myeloid Cells

Tumor-associated macrophages (TAMs) are common in HNSCCs, and are classified into two subpopulations: M1, which mediates pro-inflammatory and anti-tumor responses, and M2, which is immunosuppressive and has pro-tumor properties[53] (Figure 1). M1 produces pro-inflammatory cytokines such as IL-12, IL-23, and IFN-γ, and has been shown to have anti-tumor immune properties[16,54,55]. In contrast, M2 exhibits immunosuppressive characteristics by not only producing IL-10 and TGF-β, shown to be suppressive cytokines, but also inhibits M1's anti-tumor cytotoxic effects[56,57]. A higher level of TAMs in the TME has been shown to correlate with lymph node metastasis and advanced stage of HNSCCs[53,58–61]. A recent study has shown that HNSCC TME largely encompasses M2 TAMs and exhibits an increased level of TGF-β[62]. A likely mechanism that TAMs contribute to inflammation and tumorigenesis is by producing reactive oxygen species (ROS), reactive nitrogen species (RNS), and prostaglandins (PGs). Furthermore, TAMs have been found to produce high levels of inflammatory cytokines (e.g., TNF-α and IL-1β) and macrophage migration inhibitory factor (MIF)[54,63–65]. MIFs are ligands of chemokine receptor CXCR2, and have been shown to promote migration of SCCs, cell-matrix adhesion[54,66], as well as neutrophil recruitment to HNSCCs[67]. The recruited neutrophils can release hepatocyte growth factor (HGF), which in turn increases invasiveness of the tumor cells by feedback mechanisms of the HGF pathway[68] that regulates cell growth, morphogenesis and motility.

The effects of TAM reduction were investigated using mouse SCC models[69]. Macrophages were depleted by treating recipient mice bearing K15.Kras^{G12D}/Smad4$^{-/-}$ SCC tumors with clodronate, and it was observed that TAM reduction resulted in reduced SCC tumor volume[69]. Tumors with clodronate treatment increased SCC apoptosis but did not attenuate SCC proliferation and metastasis[69]. Given the immunosuppressive properties of these myeloid cells in the TME, quantifying TAMs may thus be useful for prognostic stratification in HNSCCs. Furthermore, strategies for targeting TAMs (through inhibition or reprogramming) in combination with checkpoint inhibitors in ongoing clinical trials have shown promising results in melanoma, lung cancer, colon cancer, and breast cancer[59,63,70–72]. While some studies have suggested that increased density of TAMs are correlated with poor clinicopathologic markers in HNSCCs, strategies for targeting TAMs in HNSCC patients have yet to be explored.

MDSC

Previous studies suggest that myeloid derived suppressor cells (MDSC) may play a pivotal role in predicting tumor response to various tumor immunotherapies[14,65,73–76]. MDSCs circulate in peripheral blood, draining lymphoid tissue, as well as in HNSCC tumor tissue[77–79]. Many studies have demonstrated that MDSCs downregulate immune responses during infection, inflammation and tumor development[14,67,79–85]. MDSCs are CD11b^{+} cells that are phenotypically subdivided into two groups, polymorphonuclear MDSC (PMN-MDSC) and monocytic MDSC (M-MDSC)[86–88]. PMN-MDSCs are similar to immature polymorphonuclear cells and phenotypically express Ly6C^{lo} and Ly6G^{+}. M-MDSCs are immature mononuclear cells characterized by cell surface markers, Ly6C^{hi} and Ly6G^{-}, and can differentiate into TAMs as a result of signal transducer and activator of transcription 3 (STAT3) downregulation[64,89–91]. One study on murine lymphoma and colon carcinoma showed that intratumoral MDSCs had significantly lower density of activated STAT3 than peripheral blood or spleen MDSCs[90]. The downregulation of STAT3 activities was suggested to facilitate higher frequencies of MDSC differentiation into TAMs, but further studies are needed to verify whether lowered STAT3 activation is observed in the MDSCs of HNSCCs.

