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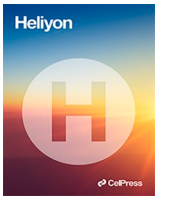

Review article

Molecular basis, potential biomarkers, and future prospects of OSCC and PD-1/PD-L1 related immunotherapy methods

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ABSTRACT

Oral squamous cell carcinoma (OSCC) affects a large number of individuals worldwide. Despite advancements in surgery, radiation, and chemotherapy, satisfactory outcomes have not been achieved. In recent years, the success of drugs targeting programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) has led to breakthroughs in cancer treatment, but systematic summaries on their effectiveness against OSCC are lacking. This article reviews the latest research on the PD-1/PD-L1 pathway and the potential of combination therapy based on this pathway in OSCC. Further, it explores the mechanisms involved in the interaction of this pathway with exosomes and protein-protein interactions, and concludes with potential future OSCC therapeutic strategies.

1. Introduction

Oral squamous cell carcinoma (OSCC) is the most prevalent type of head and neck squamous cell carcinoma (HNSCC), with approximately 300,000 new cases diagnosed worldwide annually. Despite advances in surgery, radiotherapy, and chemotherapy, the 5-year overall survival rate for OSCC has not improved significantly in recent years. The current primary treatment for OSCC is surgical resection with radiotherapy, but both procedures can cause physiological impairment and reduce patients' quality of life [1,2].

The success of drugs that block the interaction between programmed cell death 1 (PD-1) and programmed cell death 1 ligand 1 (PD-L1) has led to breakthroughs in cancer treatment over the past decade. The U.S. Food and Drug Administration (FDA) has approved these drugs for the treatment of subgroups of lung cancer, kidney cancer, bladder cancer, melanoma, Hodgkin's lymphoma, and other types of tumors, making them a hot topic of research for scholars around the world [3–7].

The *PD-L1* gene, located on human chromosome 9, p24.1, is widely expressed in tumor cells [8,9]. Under normal physiological conditions, the PD-1/PD-L1 pathway serves as an auto-tissue protection mechanism to maintain peripheral tolerance [10]. However, when the PD-L1 ligand from tumor cells binds to PD-1, T lymphocytes become dysfunctional, leading to immunosuppression. Tumors become immune tolerant, which promotes immune escape and allows tumor cells to proliferate and invade by escaping immune recognition and elimination [11,12].

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Although research on the prognostic value of PD-L1 expression in OSCC has increased every year, the conclusions remain controversial, and several meta-analyses of data from large sample studies have yielded inconsistent findings [13–18]. In order to delve deeper into PD-1/PD-L1 blockade therapy for OSCC, it is important to find effective predictors before treatment and to summarize the vast body of literature.

This article reviews the latest research on PD-1/PD-L1-based targeted therapy, immune checkpoint blockade (ICB), radiotherapy, and chemotherapy for OSCC. We conclude with recommendations for addressing the most pressing challenges and opportunities for development in this important area. The aim is to provide additional ideas for the design of efficient and effective combination regimens against OSCC and other malignancies.

2. Expression of PD-1/PD-L1 in OSCC is of great significance

PD-L1 is a co-inhibitory immune response factor that generally shows high expression (40–70%) in OSCC and in most $CD8^+$ tumor-infiltrating lymphocytes (TILs) [19]. The immune regulation of the PD-L1/PD-1 pathway starts before the malignant transformation of precancerous oral lesions [20]. Studies have shown that in precancerous lesions such as actinic labyrinthitis [21] and oral leukoplakia [22], the expression of PD-1 and PD-L1 is up-regulated. The expression of PD-1 and PD-L1 in the epithelium (E) of the oral lichen planus (OLP) is different from that in the lower subepithelium (S), and the malignant transformation rate of tissues with elevated PD-L1 expression is significantly enhanced over a 5-year period [23].

Under normal conditions, the interaction of PD-1 and PD-L1 can prevent autoimmunity and modulate inflammatory responses in target organs or protect against autoimmunity in peripheral tissues [24]. Blocking PD-1/PD-L1 can enhance the anti-tumor effects of the immune system and prolong survival in both animal and human cancer models [25]. Accordingly, immunotherapy has proven successful in the clinical treatment of advanced OSCC [26]. In OSCC, the forward cellular exogenous immunogenic PD-1/PD-L1 pathway is represented by PD-L1 expression on the surface of tumor cells. The binding of PD-L1 to the PD-1 expressed on the surface of immune cells leads to the inhibition of antitumor immunity via signaling pathways downstream to PD-1. Reverse signaling is induced when PD-1 binds to the cell surface PD-L1, leading to intracellular PD-L1 signaling [27].

