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Review

Unraveling the immunomodulatory role of TIM-3 in head and neck squamous cell carcinoma: implications for targeted therapy

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Abstract
Head and neck squamous cell carcinoma (HNSCC) ranks among the most prevalent cancers globally, and despite improvements in treatment options such as surgery and radiotherapy, its survival rate remains low. With increased research in immunotherapy, antibodies against various immune checkpoints like programmed death receptor 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) have been shown to be effective against a wide range of tumors. Nonetheless, survival benefits gained by HNSCC patients remain limited. T-cell immunoglobulin mucin-3 (TIM-3), an emerging immune checkpoint molecule, is found to be expressed in HNSCC and is involved in shaping the tumor immune microenvironment (TIME). TIM-3 is significant in the initiation and progression of HNSCC by modulating effector T cells, innate immune cells, and other components of the immune system. Inhibiting TIM-3 can restore T cell function and enhance the immune response against HNSCC, making it a promising immunotherapeutic target for this disease. This article reviews the expression of TIM-3 in HNSCC and its immunomodulatory mechanism and briefly introduces the combined application and development prospects of TIM-3 as a potential immunotherapeutic target.

Keywords T-cell immunoglobulin mucin-3 · Head and neck squamous cell carcinoma · Tumor immune microenvironment · Combination immunotherapy · Human papillomavirus

1 Introduction

Head and neck cancer (HNC) is a heterogeneous epithelial tumor occurring in various anatomical mucosal sites, such as the oropharynx, hypopharynx, larynx, and lips, as well as the oral cavity [1, 2]. The predominant histological subtype of HNC is squamous cell carcinoma of the head and neck [3]. Previous studies have identified tobacco and alcohol as major risk factors for HNSCC, and in recent years, human papillomavirus (HPV) infection has gradually become one of its high-risk factors. Currently, HNSCC has become the sixth largest malignant tumor worldwide, with the incidence increasing. The latest statistics show that the number of new cases of HNSCC will exceed 740,000 in 2022, accounting for about 3.7% of all new cancers [4, 5]. HNSCC has seriously jeopardized people's lives and health, and despite the improvement of surgical, radiotherapy, and other treatment protocols, the survival rate remains low owing to the locally advanced stage, recurrence, and metastasis.

As the efficacy of immune checkpoint inhibitors such as PD-1 and CTLA-4 has become increasingly clear in tumors such as melanomas, hepatocellular carcinomas, and lung cancers, blocking immune checkpoints has emerged as a new

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direction in cancer immunotherapy [6]. For the past several years, the application of immunotherapy in HNSCC has been developed, mainly to inhibit PD-1 and PD-L1 immune checkpoints [7]. Trials have indicated that this does improve the overall survival of patients. However, the objective response to anti-PD-1 monotherapy is only 15 to 20 percent, and even many patients do not react to blocking PD-1/PD-L1 checkpoint therapy [8, 9]. Locally advanced stages and high rates of recurrence or metastasis continue to be research challenges for head and neck cancer research teams. Therefore, there is an urgent need to seek new immunosuppressive sites and corresponding block measures to enhance the efficacy and prognosis of immunotherapy in patients with HNSCC. TIM-3, a novel immune checkpoint molecule, is upregulated in a variety of tumor microenvironments and promotes tumor-associated immune tolerance by binding to ligands to induce T-cell dysfunction and affect innate immune cell function. Currently, TIM-3 inhibitors have shown initial efficacy in preclinical studies of a variety of tumors and have demonstrated promising applications in the immunotherapy of HNSCC. In this paper, we will describe the expression and immunoregulatory mechanism of TIM-3 in the HNSCC tumor microenvironment and briefly introduce its therapeutic prospect in HNSCC.

2 Literature search strategy

This review systematically analyzed articles published in the past decade (2014–2024) retrieved from PubMed (https://pubmed.ncbi.nlm.nih.gov/) and CNKI (China National Knowledge Infrastructure; https://www.cnki.net/), including reviews, original research articles, and clinical studies. Key search terms comprised "TIM-3," "tumor" (or "cancer"), "HNSCC," "immunotherapy," "tumor immune microenvironment," and "HPV," combined with Boolean operators (e.g., "TIM-3 AND HNSCC AND immunotherapy"). Eligibility assessment commenced with a title/abstract review to discard non-relevant articles, followed by systematic appraisal of the full texts from retained publications. The focus was on high-impact original research, meta-analyses, and clinical trials. The goal was to provide a comprehensive synthesis of the latest advances. Inclusion criteria prioritized studies published within the last decade to reflect current evidence, while seminal older publications were selectively cited to provide essential background context.

3 The structure and function of TIM-3

3.1 Structure and signal of TIM-3

TIM-3 is an immune checkpoint molecule encoded by the HAVCR2 gene located in the 5q33.2 region of the human genome and has been implicated in asthma, allergy and autoimmune diseases [10]. TIM-3 proteins belong to the TIM family and have a structure consisting of a mucin domain, an N-terminal immunoglobulin-like domain (IgV domain), a transmembrane domain, and a cytoplasmic tail containing tyrosine phosphorylation motifs [6]. Among them, the IgV domain is responsible for binding to ligands, including galectin-9 (Gal-9), phosphatidylserine (PtdSer), high mobility group protein B1 (HMGB1), and carcinoembryonic antigen-associated cellular adhesion molecule 1 (CEACAM1) [11], whereas the mucin-like domain regulates its function through glycosylation modifications [12]. TIM-3 was initially thought to be a marker for T helper 1 (Th1) cells and $CD8^+$ T cells, but it has since been found that in addition to being expressed on T lymphocytes, TIM-3 is also widely found on cells like natural killer cells (NKs), dendritic cells (DCs), macrophages, and monocytes [13, 14].

At the mRNA level, TIM-3 expression is regulated by a variety of transcription factors, mainly members of the T-box transcription factor 21(T-bet) and Signal Transducer and Activator of Transcription(STAT) families. T-bet is a key transcription factor in Th1 cell differentiation and binds directly to the promoter region of the TIM-3 gene to promote its transcription [14]. Similarly, STAT1 and STAT4 activate TIM-3 expression in Th1 cells through the interferon-γ(IFN-γ) and interleukin-12 (IL-12) signaling pathways [15]. In addition, cytokines such as IL-2, IL-15, and IL-18 can also upregulate TIM-3 mRNA levels through activation of the PI3K/Akt/mTOR signaling pathway [16]. At the protein level, TIM-3 expression is regulated by post-translational modifications, particularly glycosylation, and the glycosylation status of TIM-3 affects its ability to bind ligands [12]. The presence of CEACAM1 stabilizes the protein expression of TIM-3, and the absence of CEACAM1 leads to the destabilization and degradation of the TIM-3 protein [17]. TIM-3 exerts immunosuppressive effects by binding to various ligands and plays a key role in innate and adaptive immunity.