Studies have found that the frequency of M-MDSC is negatively correlated to the response of chemotherapy in SCCs, and M-MDSCs are highly immunosuppressive via an antigen-nonspecific mechanism[59,80,81]. While PMN-MDSCs are also immunosuppressive, they have been found to promote T cell tolerance in an antigen-specific manner[80]. It has been shown that peripheral MDSCs from lymphoid organs suppress antigen-specific CD8^{+} T cells, while TME MDSCs can suppress both antigen-specific and antigen-non-specific T cell function[80,82,92]. Peripheral MDSCs can suppress antigen-specific immune responses of T cells, which requires close cell-to-cell contact, via the production of nitric oxide (NO) and ROS[80]. In addition, peripheral MDSCs can reduce T cell proliferation by depleting essential amino acid levels, such as L-arginine and tryptophan, attributed to the activity of Arginase-1 and indole amine 2,3 dioxygenase (IDO), respectively[79,80,83,91]. However, TME MDSCs in HNSCC patients not only exhibit more potent antigen-specific immunosuppressive properties through NO production and Arg1 activities, but also suppress antigen-specific and -non-specific T cell response via inhibiting CD3/CD28 expression on T cells[92,93]. Another

way for MDSCs to suppress cytotoxic $CD8^+$ T cell responses is to induce immunosuppressive cytokines (e.g. IL-10 and TGF-β) and Tregs[46,47], which downregulate effector T cell proliferation and activation, thereby leading to tumor growth and metastasis.

A recent study has discovered that tumor-associated hypoxia caused an increase of PD-L1 expression on tumor-infiltrating MDSCs[94]. This upregulation of PD-L1 on MDSCs was due to the transcription factor, hypoxia-inducible factor 1-α (HIF-1α), which resulted in more potent immunosuppressive effects of MDSCs[94]. Another mechanism that can increase the immunosuppressive activities of MDSCs is the upregulation of CD38 on MDSCs. MDSCs that express a higher level of CD38 evidently have a greater capacity to promote tumor growth and exhibit more potent immunosuppressive effects[95]. CD38 also promotes the expansion of M-MDSC populations[95,96]. Furthermore, it has been found that IFN-γ, TNF-α, and other cytokines can induce CD38 expression in MDSCs[97,98], suggesting a negative feedback loop that prevents anti-tumor immunity. Studies have detected a delay in tumor progression in murine models of myeloma and hematological tumors after administering anti-CD38 mAb that could target $CD38^+$ MDSCs[97,99–101]. Thus, we suggest that targeted therapies that selectively inhibit certain subtypes and aspects of MDSCs may provide a functional remedy to combat HNSCCs with a high density of MDSCs.

Current and future immunotherapies in HNSCC

When HNSCC is diagnosed at an early stage, it is typically treated with surgery or radiotherapy; however, treatment for HNSCC can be quite morbid due to significant functional impairments and aesthetic deformities to the patients. HNSCCs are genetically heterogeneous that can hinder the classification and development of specific targeted therapies[102]. Current treatment strategies for HNSCCs are not adequate and may lead to resistance. Thus, to rectify this issue, new treatment strategies and specific molecular or cellular markers need to be developed and identified to improve and better predict treatment outcome and survival of HNSCC patients.

The breakthrough findings that blocking certain immune checkpoints can help rescue T cell responses have prompted investigators to develop treatments to restore anti-tumor immune responses[30,31,103]. In recent years, immune checkpoint blockade therapies in HNSCCs, such as pembrolizumab, nivolumab, and durvalumab, that target PD-1/PD-L1, have been shown to have limited advantageous safety profile and response rate[104–107]. Although anti-PD-1/PD-L1 has been approved by FDA for treating HNSCCs, the overall response rate remains low[104–107]. The mechanisms underlying the unresponsiveness to anti-PD-1/anti-PD-L1 remains poorly understood and the markers to predict responses are not well-characterized. There are many ongoing HNSCC clinical trials evaluating the various indications of anti-PD-1/anti-PD-L1 alone or in combination with radiation, targeted therapy and chemotherapy[3,105,106,108], but their curative effect and safety profile need further experimental investigation and verification.