In patients with advanced OSCC, treatment failure often occurs because cancer cells become resistant to the primary chemotherapeutic agent, cisplatin [28]. Unfortunately, second-line treatment options have been limited, leading to a poor prognosis. Therefore, the advent and progress of immunotherapy have generated new-found hope, as attested by the recent FDA approval of Pembrolizumab as a first-line treatment for patients with PD-L1-positive metastatic or recurrent HNSCC that is not surgically treatable [29].

In OSCC, PD-1/PD-L1 therapy is particularly significant. First, the pathogenesis of OSCC is highly associated with immune impairment, particularly the effects of defective T cell responses and suppressive cytokines [30]. Moreover, OSCC is also considered highly immunosuppressive owing to its PD-L1 expression [31]. Second, TILs are closely involved in tumorigenesis in vivo, OSCC tissue is very near to lymphoid tissue, and immune cell infiltration is one of the main features of OSCC [32].

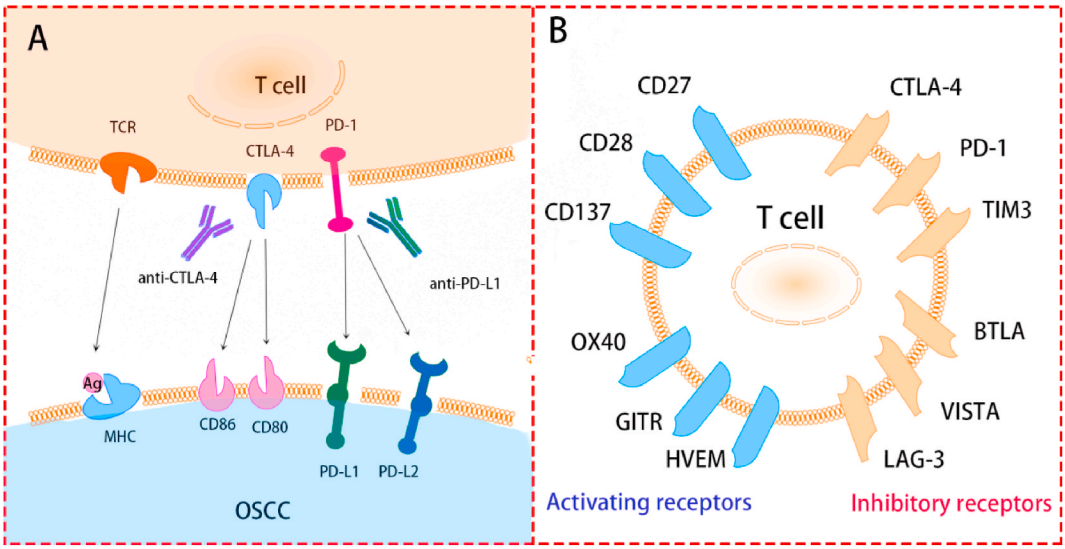

Fig. 1. ICB treatment mechanisms.
A: PD-1 and its ligand are type I transmembrane glycoproteins (CD28/CTLA-4 receptors). They share a basic structural model, including the IgV extracellular domain, transmembrane domain, and cytoplasmic tail region. The basic structural model consists of these three domains. Specific antibodies can bind to PD-L1 and inhibit T cell function, leading to the weakening of the inflammatory response and serving as a tumor immune switch.
B: Immune checkpoints associated with the immune escape of tumor cells
The main immune checkpoints on T cells playing a role in immune escape can be divided into activating and inhibitory receptors.