3.2 Ligands of TIM-3 and their functions

3.2.1 Gal-9

Gal-9 has a carbohydrate recognition domain that specifically recognizes the N-bonded sugar chain structure in the TIM-3 IgV domain. Binding of Gal-9 to TIM-3 oligomerizes TIM-3 on the cell surface, inducing the release of HLA-B-associated transcript 3 (BAT3) from the intracellular tail of TIM-3. This process results in T-cell suppression and ultimately leads to cell death [12]. The interaction between TIM-3 and Gal-9 can modulate the immune response through various mechanisms and in different cell types. Gal-9 binding to TIM-3 induces apoptosis in Th1 cells and inhibits the production of IFN-γ, thereby suppressing tissue inflammation and inhibiting autoimmune diseases. In addition to this, it induces cell death of TIM-3^+ $CD8^+$ TILs in colon cancer [15]. However, in NK cell lines, Gal-9 interacts with TIM-3 to increase TIM-3-mediated IFN-γ production [18].On monocytes/macrophages, the binding of Gal-9 to TIM-3 may alter cytokine production, impacting the Th1 or Th17 response by changing the levels of IL-12 and IL-23 [19, 20]. It has also been found that blocking the TIM-3/Gal-9 pathway reduced the immunosuppressive capacity of TIM-3^+ Treg [12]. Jianfeng Dong et al. found that $CD4^+$ T cells in HPV^+ HNSCC patients significantly overexpressed Gal-9, a subpopulation that drives TIM-3^+ monocyte expansion via the TIM-3/Gal-9 axis, which in turn inhibits IFN-γ secretion. Thus, we learned from this that the monocyte inflammatory response in HPV^+ HNSCC patients is negatively regulated by the TIM-3/Gal-9 pathway [21]. The TIM-3/Gal-9 axis functions as a critical immunosuppressive mechanism in tumor immunity, with therapeutic blockade exerting broad immunomodulatory effects on multiple cellular components, including effector T cells, regulatory T cells (Tregs), macrophages, and monocytes [22].

3.2.2 CEACAM1

CEACAM1 is a transmembrane protein on the cell membrane that binds to the CC′ and FG loops of TIM-3 and regulates angiogenesis and immune responses [23]. TIM-3 glycosylation and protein stability are dependent on CEACAM1 co-expression; lack of CEACAM1 expression results in impairment of TIM-3 inhibitory function [6]. TIM-3 function is dependent on CEACAM1 co-expression, and this dependence stems from the cis interaction between the two proteins. The cis interaction promotes stable expression of mature TIM-3, and the trans interaction inhibits the function of effector T cells, both of which mediate T-cell immune tolerance. In addition to being expressed via T cells, CEACAM1 is also present on monocytes, DCs, and macrophages. Therefore, the TIM-3-CEACAM1 axis has the capacity to inhibit both cis- and trans-immune responses in T cells as well as myeloid cells [6, 12]. CEACAM1 and TIM-3 are co-expressed on activated T cells and form heterodimers, which inhibit T cell function and reduce their anti-tumor immunity [17]. The interaction between TIM-3 and CEACAM1 leads to the release of BAT3 from its binding site on the cytoplasmic tail of TIM-3, which enables TIM-3 to mediate the inhibition of T cell antigen receptor responses [17]. In the absence of ligand engagement, BAT3 interacts with the cytoplasmic tail of TIM-3, facilitating the recruitment of lymphocyte-specific protein tyrosine kinase to maintain T cell function [24].

CEACAM1 is widely expressed on the surface of T cells and maintains immune homeostasis by inhibiting T-cell hyperactivation, whereas deficiency results in T-cell hyperactivation, increased inflammation, and decreased expression of TIM-3 and regulatory cytokines. However, the restoration of T-cell-specific CEACAM1 expression can reverse these effects, highlighting the crucial role of CEACAM1 in TIM-3-mediated T-cell suppression and indicating that TIM-3 is co-expressed with CEACAM1, contributing to T-cell suppression [13, 17]. CEACAM1 is overexpressed in HNSCC and is particularly high in stages III-IV disease. The study revealed a positive correlation between the presence of TIM-3^+ TILs and the amount of $CEACAM1^+$ TILs in the tumor microenvironment, along with CEACAM1 expression in HNSCC tissues. In early-stage HNSCC, the predictive role and relationship between the number of TIM-3^+ TILs and patient survival were not significant, whereas in advanced-stage HNSCC, TIM-3 and CEACAM1 were highly expressed, suggesting a facilitative role of CEACAM1 in HNSCC metastasis and suggesting its association with poor prognosis [13]. Emerging evidence reveals that TIM-3 and CEACAM1 co-expression on $CD4^+$ and $CD8^+$ TILs not only protects T cells from apoptosis and facilitates the growth of immunosuppressive cell populations but also leads to T cell exhaustion [25, 26].

3.2.3 HMGB1

HMGB1 is an important molecular pattern protein that can detect and respond to endogenous danger signals within the body. In activated DCs, it is actively released from the nucleus into the extracellular space, thereby stimulating the responses of T cells and B cells [6, 27]. The binding of TIM-3 to HMGB1 has been demonstrated to impede the entry of nucleic acids into the nuclear endosome, thus preventing the activation of innate immune responses mediated by pattern recognition receptors in response to tumor-derived nucleic acids. Therefore, tumor-infiltrating DCs expressing TIM-3 interact with HMGB1, resulting in the attenuating nucleic acid-mediated innate immune responses [28].

3.2.4 PtdSer

PtdSer, a phospholipid defined as a surface marker of apoptosis, is a typical ligand for members of the TIM family [29, 30], but its affinity for TIM-3 is lower than that of other family members [12]. The interaction between PtdSer and TIM-3 is essential for promoting apoptosome clearance and cross-presentation of TIM-3^+ DCs [31]. However, the biological significance of the interaction between TIM-3 and PtdSer in T cells is not yet clear.

4 Expression and immunomodulation of TIM-3 in HNSCC

4.1 TIM-3 and effector T cells

TIM-3 expression was first identified on $CD4^+$ and $CD8^+$ T cells, inhibits cytotoxic T-lymphocytes (CTL) and effector Th1 cell function, and is considered a marker of T cell exhaustion [11]. TIM-3 was initially recognized as an inhibitory receptor found on T cells; in the tumor environment, elevated levels of TIM-3 expression are linked to T cell immune responses and T cell dysfunction [32]. A key to the success of anti-tumor immunity is T-cell dysfunction, usually manifested by impaired generation of pro-inflammatory cytokines and cytotoxicity [12]. TIM-3 functions as an immunosuppressive checkpoint that drives T-cell exhaustion and dampens innate immunity, and blocking this target has been shown to be beneficial in preclinical tumor immunotherapy [6].

TIM-3 mainly achieves immunosuppression by affecting the function of $CD8^+$ and $CD4^+$ T cells [33]. Blockade of TIM-3 has been observed to significantly increase the immune response of both $CD4^+$ and $CD8^+$ T cells in the HNSCC mouse model. This is achieved by modulating the activity of $CD4^+$TIM-3^+ cells and $CD8^+$TIM-3^+ cells, which in turn suppresses tumor formation [4]. It has been shown that $CD8^+$ CTL induces apoptosis in target cells through multiple mechanisms. These mechanisms include perforin and granzyme promoting direct contact and lysis of target cells, as well as Fas receptor (Fas)/Fas ligand (FasL) signaling and secretion of IFN-γ and tumor necrosis factor (TNF) [34]. $CD8^+$ T cells represent the most crucial component of TILs in exerting anti-tumor effects. TIM-3^+CD8^+ TILs have been demonstrated to possess the capacity to diminish cell proliferation and cellular activity as well as inhibit the production of effector cytokines (IFN-γ and TNF-α) [35]. This may be because TIM-3 antagonizes the T cell-specific transcription factor (TCF-1), which affects the function of $CD8^+$ T lymphoid stem cells [34]. Furthermore, the expression of TIM-3 on $CD8^+$ TILs was found to be strongly correlated with that of PD-1. Co-expression of TIM-3 and PD-1 on $CD8^+$ T cells was observed to be more functionally "depleted" than on PD-1 single positive $CD8^+$ T cells. This implies that concurrently blocking TIM-3 and PD-1 may potentially lead to enhanced therapeutic outcomes. In brief, the $CD8^+$ T-cells that demonstrate high levels of TIM-3 expression are linked to an unfavorable prognosis with regard to tumor progression [6, 36].