A likely key factor that can predict responsiveness to PD-1 blockade in HNSCCs is the production of IFN-γ. In a 2017 study, it was identified that IFN-γ signature score can predict clinical response to PD-1 blockade in HNSCCs[109]. Furthermore, it was shown that

the T cell-inflamed gene expression profiles, which contain IFN-γ-responsive genes, also predicted clinical responses to PD-1 blockade[109]. However, these features associated with T cell-inflamed phenotypes were necessary, but not always sufficient, for clinical benefit, because one category of non-responders to PD-1 blockade clearly exhibited a high level of IFN-γ signature score and T cell inflammatory gene expression, yet, these patients had no clinical benefit[109]. Hence, we need to better understand the resistance mechanisms in tumors that exhibit evidence of T cell-inflamed phenotypes yet still lack clinical response. In this regard, activated T cells and NK cells in the TME can produce IFN-γ, which can directly upregulate PD-L1 and PD-L2 on tumor cells or other cells in the TME to induce a feedback inhibition loop by activating PD-1 on TILs (Figure 1). Therefore, blocking PD-1 or PD-L1 can disrupt this feedback inhibition loop and control tumor growth. However, IFN-γ production may also trigger inhibitory feedback loops that involve additional pathways other than PD-1/PD-L1, for instance, other immunosuppressive molecules such as LAG-3 and IDO1 could be overexpressed in an IFN-γ rich TME.

HNSCCs in heavy smokers often harbor extensive DNA damage, and respond poorly to conventional therapies[110]. To solve the challenge and enhance the sensitivity of HNSCCs to immune checkpoint inhibitors, new therapeutic strategies are needed such as developing vaccine-based immunotherapy for HNSCCs using neoantigens. Neoantigens are newly formed antigens by somatic mutations in cancers; thus, they are absent in the normal host tissues[111–114]. Neoantigens hold great promise to induce cancer-specific immune responses that can potentially eradicate cancers, while sparing normal tissues, thereby minimizing side-effects. Recent advances in next-generation sequencing (NGS) and epitope prediction algorithms have made the identification of tumor-specific neoantigens feasible[111,115]. By combining genomic, bioinformatics, and immunological approaches, neoantigens were identified in both mouse models and human patient samples[111,116–123]. Preclinical studies of mouse models have indicated the potential benefits of tumor-specific neoantigens in immunotherapy[116,121,122]. Results of the therapeutic use of neoantigens in human cancers are also encouraging[124–127]. It would be of great interest to test whether HNSCCs harbor neoantigens and whether neoantigen-based immunotherapy can be effective in HNSCCs.

Another novel advance in adoptive immunotherapy is the administration of genetically modified antigen-specific T cells that target antigens expressed on the surface of tumor cells. In recent years, synthetic chimeric antigen receptor (CAR)-T cell therapy has encouraging therapeutic potential in HNSCCs and hematological cancers[128–130]. A previous study identified nine overexpressed genes on the surface of HNSCCs as potential targets for CAR-T cell therapy[128], but only a few targeted antigens have shown favorable results. Pre-clinical and clinical data on HER2-specific, CD70-specific, and T4-immunotherapy (T1E28ζ/4αβ) CAR-T cell therapy on HNSCCs demonstrate potent anti-tumor activity, but the risk of on-target off-tumor toxicity remains a challenge to overcome[128,129,131]. $T4^{+}$ CAR T-cells are retrovirally transduced to co-express (a) T1E28ζ, a CAR coupling ErbB ligand derived from EGF and TGFα to a fused CD28/CD3ζ endodomain; and (b) 4αβ, a chimeric cytokine receptor containing the IL-4Rα ectodomain coupled to the IL-2Rβ endodomain[131].