3. ICB in OSCC

In the last few years, ICB has achieved remarkable results in clinical and animal experiments. ICB therapy is designed to co-inhibit the interaction between PD-L1 and PD-1 and thereby achieve the functional inhibition of tumor-infiltrating T cells (Fig. 1). ICB mainly acts against Cytotoxic T lymphocyte antigen-4 (CTLA-4) and the PD-1/PD-L1 pathway. Anti-PD-1/PD-L1 treatment is still the most promising immunotherapy strategy. It can have a long-term inhibitory effect on tumors and also be effective against refractory tumors [33]. However, the effectiveness of this therapy in patients with OSCC is very limited, as less than 30% of patients show prognostic improvements [34]. In order to identify ICB therapies that could be effective against OSCC, scholars have proposed many different classification methods. For example, Cao et al. classified OSCC into immune-enhanced and immune-reduced subtypes based on the expression of immune-related genes [35]. Walter et al. proposed classification into basal, mesenchymal, atypical, and classical subtypes based on the combined genomic characteristics of patients [36]. Meanwhile, Saloura et al. classified OSCC into $CD8^+$ high and $CD8^+$ low subtypes based on the density of $CD8^+$ T cells [37], and others classified it into $m6A^{high}$ and $m6A^{low}$ subtypes based on the mRNA methylation levels of n6methyladenine (m6A) [38]. Various factors influence the efficacy of ICB treatment, and the recent relevant literature is summarized in Table 1.

Recent studies have found that adaptive immune resistance is a significant barrier to ICB efficacy [39]. When ICB is activated, tumor antigen-specific T cells promote the tissue production of interferon-γ (IFN-γ), which amplifies the immune response by attracting other white blood cells. It also promotes the production of immunosuppressive factors, which combine with PD-1 to promote the immune escape of tumor cells [40]. In addition, regulatory T cells (Tregs) inhibit the function of conventional T cells in maintaining immune homeostasis while also limiting the function of tumor antigen-specific T cells [41]. This is one of the factors contributing to malignant progression and poor prognoses [42]. Thus, blocking PD-L1 and Tregs is also a potential scheme being explored to heighten the effects of ICB. T cell depletion indicates the impairment of acquired T cell function and is a hallmark of cancer and chronic viral infections [43]. Studies have demonstrated that ICB agents that can reverse T cell depletion are highly effective against cancer [44]. It is indisputable that T cell status and personalized development of a rational immunotherapy strategy are key for successful tumor control. Chimeric antigen receptor (CAR)-T cell therapy has proven effective against hematological malignancies [45], but T cell depletion for the treatment of solid tumors is still not viable for clinical application [46]. Notably, the cellular mechanism of tumor rejection induced by ICB remains unclear. Therefore, identifying the mechanisms that regulate depleted T cells is a primary goal of cancer immunotherapy research and could be a focus of future studies [47].

Currently, a promising new treatment option is available for OSCC. In the second-line clinical trials of two immune checkpoint inhibitors (ICIs) approved by the FDA, pembrolizumab and nivolumab showed promising results for the first time in 2016 [48]. A phase I clinical trial showed that pembrolizumab is relatively safe for the treatment of recurrent or metastatic HNSCC and is well-tolerated by patients [49]. The trials showing the effectiveness of ICIs included not only patients with HNSCC recurrence and metastasis (R/M) following previous platinum regimen treatment, but also patients who developed relapse within 6 months after developing locally advanced disease following treatment with a platinum agent. Activation of compensatory pathways by most targeted therapies leads to drug resistance and tumor recurrence. In contrast, immunotherapy can lead to prolonged and even durable responses, although only a minority of patients with OSCC respond to this treatment option [50]. In summary, ICB is a novel treatment option for ICB that urgently

Table 1
Factors influencing the effectiveness of ICB: Recent studies have shown that many factors influence the efficacy of ICB treatment. New results from recent studies have been summarized.