The traditional perspective on immunoediting typically indicates that an effective antitumor response is characterized by an elevation in Th1 and Tc1 cells, alongside a reduction in Th2 cells. Elevated levels of Th1, Tc1, and Th17 cells have been found in lymph node cells from both oral precancerous mice and HNSCC mice [37]. $CD4^+$ Th1 cells are responsible for the production of substantial quantities of IFN-γ and TNF-α in response to antigenic stimulation, thereby mediating immune responses against intracellular pathogens and tumor cells [38]. However, TIM-3 binds to Gal-9 and induces Th1 apoptosis and down-regulates the Th1 immune response, leading to immune tolerance [39]. Blockade of TIM-3 upregulates inflammatory cytokines, including IL17α, IFN-γ and TNF-α in tumors, and increases $CD4^+$ T cell dependence [7]. Additionally, IL-12 promotes TIM-3 expression on Th1 cells while suppressing the secretion of cytokines including TNF and INF-γ, resulting in decreased immunocompetence [12]. $CD4^+$ T cells derived from patients with HPV^+ oral HNSCC exhibit high expression of Gal-9 and can promote TIM-3^+ monocyte/macrophage expansion via a TIM-3/Gal-9-dependent pathway. Monocytes/macrophages treated with exogenous Gal-9 and $CD4^+$ T cells demonstrated the capacity to suppress

autologous $CD8^+$ T cell responses, as evidenced by a reduction in cytokine secretion. However, this immunosuppressive effect was reversed through the blockade of TIM-3/Gal-9 [21].

Myeloid-derived suppressor cells (MDSCs) participate in immunosuppression by suppressing T cells, and TIM-3 expression on T cells promotes MDSC production by interacting with Gal-9 [40]. CXCL1 induces the recruitment of MDSCs by binding to CXCR2, a receptor expressed by MDSCs, and blocking TIM-3 reduces $CD11b^+Gr1^+$ MDSCs, which are thought to be required to maintain an immunosuppressive milieu, by decreasing CXCL1, a finding also validated in homozygous mouse tumor model studies [37]. It is commonly reported that MDSCs are related to the progression of HNSCC. In HNSCC mouse model experiments, targeting $CD4^+TIM\text{-}3^+$ cells and $CD8^+TIM\text{-}3^+$ cells led to a decrease in MDSCs within both the tumor microenvironment and peripheral environment, which in turn resulted in the restoration of effector T cells. It can therefore be posited that the inhibition of TIM-3 reverses immunosuppression, reactivating T cells and preventing the aggregation of MDSCs [4].

4.2 TIM-3 and $FoxP3^+$ Tregs

Typical Tregs are subpopulations of T lymphocytes recognized by $CD4^+CD25^+Foxp3^+$ and are important suppressor cells in TILs. In cancers affecting humans, 25%–50% of TIL Tregs express TIM-3 [8]. TIM-3 is present on $CD4^+Foxp3^+$ Treg cells and enhances the inhibitory function of $Foxp3^+$ Tregs [41]. Tregs can inhibit the activation of $CD8^+$ T cells and inflammation by direct contact or by the production of transforming growth factor-β (TGF-β) and IL-10 [42]. Human $CD4^+CD25^+Foxp3^+$ Treg cells can be co-activated by CD3 and CD46 antibodies, express granzyme A, and lyse activated $CD4^+$ and $CD8^+$ T and NKs in a perforation-dependent, Fas-FasL-independent manner [43–45]. It was shown that TIM-3 expression levels in $Foxp3^+$ Tregs were upregulated at the tumor site [38], and that $TIM\text{-}3^+$ Tregs at the tumor locus were more inhibitory than $TIM\text{-}3^-$ Tregs, which expressed stronger TGF-β,IL-10, CD73, CD39, perforin, granzyme A, and granzyme G [41], and expressed high numbers of other checkpoint receptors such as LAG-3, CTLA-4 and PD-1 [6]. Significant enrichment of granzyme B on $TIM\text{-}3^+$ TILs Treg and higher IFN-γ receptor expression were observed in the HNSCC mouse model, which may account for the important role of TIM-3 in the anti-tumor immune response [8]. Administering an anti-TIM-3 monoclonal antibody resulted in a decrease in $CD8^+$ Tregs and an enhancement of IFN-γ production in a transgenic mouse model of HNSCC, suggesting that by attenuating the repression of negative immune factors, TIM-3 blockade may enhance the anti-tumor immune response [46]. In conclusion, TIM-3 is an important regulator of Tregs, signaling an enhanced suppressive function of the $Foxp3^+$ Treg cell population, and $TIM\text{-}3^+$ Tregs are involved in immune regulation through multiple mechanisms [47].

4.3 TIM-3 and innate immune cells

TIM-3 is expressed not only on T lymphocytes but is also extensively present on tumor-associated macrophages (TAMs), DCs, and NKs. The suppressive function of TIM-3 in non-T cell populations within the immune system is consistent with its characterization in T cells. TIM-3 has been shown to suppress innate anti-tumor immunity and plays a pivotal role in the innate immune response in most in vivo studies [6].

4.3.1 TAMs

TAMs can be categorized into two distinct types: classical activation (M1) and alternative activation (M2). M1 macrophages exhibit anti-tumor properties, whereas M2 macrophages have been shown to exert immunosuppressive effects, impeding anti-tumor responses mediated by effector T cells while concomitantly facilitating tumor cell proliferation and metastasis [33]. In experiments conducted with genetically identical mice, treating tumor-associated macrophages with Gal-9 protein was found to induce the secretion of IL-10, IL-8, and IL-6. This phenomenon may represent a significant mechanism by which TIM-3 promotes tumor progression [39]. The elevation of TIM-3 levels in macrophages has been demonstrated to facilitate M2 polarization and enhance IL-6 secretion, which in turn serves to stimulate tumor growth [11]. Osteosarcoma cells induce macrophage M2-type differentiation mainly through exosome MG63-mediated TIM-3, which subsequently facilitates the invasion, migration, and epithelial-mesenchymal transition of osteosarcoma cells by secreting cytokines comprising TGF-β, VEGF, and IL-10 [48]. Similarly, PTEN-deficient glioma cells secrete high levels of Gal-9 through the AKT-GSK3-IRF1 pathway and activate TIM-3 and downstream pathways in macrophages to drive macrophage M2 polarization, thereby stimulating angiogenesis and promoting glioma growth.

Thus, inhibiting the Gal-9/TIM-3 signaling pathway effectively reduces macrophage M2 polarization and angiogenesis, thereby delaying tumor growth [49]. However, blocking TIM-3 in an HNSCC mouse model experiment did not significantly reduce the number of M2 macrophages, which may be because of the limited expression of TIM-3 on macrophages in this mouse [22]. It was observed that toll-like receptor 3 (TLR-3) signaling significantly enhanced the expression of co-stimulatory molecules, like CD40, CD80, and CD86, along with the production of cytokines such as TNF-α, IL-6, and IL-12 in macrophages. Additionally, a down-regulation of TIM-3 was noted in a tumor mouse model. This resulted in both the activation of T cells and the inhibition of tumor progression, suggesting that TLR-3 stimulation biased macrophages toward the M1 phenotype. It was thus found that promoting the transformation of the M2 phenotype into the M1 phenotype could prove an effective therapeutic strategy [50]. The experiment further demonstrated that in the oropharyngeal region of HNSCC, Gal-9-expressing $CD4^+$ T cells promote TIM-3^+ monocyte/macrophage expansion via the TIM-3/Gal-9 signaling pathway. However, this does not result in a bias towards M1 or M2 macrophages, but rather the inhibition of cytokines that are characteristic of both types [21].