In addition to T cell-specific immunotherapy, recent studies have seen the potential importance of targeting MDSC populations in cancers. Studies have determined the

immunosuppressive properties of tumor infiltrating MDSCs, and by inhibiting them directly or targeting $CD38^+$ MDSCs by administering anti-CD38 mAb have emerged as potential immunotherapies for MDSC-high cancers in mouse models of myeloma or other hematological cancers[99,101,132]. Furthermore, other immunotherapies are being studied that can potentially extend survival and suppress tumor growth. For example, recent investigations on targeting vascular endothelial growth factor, HIF-1α and nuclear factor-κB as therapeutic targets in the TME have been promising[92,94,133]. However, all these immunotherapies face multiple factors that can be challenging, such as the need to identify tumor-associated antigens that are specifically overexpressed on the tumor cells and not in normal tissues.

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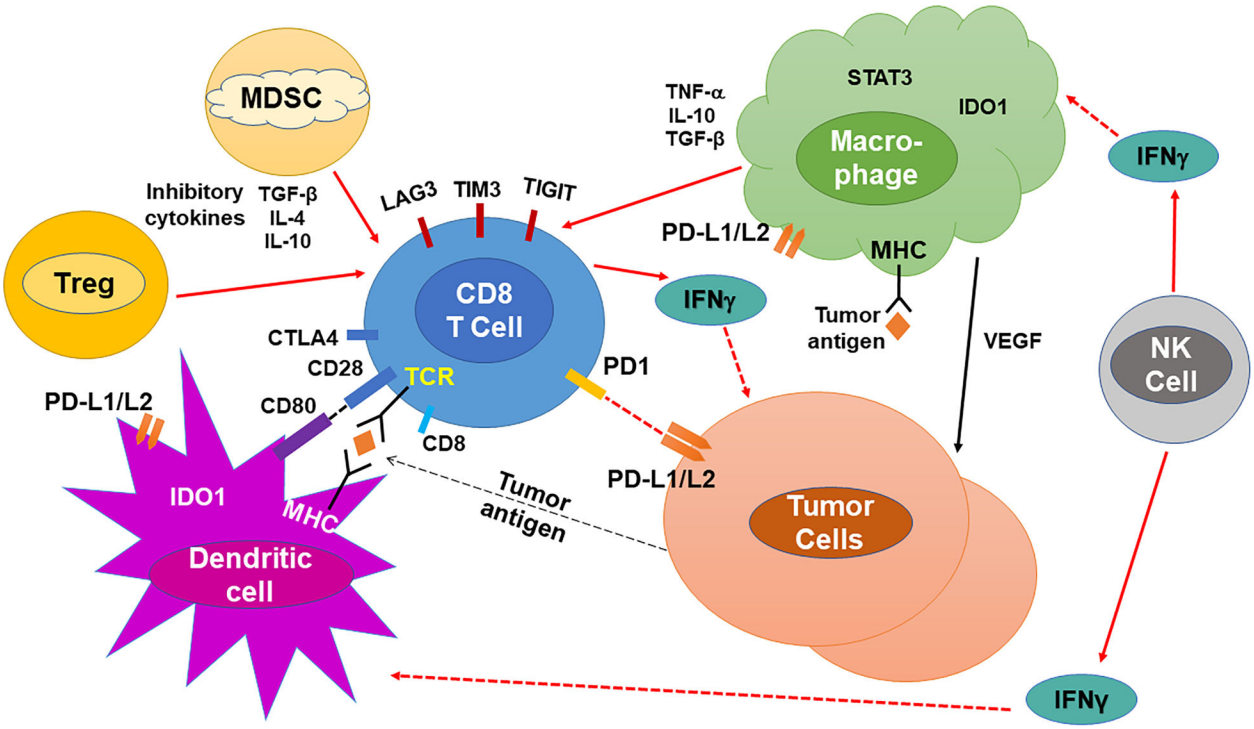

Figure 1.

A schematic illustration of the tumor-associated immune cells and factors responsible for the immune-suppressive mechanisms in the tumor microenvironment (TME) of HNSCC.