Influencing Factors	Mechanism	References
Tumor mutation or neoantigen burden	Tumor-specific missense mutations may generate individual neoantigens that mediate responses to drugs and other immune checkpoint inhibitors, and the association between neoantigen load and clinical benefits is significant.	[52,53]
Intrinsic factors in cancer cells	The immune evasion of malignant cells, cell-cell interactions, and drug effects in the tumor ecosystem are associated with immunotherapeutic responses.	[54,55]
T cell infiltration	Adaptive immune factors detected in tumor biopsies obtained early in the treatment process can be highly predictive of the response to ICB and serve as a potential mechanism underlying treatment resistance to ICB.	[56,57]
IFN-γ signaling pathway activity	DNA methylation in PD1+ $CD8^+$ tumor-infiltrating T cells (TILs) can lead to the graded downregulation of cytokines such as IFN-γ. The epigenetic factor 5-Aza-2′-deoxycytidine (DAC) can block DNA methylation in activated PD1+ $CD8^+$ TILs and help in enhancing the antitumor influence of ICB therapy.	[58,59]
Antigen presentation	Human leukocyte antigen class I (HLA-I) molecules present tumor polypeptides, which are then recognized by $CD8^+$ T cells. The epitope design of immune recognition factors, cancer vaccines, and immunotherapy should consider the influence of specific HLA-I mutations. Patients with heterozygosity for HLA-I loci have a higher survival rate than those with pure heterozygosity for one or more HLA-I genes.	[60,61]
Immunosuppressive tumor microenvironment (TME)	Patients whose tumors contain large numbers of neoantigens derived from genetic mutations not recognized by the immune system show a strong antitumor T cell response associated with clinical responses following ICB, which is associated with Treg-mediated resistance suppression. Limiting the potential of Treg-mediated immunosuppressive strategies could expand the therapeutic scope of ICB.	[62,63]
Gut microbiome composition	Macrogenomic studies have revealed the functional differences in gut bacteria following anti-PD-1 immunotherapy, including the enrichment of anabolic pathways. Immunoassays showed that when the feces of responders with good intestinal microbiota were transplanted into sterile mice, the anti-tumor immunity of recipient mice was enhanced.	[64,65]

needs to be improved further and studied more intensively [51].

4. Post-translational modifications (PTMs) regulate the PD-1/PD-L1 pathway in OSCC

Glycosylation, phosphorylation, and ubiquitination interact to jointly influence the protein stability of PD-1/PD-L1 and thus influence protein-protein interaction [66].

4.1. Glycosylation

In combination therapy for advanced OSCC, cetuximab resistance is often observed. This occurs mainly due to increased expression of immune checkpoint molecules and glycosylation in tumor cells [67]. Programmed death ligand 2 (PD-L2) is another ligand of PD-1, and its expression in OSCC is higher than that of PD-L1. As an immune checkpoint molecule (ICM), it can promote T-cell dysfunction and immune escape [68]. Glycosylation not only plays a role in protein stabilization but also in subcellular localization [69]. ICMs closely influence the efficiency of signal transduction, immune monitoring, and targeted therapy [70]. Approximately 20–90% of the cell surface shows N-glycan focalization, which is catalyzed by alpha-1,6 focal transferase (FUT8). Glycosylated PD-L2 can affect the efficacy of current OSCC immunotherapies [71].

The role of PD-L1 glycosylation and the epidermal growth factor receptor (EGFR) signaling pathway in triple-negative breast cancer and non-small-cell lung cancer has been confirmed [72]. A study by Dressler et al. showed that deglycosylation reduces the diagnostic performance of PD-L1 antibodies in OSCC clinical samples, suggesting that enzymatic glycosylation prior to immunohistochemistry enhances the predictive diagnostic performance of PD-L1 [73]. Glycosylated PD-L2 modulates cetuximab treatment by regulating the EGFR/STAT3 signaling pathway, and the combination of PD-L2 glycosylation inhibition and cetuximab is equally effective in an in situ mouse model [74]. Research on glycosylation-related genes has revealed that 11 risk markers related to glycosylation in OSCC are significantly associated with patient prognosis and are potential prognostic markers. These results indicate that the immune microenvironment of OSCC can be affected by glycosylation, and the genes involved in this regulation can serve as prognostic risk markers for OSCC [75].

4.2. Phosphorylation

Shi et al. found that Interferon induced transmembrane protein 4 pseudogene (IFITM4P) acts as a scaffold in the cytoplasm, causing SAM And SH3 domain containing 1 (SASH1) to bind and phosphorylate transforming growth factor-β (TGF-β)-activated kinase 1 (TAK1). This in turn increases the phosphorylation of nuclear factor-κB (NF-κB) and simultaneously induces PD-L1 expression, activating the immunosuppressive program and promoting cellular escape from anticancer immunity in the cytoplasm [76]. A study confirmed that IFN-γ Induces a significant increase in signal transducer and activator of transcription 1 (STAT1) and STAT3 phosphorylation levels, thereby regulating the IFN-γ induction-related reduction in PD-L1 expression [77]. Another study showed that PD-L1 was upregulated in OSCC via the EGFR/phosphatidylinositol 3 kinase (PI3K)/AKT pathway, EGFR/STAT1 pathway, and EGFR/MEK/extracellular signal regulated kinase (ERK) pathway. The phosphorylation of EGFR and STAT1 is common in PD-L1+ patients, and it is related to the phosphorylation of EGFR and lymphocyte infiltration. The phosphorylation patterns of related molecules differ among patients. This suggests that different tissue microenvironments affect the expression of PD-L1, it is essential to design appropriate PD-1 blockade combination therapy regimens for each patient during any treatment and research programs [78].