4.3.2 DCs

DCs sense environmental signals and adopt an immunostimulatory or regulatory phenotype to fine-tune the immune response. The TIM-3 protein is a key regulator of the immune response, inhibiting DC activation and the capacity of T cells to initiate an immune response in the context of cancer [51]. There are two main types of DCs: cDC1 and cDC2. cDC1 and cDC2 are usually antigen-presenting via major histocompatibility complex class I (MHC I) or MHC II and play a special role in the activation of $CD8^+$ T cells and $CD4^+$ T cells. In tumor-infiltrating DCs, the TIM-3 receptor binds to the HMGB1 ligand, thereby facilitating immune evasion. This is achieved by inhibiting the correct transport of nucleic acids and preventing the activation of tumor-associated DCs, which in turn suppresses nucleic acid immune responses [6]. Binding between the ligands PtdSer and TIM-3 mediates the trapping of apoptotic material, and expression on mouse macrophages and DCs promotes cross-presentation [12, 22]. Several experimental studies have shown that TIM-3 is specifically expressed in DCs, both in mice and humans. TIM-3 shows constitutive expression in DCs and macrophages in both humans and mice. DCs upregulate CD80/CD86 expression and secrete pro-inflammatory factors like TNF-α after Gal-9 stimulation [52]. It has been evidenced that the anti-tumor immunity of the STING agonist ADU-S100 is enhanced by the blockade of TIM-3, which modulates the release of $CD4^+$ T cells from cDC2 [53]. The conditional deletion of TIM-3 in DCs has been observed to enhance the activation of NLRP3 inflammatory vesicles in DCs, leading to the accumulation of IL-1β/IL-18, which in turn promotes TIM-3 function and is associated with the maintenance of $CD8^+$ effector cells and stem cell-like T cells [54].

4.3.3 NKs

NKs are an important component of innate immunity, capable of directly clearing infected and tumor cells earlier than T cells without the need for presensitization and activation. TIM-3 showed expression on mature NKs, whereas it also induced expression on immature $CD56^{bright}$ CD^- NKs after stimulation with IL-18, IL-15, and IL-12. TIM-3 expression is elevated on NKs and has been demonstrated to suppress the anti-tumor activity of NKs in several cancer studies [6]. Inhibiting TIM-3 enhances the natural cytotoxicity of NKs against tumor cells and reverses this inhibition. When TIM-3 on NKs binds to its ligand, the ability of NKs to secrete cytokines and kill target cells is diminished [55]. It was shown that the interplay between Gal-9 and TIM-3 inhibited the proliferation, activation, and cytotoxic function of NKs and mediated alterations in the expression of corresponding molecules in the TIM-3^+ NKs population. In the HNSCC assay, the functional failure of NKs was clearly indicated to be driven by Gal-9 in NKs in a TIM-3-dependent manner mediating the inactivation of the IL-2/STAT5 signaling pathway through the establishment of a HAVCR2 (TIM-3) knockdown model in NK cell lines [56].

Whereas CEACAM1 binding to TIM-3 significantly inhibited the direct killing and indirect regulatory functions of NKs, the downstream pathways triggered by the CEACAM1-TIM-3 interaction remain unidentified [57]. When TIM-3 is not available for ligand binding, it binds to BAT3 and recruits the tyrosine kinase LCK to maintain T-cell function. Jiyong Yang et al. found that BAT3 could promote cytotoxicity in NKs by inhibiting TIM-3 signaling in experiments with a mouse model of HNSCC. Meanwhile, this study also pointed out that HNSCC cells induced the downregulation of BAT3 in tumor-infiltrating NKs, suggesting that HNSCC enhances TIM-3 signaling by downregulating BAT3, thereby inhibiting NK cytotoxicity [58]. BAT3 not only interacts with TIM-3 but is also released from cancer cells, activating Nkp30 and helping to regulate NKs function [58]. In addition to this, in HCC, TIM-3 can block the downstream Akt/mTORC1 signaling pathway

by competing with PI3K p110 for binding to PI3K p85, leading to NK dysfunction [59]. TIM-3 was stably expressed on steady-state NKs in HNSCC peripheral blood and at high levels on tumor-infiltrating NKs. NKs exhibit immune diversity in the TIME of HNSCC, demonstrating cytotoxic activity for the direct killing of malignant cells while also recruiting other important immune cells, in addition to tumor-resident properties. In TIME of HNSCC, an increased degree of NK infiltration was directly correlated with an improved overall survival in patients with HNSCC. Moreover, a high level of TIM-3 expression in NKs was negatively associated with survival in patients with HPV^+ HNSCC. Preclinical experimental studies found that Gal-9 limited cetuximab-mediated targeted killing of HNSCC cells by NKs through down-regulation of CD16 expression, but this finding needs further validation by additional clinical trials [56].

4.4 Dynamic interaction network

In the TIME of HNSCC, TIM-3 orchestrates a sophisticated immunosuppressive network by modulating the functional states of multiple immune cell subsets. Of interest, TIM-3^+ effector T cells form a dynamic balance with Tregs. In a healthy immune system, a precise balance is maintained between effector T cells (e.g., CTLs and Th1 cells), which provide the anti-tumor immune response, and Tregs, which suppress excessive immune reactions to maintain self-tolerance. However, in the HNSCC tumor microenvironment, TIM-3 expression disrupts this equilibrium. TIM-3^+ effector T cells typically exhibit an "exhausted" phenotype (often co-expressing PD-1), with significantly compromised antitumor functionality. Conversely, TIM-3^+ Tregs demonstrate markedly enhanced immunosuppressive capacity. Secretion of cytokines such as IFN-γ by TIM-3^+ effector T cells can indirectly affect their activity by regulating the metabolic or functional state of Treg, whereas the inhibitory function of Treg indirectly promotes the expression of TIM-3 on effector T cells by inducing T cell depletion [22, 60]. This mutually reinforcing effect creates a vicious cycle, resulting in continuous inhibition of effector T cell function and an abnormal increase in the number and activity of Treg, which ultimately leads to immune escape and further tumor development.

In addition, there are multiple levels of synergism between cell populations in the innate immune system. Binding of C–C motif chemokine ligand 22 (CCL22) secreted by M2-type TAMs to the C–C chemokine receptor type 4 (CCR4) receptor on the surface of Treg chemotaxis TIM-3^+ Treg toward tumor infiltration, which in turn promotes M2-type polarization of TAMs by regulating cytokines [21]. Indoleamine 2,3-dioxygenase (IDO) is an immunosuppressive enzyme that degrades tryptophan (an essential amino acid for T-cell activation) to kynurenine, thereby inhibiting T-cell function [61]. TIM-3^+ DCs may up-regulate IDO expression through activation of the STAT3 signaling pathways, and metabolites of IDO can directly act on $CD4^+$ T cells to promote their differentiation into $FoxP3^+$ Tregs, while inhibiting metabolic reprogramming of $CD8^+$ T cells [62]. The relationship between Tregs and NKs is complex and bidirectional, with both mutual inhibition and synergistic regulation under specific conditions. Under normal conditions, NKs can eliminate Tregs through direct killing, antibody-dependent cell-mediated cytotoxicity (ADCC), cytokine modulation, etc. [63]. However, in the tumor microenvironment, Tregs predominate and promote immune escape by inhibiting NKs. In HNSCC, TIM-3 signaling creates a vicious cycle of immunosuppression by inhibiting the cytotoxicity and cytokine secretion of NKs and weakening their ability to clear Tregs. This fine-grained immunoregulatory network highlights the complexity of immune cell interactions in the tumor microenvironment and explains why single immune checkpoint inhibitors have limited efficacy in HNSCC. Clinical studies have demonstrated that this synergistic network is therapeutically resistant: during anti-PD-1 therapy, TIM-3^+ TILs are adaptively upregulated through the PI3K/Akt pathway, which, together with increased Tregs infiltration and MDSC amplification, constitutes the core mechanism of acquired resistance [64]. Breakthroughs in this mechanism will provide new targets for combination immunotherapy.

5 Immunomodulation of TIM-3 in HNSCC and its clinical significance

The tumor immune microenvironment is composed of numerous immune cells, including TILs, DCs, TAMs, MDSCs, Tregs, and a variety of cytokines. These components are essential in the initiation, progression, and deterioration of HNSCC, with immunosuppression being a key feature [7].