4.3. Ubiquitination

Ubiquitination is crucial for regulating protein stability. The major members of this pathway include ubiquitin-activating enzyme (E1), ubiquitin-binding enzyme (E2), and ubiquitin-ligase (E3) [79]. E3 ubiquitin ligases STUB110, Cullin3^{SPOP}, and β-TrCP are directly involved in the ubiquitination and degradation of PD-L1 [80]. PD-L1 ubiquitination is removed via the cyclinD-CDK4/SPOP/Cdh1 pathway, and SPOP expression is induced by cyclinD-CDK4 phosphorylation at the serine 6 site, followed by 14-3-3γ uptake toward SPOP. This inhibits the degradation of SPOP by APC/cdh1 — a process that leads to PD-L1 ubiquitination and degradation via the SPOP ubiquitin ligase [81]. Gene mutations often disable SPOP, and the stability of the PD-L1 protein is thereby strengthened, leading to tumor immunosuppression. The interaction of glycogen synthase kinase 3β (GSK3β) with PD-L1 results in tyrosine-180/serine-184 site phosphorylation, and ultimately, the β-TrCP ubiquitin ligase-mediated ubiquitination and degradation of PD-L1 [89]. Tumor cells actively inhibit PD-L1 ubiquitination and degradation to achieve immune escape. A study showed that PD-L1 prevents the ubiquitination and degradation of PD-L1 by binding to the cell membrane protein CMTM4/6, thereby impairing T-cell immune function [82]. In the tumor microenvironment (TME), the increased expression of the deubiquitinase CSN5 occurs due to the sensitization of the NF-κB pathway in cancer cells via the TNF-α secreted by macrophages. This reduces the ubiquitination and degradation of the PD-L1 protein, thus stabilizing it [83]. EGFR activation induces GSK3β phosphorylation through the action of EGF, which promotes PD-L1 glycosylation by inhibiting the binding of GSK3β to PD-L1. Accordingly, phosphorylation, glycosylation, and ubiquitination act in coordination and together inhibit the degradation of PD-L1 by β-TrCP ubiquitin ligase 13 in OSCC, which leads to PD-L1 glycosylation and an enhancement of PD-L1 stability [82,84]. A model summarizing the interaction of PD-1/PD-L1-related ubiquitination, glycosylation, and phosphorylation in OSCC is presented in Fig. 2.

5. Anti-PD-1/PD-L1 combination therapy in OSCC

Due to the clinical limitations of anti-PD-1/PD-L1 monotherapy, an increasing number of combination therapies are emerging. Most of them are based on the principle of improving the presentation of tumor antigens or rescuing dysfunctional immune effector cells to improve the blocking effect of PD-1. Different cancer therapies can improve response rates. However, the choice of combination therapy partner, among others, can affect efficacy and adverse effects [85].

5.1. Targeted EGFR therapy in combination with anti-PD-1/PD-L1 treatment

EGFR is highly expressed in most OSCC patients [86], and the activation of EGFR can determine PD-L1 and IFN-γ expression. The main molecules downstream of EGFR are STAT, Ras/Raf/ERK/mitogen activated protein kinase (MAPK), and the Akt/PI3K pathway. The key factors that produce the regulators of PD-L1 are still unclear, and more exploration is needed [87]. Cetuximab, a specific antibody against EGFR, is one of the main targeted therapies against OSCC. Unfortunately, the effectiveness of this drug is less than 20%, often due to the enhanced expression of ICMs, which leads to cetuximab resistance [88]. The loss of PD-1/PD-L1 expression with EGFR overexpression in OSCC may be associated with the improved efficacy of cetuximab. In patients with R/M OSCC who show durable complete responses following single-agent cetuximab treatment, comprehensive multi-platform biomarker analysis revealed EGFR overexpression, PI3K kinase mutations, and PD-1/PD-L1 deletions. When PI3K is activated, cetuximab induces tumor regression mainly by producing an immune-mediated reaction, rather than EGFR signal blocking. This effect may be enhanced by the lack of PD-1/PD-L1 expression. This hypothesis, however, needs to be tested in larger clinical trials [89].