TIM-3, as an immune checkpoint molecule, is important in the initiation, progression and prognosis of HNSCC. Its expression level is closely associated with lymph node metastasis, TNM staging, prognosis and survival. TIM-3^+ TILs were correlated with tumor size, TNM stage, and lymph node metastasis in an experiment using immunochemistry to detect infiltration of TIM-3^+ TILs in HNSCC tissue, and the median survival time of HNSCC patients with low infiltration of TIM-3^+ TILs was markedly longer than that of HNSCC patients with high infiltration of TIM-3^+ TILs; overall survival (OS) and progression-free survival

(DFS) were significantly higher. Multivariate analysis showed that TIM-3$^+$ TIL infiltration still has an impact on prognosis. The findings were similarly obtained in tumors such as gastric, liver, and colorectal cancers. In patients with stage III to IV HNSCC, OS and DFS times were shorter in patients with high infiltration of TIM-3$^+$ TILs than in patients with low infiltration of TIM-3$^+$ TILs, whereas there was no such difference in stage I and II. This suggests that in early-stage HNSCC, the level of TIM-3$^+$ TILs is not significantly correlated with the prediction of patient survival, and the expression of TIM-3 in TILs contributes to the aggressiveness of advanced tumors [13]. This is supported by data from clinical studies, where TIM-3 expression was significantly elevated in recurrent HNSCC compared to primary HNSCC. The potential mechanism by which elevated TIM-3 expression leads to effector T cell exhaustion and ineffective anti-tumor immune responses is not yet fully elucidated [4].

In the immune microenvironment of HNSCC, TIM-3 achieves immunosuppression by affecting the function of CD8$^+$ and CD4$^+$ T cells, and the expression of TIM-3 was upregulated in CD4$^+$ and CD8$^+$ T cells and closely associated with MDSCs. In a mouse model of HNSCC, the blockade of TIM-3 significantly enhances the presence of effector T cells, including CD4$^+$ and CD8$^+$ T cells, in both the tumor microenvironment and peripheral environment. This intervention markedly boosts the production of IFN-γ while inhibiting the expression of chemokine CXCL1 within tumors. Consequently, it improves the immune response of CD4$^+$ and CD8$^+$ T cells and reduces the recruitment of MDSCs, thereby suppressing tumor development [4]. Treg is an immunosuppressive subpopulation of CD4$^+$ T cells that suppresses immune effector cells by releasing inhibitory cytokines and is a suppressor of anti-tumor immune responses. The amount of circulating and infiltrating Treg was generally increased in HNSCC patients, and inhibition of TIM-3 resulted in decreased numbers of Treg and TIM-3$^+$ Treg, suggesting that blockade of TIM-3 enhances antitumor immunity by decreasing negative regulators [46]. Labeling of PD-1 inhibits Tregs, reducing their inhibitory capacity, whereas Tim-3$^+$ Tregs express more effector cytokines and chemokine genes and inhibit HNSCC more than PD-1$^+$ Tregs. Meanwhile, the expression of TIM-3 on Tregs was downregulated after anti-PD-1 Ab immunotherapy in HNSCC mice, suggesting that anti-PD-1 Ab could reverse the inhibitory function of HNSCC TIL Tregs [8]. However, in HNSCC, blocking TIM-3 is not sufficient to eliminate Treg, and the remaining Tregs are highly proliferative and may continue to expand, which is closely associated with disease progression and relapse [65].

DCs are the most effective antigen-presenting cells within the organism, and TIM-3 is specifically overexpressed in DCs and participates in immune evasion by inhibiting DC activation and T-cell initiating capacity. One study showed that 72% of HNSCC cases were positive for DCs by immunohistochemical evaluation. It is currently believed that the presence of DCs in HNSCC correlates with a more favorable prognosis, but these cells do not function effectively due to immunosuppression [66]. In HNSCC, combining cetuximab with DCs greatly increased the killing rate of HNSCC, but the mechanism is not clear [67]. Furthermore, evidence suggests that the deficiency of cDC1 is a significant factor contributing to anti-PD-1 resistance in HNSCC. In models exhibiting anti-PD-1 resistance, intratumoral cDC1 vaccination has proven sufficient to restore anti-PD-1 responsiveness and enhance tumor control by promoting T cell infiltration and increasing antigen-specific responses [68]. Nevertheless, the mechanism of the role of DCs in HNSCC is unclear and requires further investigation. Increased expression of TIM-3 in macrophages facilitates M2 polarization, which in turn supports tumor growth. Although blocking the TIM-3/Gal-9 pathway significantly inhibited M2 polarization in glioma cells, thereby delaying tumor growth, blocking TIM-3 did not significantly reduce the number of M2 macrophages in the HNSCC mouse model, which may be attributed to the limited expression of M2 macrophages in HNSCC tissues [22, 49]. HNSCC tumors have now been found to exhibit relatively high numbers of NK cell infiltration and to exhibit immune diversity.

In HNSCC, TIM-3 binding to the ligand Gal-9 mediated NK cell failure; binding to CEACAM1 inhibited the direct killing and indirect regulatory functions of NKs, and when TIM-3 does not bind to its ligand, it induces the down-regulation of BAT3 in tumor-infiltrating NKs, which promotes its cytotoxicity by inhibiting TIM-3 signaling [56–58]. Although TIM-3 has numerous ligands, only Gal-9 inhibits peripheral blood-derived NKs from HNSCC patients in HNSCC and significantly limits the overall effectiveness of cetuximab-mediated NKs in HNSCC via the TIM-3/Gal-9 immunosuppression axis. The current study concluded that NK cell infiltration is directly related to the overall survival of HNSCC patients and suggested that high expression of TIM-3 in tumor-infiltrating NKs correlates with a poor prognosis in HPV$^+$ HNSCC patients [56]. This also reveals the importance of TIM-3 in HNSCC tumors caused by viral infection (Figs. 1, 2 and 3).

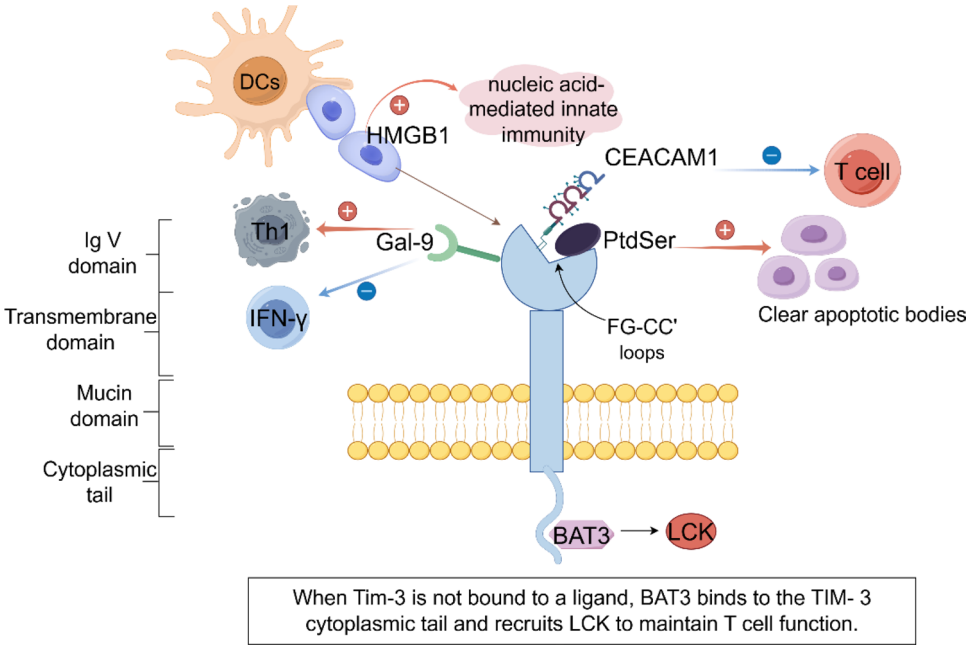

Fig. 1 (By Figdraw). Structure of Tim-3 and its role with ligands. +: express promotion −: express inhibition. The structure of Tim-3 includes an immunoglobulin domain, a mucin-like domain, a transmembrane region composed of a hydrophobic amino acid sequence, and a cytoplasmic tail. Tim-3 has four ligands: binding to Gal-9 induces apoptosis in Th1 cells and inhibits IFN-γ production; interaction with CEACAM1 suppresses T cell function; binding to HMGB1 weakens nucleic acid-mediated innate immune responses; and interaction with PtdSer promotes the phagocytosis of apoptotic cells. When Tim-3 is unbound to ligands, BAT3 associates with its cytoplasmic tail to recruit LCK, thereby maintaining T cell function