The EGFR inhibitor erlotinib is the compound of choice for promoting the T cell-mediated elimination of tumor cells. It acts by increasing basal and INF-γ-induced major histocompatibility complex (MHC) class I presentation and promoting the identification and elimination of specific tumor cells by $CD8^+$ cytotoxic T lymphocytes. PD-1 blockers and EGFR inhibitors are used together, showing mutual effects in a homologous model. A controlled study found that the combined use of an EGFR inhibitor and PD-1 blockade significantly delays tumor progression compared with either treatment alone in a mouse tumor model [90]. Chromosome 11q13 amplification was found to be associated with the attenuation of oncogenic and effector immune cells in the TME, with 11q13 amplification observed in more than 30% of HNSCC patients. A retrospective analysis of clinical cohorts showed that 11q13 amplification and EGFR mutations were negatively associated with PD-1 inhibitor therapy [91]. In the recently released updated Phase III KEYNOTE-048 (NCT02358031) clinical trial of pembrolizumab for R/M HNSCC, planned efficacy analyses of subjects with a PD-L1 combined positive score (CPS) of 1 and subgroups with CPS 1–19 were conducted. The results showed that the median overall survival duration of the PD-L1 group was 7.9 months and 11.3 months (hazard ratio [HR], 1.51 [95% CI, 0.96–2.37]) for combination chemotherapy with pembrolizumab and cetuximab, respectively. In the PD-L1 CPS 1–19 subgroups, pembrolizumab combined with chemotherapy showed anti-tumor activity, and the overall survival duration was longer than that with cetuximab chemotherapy. In the PD-L1 CPS 1 subgroup, neither treatment improved overall survival to a greater extent than cetuximab combined with chemotherapy. The results showed that after the increase in PD-L1 expression, the efficacy of pembrolizumab or pembrolizumab combined with chemotherapy also increases simultaneously [92]. PD-1 inhibitors in combination with anti-EGFR antibodies have shown activity in OSCC, and the selection of appropriate biomarkers to help patients choose the appropriate PD-1 inhibitor remains to be explored. The identification of biomarkers with sufficient negative predictive value is of significant importance for improving the prognosis of OSCC.

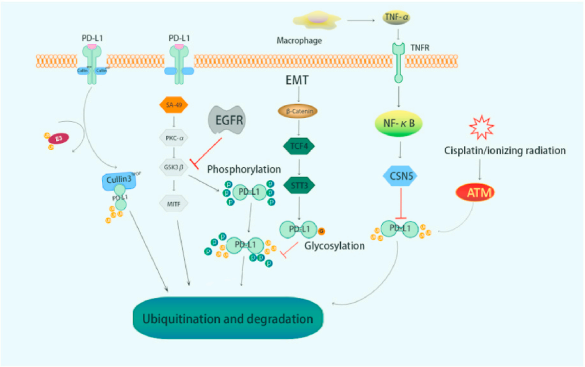

Fig. 2. Interaction of ubiquitination, glycosylation, and phosphorylation. PD-L1 is ubiquitinated and degraded by members of the E3 ubiquitin ligase family, which also trigger ubiquitination in the face of extracellular stimuli. Meanwhile, glycosylation increases PD-L1 protein stability — a process that can be reversed by EGFR inhibitors and induces PD-L1 proteasome-dependent degradation.

5.2. Targeted vascular endothelial growth factor (VEGF)/VEGF receptor 2 (VEGFR2) therapy in combination with anti-PD-1/PD-L1 therapy

Anti-angiogenic drugs can modulate the tumor immune microenvironment and exercise immune functions by inhibiting the differentiation and maturation of immune effector cells. Thus, they can be used in combination with ICI to obtain greater treatment effects [93]. Anti-VEGF drugs can enrich $CD8^+$ and $CD4^+$ T cells in neoplastic tissue, inhibit the expression of PD-1 in TILs and Treg suppressor cells, and block the immunosuppressive effects of tumor cells [94]. Angiogenic factors prevent immune cell infiltration across tumor vessels into the tumor immune microenvironment, and abnormal vascular structures can create a selective barrier for immune cells [95]. Anti-angiogenic activity leads to the aggregation of many immune cells, thus enhancing the efficacy of immunotherapy. Thus, the combination of anti-VEGF drugs with anti-PD-1 monoclonal antibodies produces effective and tolerable outcomes in several types of cancers. In one study, 43 patients with R/M HNSCC were treated with a combination regimen of anti-VEGF agents and anti-PD-1 immune checkpoint inhibitors. The combination strategy did not reduce the occurrence or severity of treatment-related adverse events compared with the use of PD-1 inhibitors or anti-VEGF drugs alone [96].