6 TIME for HPV$^+$ HNSCC

In the last few years, there has been a notable rise in the incidence of high-risk HPV infections, which have emerged as a major factor contributing to the development of HNSCC [69]. In patients with HNSCC, the extent and characterization of intratumoral immune cell infiltration vary greatly by HPV status. Although patients with HPV$^+$ HNSCC are usually diagnosed with lymph node metastases in the later stages of the disease, they have a significantly better prognosis compared to HPV$^-$ cancers [70]. It is evident that HPV infection has an impact on both the immune microenvironment and survival prognosis of patients with HNSCC, and therefore, we are compelled to discuss the impact of HPV on HNSCC.

Compared to HPV$^-$ tumors, HPV$^+$ tumor samples exhibited significantly greater numbers of tumor-infiltrating CD8$^+$ T cells, along with increased production of IL-17 and IFN-γ, suggesting a stronger immune response [71]. Similarly, HPV$^+$ HNSCC tumors have higher levels of infiltrating Tregs, and some patients with higher TIL Treg counts have an improved prognosis, whereas others show this benefit only when the CD8/Treg ratio is high in HPV$^+$ disease [72]. In patients with a positive HPV status, CD4$^+$ T cells exhibit elevated levels of Gal-9 expression, which in turn promotes the expansion of monocytes and macrophages via the TIM-3/Gal-9 pathway. The blockade of this pathway has been observed to enhance the production of IFN-γ by CD8$^+$ T cells and the secretion of cytokines by monocytes [21]. It is evident that blocking the TIM-3/Gal-9 pathway can further improve the prognosis of patients with HPV$^+$ HNSCC.

Furthermore, the researchers observed an elevated frequency of mDCs in HPV-positive neoplastic lesions, accompanied by a marginal increase in the number of pDCs and monocytes/macrophages. And the large number of macrophages infiltrating HNSCC may be related to lymph node metastasis and advanced disease [73]. HNSCC patients have been observed to present with elevated levels of antibody-antigen immune complexes, which have been demonstrated to activate monocytes and DCs through the CD16 cross-linking mechanism. It has been postulated that this may serve to enhance pro-tumorigenic and angiogenic activity [74]. However, the level of CD16 expression in tumor-infiltrating TIM-3$^+$ NK cell populations was markedly reduced in HPV$^+$ HNSCC patients in comparison to HPV$^-$ HNSCC patients [56]. The expression of Cox-2 mRNA was significantly reduced in HPV-positive tumors, while

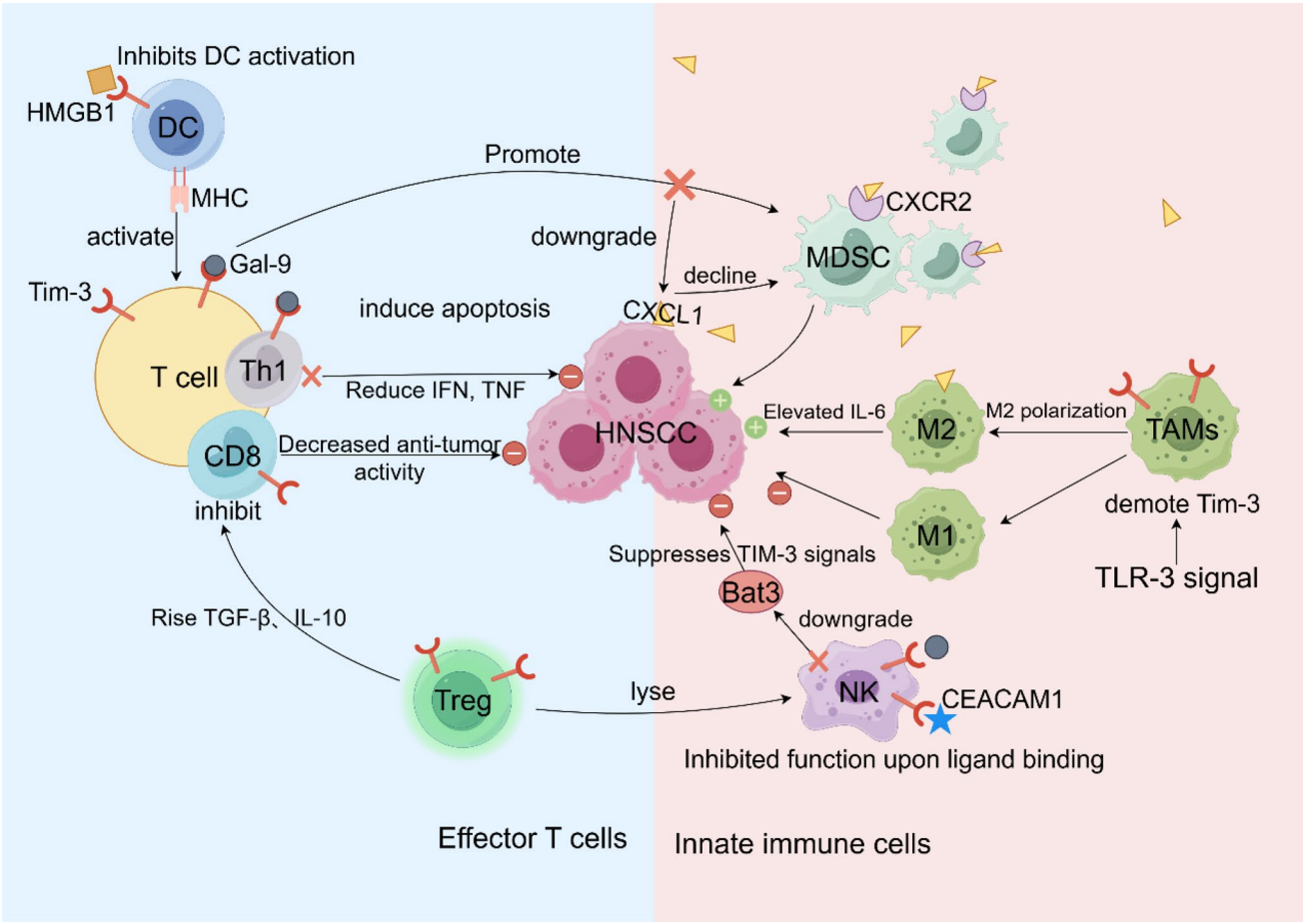

Fig. 2 (By Figdraw). Expression and immunomodulation of Tim-3 in the immune microenvironment of HNSCC.+: express promotion −: express inhibition×: express blocking**.** In the immune microenvironment of HNSCC, TIM-3 mainly affects effector T cells and innate immune cells to achieve immunosuppression. TIM-3 reduces the anti-tumor activity of CD8+T cells and, in combination with Gal-9, induces apoptosis and downregulates the immune response of Th1 cells. Tregs are activated to inhibit CD8+T cell activation and suppress NKs. In addition, Treg cells inhibit the activation of CD8+T cells by producing TGF-β and IL-10.TIM-3 expression on Tregs enhances their inhibitory function. MDSCs are often associated with HNSCC tumor progression.TIM-3 interacts with Gal-9 and promotes MDSC production. CXCL1 induces MDSCs recruitment by binding to CXCR2, a receptor expressed by MDSCs, and blocking TIM-3 downregulates CXCL1, thereby reducing MDSCs. TIM-3 is expressed on DCs and is involved in immune evasion by inhibiting DC activation and T cell initiation. Expression of TIM-3 on macrophages promotes M2 polarization, which promotes tumor growth, whereas stimulation of TLR-3 signaling biases macrophages toward an MI phenotype, which inhibits tumor progression. TIM-3 induces downregulation of Bat3 in tumor-infiltrating NKs when it is not bound to ligands, which promotes cytotoxicity by inhibiting TIM-3 signaling. However, TIM-3 could mediate NK cell failure when bound to Gal-9 or CEACAM1.

the expression of PD1 mRNA was notably elevated. Cox-2 mRNA levels were associated negatively with the number of tumor-infiltrating Th17 and Th1 lymphocytes and positively correlated with TIM-3 mRNA expression. Therefore, this may be related to the improved prognosis of HPV^{-} HNSCC patients [71]. Studies have shown that chemokines like CCL21, CCL17, CXCL12, CXCL10, and CXCL9 and cytokines including IL-23, IL-17, and IL-2 are significantly higher in cell cultures derived from HPV-positive tumor tissue than in negative patients. However, the specific role of these factors in HNSCC requires further in-depth analysis [75].

7 The use of TIM3 in HNSCC combination immunotherapy

Currently, monoclonal antibodies targeting PD-1 or CTLA-4 are undergoing research in multiple clinical trials for HNSCC patients across various stages and disease states [4]. At present, PD-1 is currently one of the most significant immune checkpoint receptors (ICRs) in clinical research, and the Food and Drug Administration (FDA) has authorized

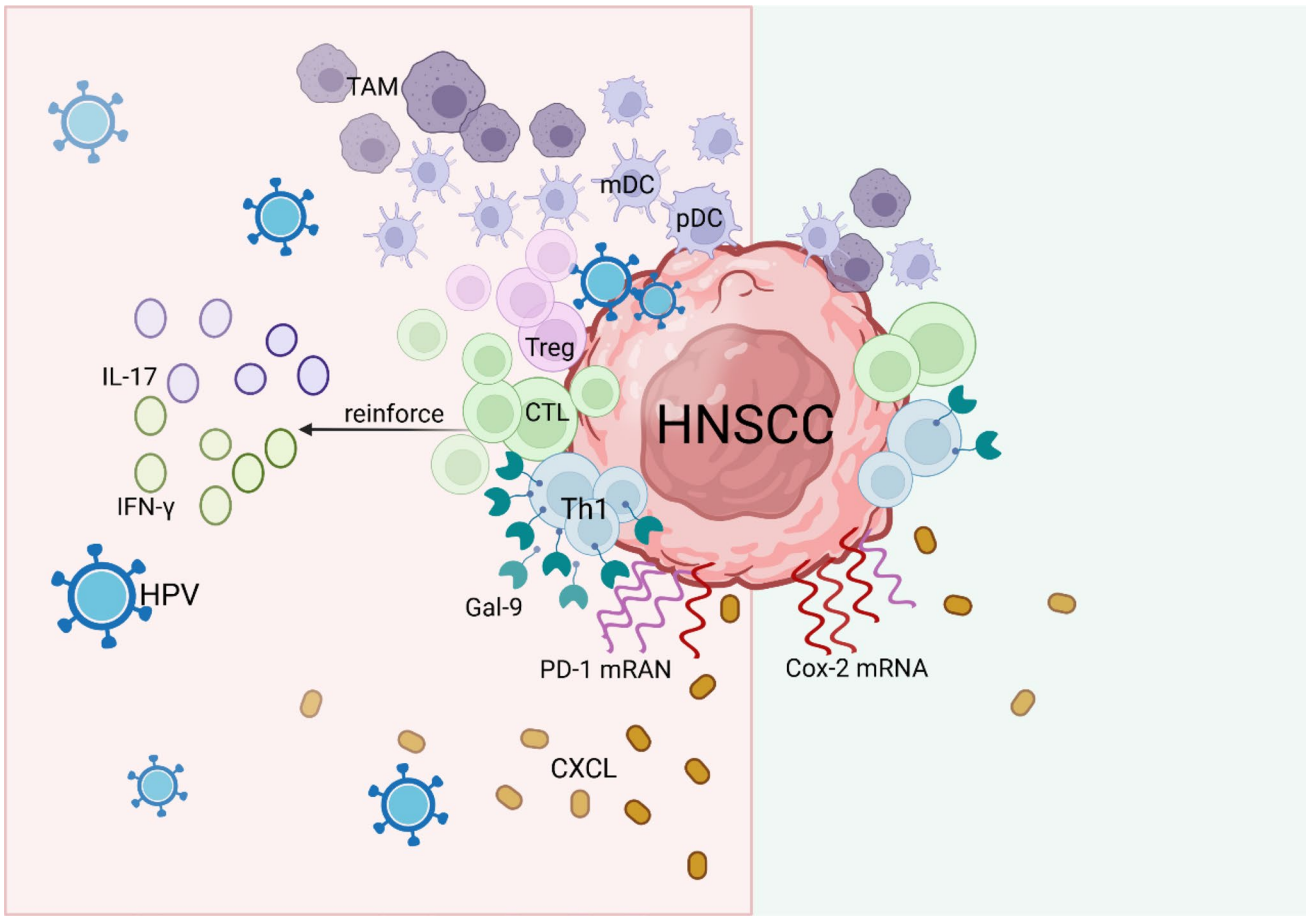

Fig. 3 (By Biorender). Immunologic microenvironment of HPV$^+$ HNSCC vs HPV$^-$ HNSCC. In HNSCC patients, the immune microenvironment varied according to HPV status. Compared with HPV$^-$ HNSCC, HPV$^+$ HNSCC patients had a stronger immune response, with significantly increased CTL expression and greater production of cytokines (IFN-γ, IL-17) in their tumor tissues; higher levels of Tregs expression; Gal-9 was highly expressed on CD4$^+$ T cells; and the number of mDCs, pDCs, monocytes/macrophages, and chemokines was also higher; PD1 mRNA expression was significantly higher, while Cox-2 mRNA expression was significantly lower.

the use of Nivolumab and Pembrolizumab for patients with relapsed or metastatic cisplatin-resistant HNSCC. Despite these advancements, the clinical survival benefit in patients with metastatic and relapsed HNSCC has been limited, with issues of drug resistance and low response rates. As tumor treatment protocols are optimized and immunotherapy advances, researchers are discovering the promise of combination immunotherapy in HNSCC.

At this juncture, a monoclonal antibody targeting human TIM-3 has been successfully developed as an inhibitor of immune checkpoints and has been subjected to phase I/II clinical trials with the objective of evaluating its safety and efficacy in the context of cancer therapy [76]. Although it has been suggested that blockade of TIM-3 alone does not significantly increase overall survival or benefit effector cell populations in an in vitro model [7]. However, a decrease in tumor growth rate was observed in HNSCC mice treated with anti-TIM-3 antibodies, and no other toxic effects were found. TIM-3 shares a common link with other checkpoint receptors, and checkpoint inhibitors targeting TIM-3 may not only circumvent some of the toxic effects of CTLA-4 or PD-1-targeted checkpoint blockade but also, when combined with other immune checkpoints, may trigger a stronger immune response [12].

The current recognition study found that TIM-3 and PD-1 co-expression was observed in both CD4$^+$ T cells and CD8$^+$ T cells, and TIM-3$^+$PD-1$^+$ T cells were the most dysfunctional. The concurrent inhibition of the TIM-3 and PD-1 axes has been proven to elicit a superior restoration of T cell responses when compared to the sole blockade of the PD-1 pathway in preclinical models of melanoma, colorectal carcinoma, and chronic viral infection in mice [12]. In patients with HNSCC undergoing cetuximab monotherapy, there was an increase in the frequency of PD-1$^+$CD8$^+$ T and TIM-3$^+$CD8$^+$ T cells within the TME. Moreover, there was a concomitant increase in the prevalence of granzyme B$^+$ and perforin$^+$ cells in these CD8$^+$ TILs, which concurrently exhibited PD-1 and TIM-3 expression, and this may also be the mechanism leading to their

immune tolerance. Thus, the utilization of combination therapy involving PD-1 and TIM-3 blockade in conjunction with cetuximab therapy improves clinical outcomes in patients with HNSCC [77]. In addition, Gulidanna Shayan and colleagues suggest that TIM-3 upregulation increases resistance to anti-PD-1 therapy. They found that TIM-3 expression in TILs was significantly upregulated after PD-1 blockade in the HNSCC mouse model, but the expression of immune checkpoints such as CTLA-4 and TIGIT was not significantly increased [8]. This is because during PD-1 antibody treatment in the HNSCC mouse model, TILs upregulated the expression of TIM-3 through the PI3K/Akt/mTOR signaling pathway, which enabled T cells to maintain their depleted state after PD-1 blockade, thus escaping the inhibitory effect of anti-PD-1 treatment, forming an adaptation, and affecting the efficacy of immunotherapy. Therefore, combined blockade of PD-1 and TIM-3 may be a more effective strategy for cancer immunotherapy.

Local tumor radiotherapy can alter the TIME and enhance the sensitivity of HNSCC tumors to PD-L1 inhibition. In an in situ HNSCC model, combined TIM-3 and PD-L1 blockade by radiotherapy (RT) was observed to improve T-cell cytotoxicity, reduce the number of Tregs, significantly delay tumor growth, and enhance survival. Nonetheless, the efficacy was not durable, and analysis of recurrent tumors showed a decrease in $CD8^+$ T cells and reappearance of Tregs. However, further targeting Treg depletion in mice receiving RT and dual immune checkpoint inhibitors restored anti-tumor immunity [65]. In addition to this, a significant increase in Tregs in the HNSCC microenvironment and inhibition of cetuximab-induced NK cytotoxicity during cetuximab treatment correlated with poor prognosis [77]. Therefore, targeting Treg inhibitors could be crucial for attaining lasting tumor responses to the combination of radiation and immunotherapy.

It has been demonstrated that virus-associated tumor types exhibit a heightened susceptibility to immune checkpoint inhibitor therapy, attributable to their intrinsic characteristics, including elevated immune infiltration, high PD-L1 expression, and a baseline of tumor immunogenicity. The immunosuppressive TME is less pronounced in HPV^+ OPSCC than in HPV^- HNSCC, implying that HPV^+ patients have a higher sensitivity to the immune checkpoint inhibitor response, better immunotherapy responsiveness, and better prognosis [78]. Clinical studies have demonstrated that HPV^+ HNSCC has a relatively good prognosis, with a local control rate > 90% and a distant metastasis rate of about 8–10% with conventional therapy. However, it has also been suggested that nabumab is beneficial regardless of HPV status [79]. Therefore, no definitive conclusions have been reached regarding the inclusion of HPV status in treatment plans. Currently, vaccines against HPV viral infection have been widely used in cervical cancer and other diseases, and in HPV^+ HNSCC, our study found that HPV^+ oropharyngeal cancer patients induced an increase in the secretion of IFN-γ and improved immunity to virus-associated tumor antigens after HPV vaccination [80]. As you can see, vaccination offers new hope for HPV^+ patients.

Combined with the above studies, it is not difficult to realize that perhaps there is a problem in the previous studies of HNSCC, that is, there is no stratification according to HPV status. Because we found that, according to the different HPV statuses, the immune microenvironment of HNSCC is different, and the immune response produced is also different, is this effect related to the experimental conclusion? This is a question worth thinking about.

8 Conclusion

TIM-3, an emerging immune checkpoint with established immunosuppressive functions in the context of numerous cancers, has also been identified as a key contributor to the development of HNSCC. TIM-3 is markedly elevated in HNSCC and contributes to the development of the immunosuppressive microenvironment associated with HNSCC through several mechanisms, including the mediation of T-cell exhaustion and apoptosis, the enhancement of Treg-mediated immune suppression, the promotion of TAM M2 polarization, and the inhibition of NK and DC function. Its interaction with ligands such as Gal-9 and CEACAM1 creates a dynamic immunosuppressive network that correlates with advanced tumor stage, lymph node metastasis and poor prognosis. Clinical research has shown that targeting TIM-3 has an anti-tumor effect, and the co-association between TIM-3 and other immune checkpoints, as well as its co-expression with PD-1, provides a theoretical basis for combination immunotherapy. Combination immunotherapy efficacy has been preliminarily validated in preclinical studies in a variety of tumors, and the use of combined checkpoint inhibitors has proven successful in enhancing tumor immunity and improving survival rates. Meanwhile, combination chemotherapy, radiotherapy, and targeted therapy have shown synergistic anti-tumor effects. In addition to this, vaccines against HPV viral infections have also been widely used in the clinic. Notably, HPV^+ HNSCC exhibits a unique immune profile, and vaccines against HPV infection are in widespread clinical use. In conclusion, TIM-3 is crucial in the initiation and progression of HNSCC and holds significant promise as a therapeutic target for addressing this disease.

Despite these insights, there are some limitations worth noting. First, most mechanistic studies rely on preclinical models, which may not fully reproduce the complexity of human HNSCC heterogeneity. Second, clinical validation of TIM-3 inhibitors is in its infancy, and there are limited data on safety, efficacy, or optimal dosing in patients with HNSCC. Third, the interaction between TIM-3 and HPV-driven tumorigenesis needs to be explored in greater depth, as current analyses often lack HPV status stratification and may mask subtype-specific treatment responses. In addition, the role of TIM-3 on adaptive resistance after radiotherapy or chemotherapy remains underexplored.

In the future, the following three strategic priorities should be emphasized to advance TIM-3-targeted therapy for HNSCC. First, mechanistic elucidation should be strengthened to reveal the cross-talk of TIM-3 signaling with other checkpoints and its role in non-T cell populations. In response to the ligand specificity, we should develop inhibitors targeting different TIM-3 ligands to tailor the therapeutic regimen for HPV^+ or HPV^- HNSCC subtypes. Second, clinical translation should be enhanced by conducting stratified clinical trials to assess the efficacy of TIM-3 blockade alone or in combination with PD-1 inhibitors, with endpoints including HPV status, TIM-3 expression levels, and immune cell dynamics. Multimodal integration is explored to utilize synergies between TIM-3 inhibitors and conventional therapies to address mechanisms of resistance and improve durable responses. Finally, predictive biomarkers will be further identified to guide patient selection and monitor efficacy. Notably, TIM-3-mediated adaptive changes during the course of the trial must be considered in order to design sequential or alternating treatment regimens. By bridging these gaps, TIM-3-targeted strategies may redefine the therapeutic paradigm and offer hope for patients with HNSCC who have limited response to current immunotherapies.

Author contributions All authors contributed to the study conception and design. Specific contributions are as follows: Literature search and Data analysis: Yang Luo and Yuzhu He Methodology and Writing—original draft preparation: Shuang Xu Software and Visualization: Yuxiang Chen Funding acquisition and Resources: Fengfeng Qin Writing—review and Supervision: Wenjian Hu All authors commented on the previous manuscript, and all authors read and agreed to submit the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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