In terms of combination with cytokines, the combination of PD-L1 + VEGFR is currently being studied more frequently. Mechanistically, bevacizumab, which targets VEGF, itself has an anti-angiogenic effect. Thus, it not only has a direct effect on tumor angiogenesis and cancer cell proliferation but also enhances tumor immunogenicity and T-cell infiltration, among other processes. The combination of bevacizumab and an anti-PD-L1 monoclonal antibody increases the response of activated T cells to tumor antigens and further enhances their ability to kill cancer cells [97]. These studies provide a potential anti-cancer strategy for OSCC patients, and a combinatorial immunomodulator strategy based on PD-1/PD-L1 and VEGF and immune targets may benefit more patients in the future.

Table 2
OSCC-related antibody therapies: Only combination regimens of PD-1/PD-L1 with chemotherapy, angiogenesis inhibitors, and α-CTLA-4 have been approved by the FDA and NMPA. The antitumor activity of most combination regimens was studied in OSCC at a tenth limit, and providing individualized combination therapy for patients will be the general direction of tumor immunotherapy in the future.

Drug	Target	Listed	Availability Date (FDA approval)	Recent Research in OSCC	References
Pembrolizumab	PD-1	YES	April 9, 2014	In a recent study, 33 platinum resistant R/M HNSCC participants received pemphumab in combination with cetuximab, and an overall response rate of 45% (95% CI 28–62) was achieved at 6 months, with 15 patients achieving a partial response (PR). The most common treatment-related adverse event was oral mucositis (3 [9%]), and 5 (15%) participants had serious treatment-related adverse events. There were no deaths due to treatment. Hence, pembrolizumab in combination with cetuximab had good clinical activity in R/M HNSCC.	[107]
Nivolumab	PD-1	YES	12/22/2014	In patients with PD-L1 expressed in more than 50% of tumor cells treated with nivolumab in combination with radiotherapy and nimotuzumab, clinical performance and radiology showed that patients achieved a PR and also had a good response to anti-PD-1 inhibitors in combination with nimotuzumab (anti-EGFR monoclonal antibody) plus paclitaxel.	[108]
Cemiplimab	PD-1	YES	9/28/2018	A phase I trial of cemiplimab combined with radiotherapy, cyclophosphamide, and GM-CSF in treatment-naïve patients with R/M HNSCC who clinically required palliative radiotherapy showed a disease control rate of 40.0% (95% confidence interval [CI], 16.3–67.7; 5 patients had stable disease). The combination was tolerable but not more effective than anti-PD-1 inhibitors as monotherapy for R/M HNSCC.	[109]
Toripalimab	PD-1	YES	/	Twenty-three HNSCC patients treated with two cycles of the combination of toripalimab and cisplatin achieved an objective remission rate of 45.0%. The expressions of CD4, CD8, CD20, and CD38 in tumors increased after neoadjuvant chemotherapy. In patients with advanced OSCC, the rates of pathological complete response (pCR) and major pathologic response (MPR) showed a good trend.	[110]
Camrelizumab	PD-1	YES	/	In a phase I trial, 20 OSCC patients who received three cycles of preoperative camrelizumab in combination with apatinib had a local recurrence rate of 10.5% (95% CI: 0–24.3%), and the survival rate was 95% (95% CI: 85.4–100.0%). Patients with MPR had more $CD4^+$ T cell infiltration and the levels of CD31 and α-SMA decreased.	[111]
Durvalumab	PD-L1	YES	5/1/2017	A phase III study evaluated the efficacy of durvalumab or durvalumab plus tremelimumab versus standard of care (SoC) in patients with R/M HNSCC. Durvalumab or durvalumab plus tremelimumab did not differ significantly from the SoC in terms of overall survival. However, the higher 12- to 24-month survival and response rates demonstrated the clinical activity of durvalumab.	[112]
Avelumab	PD-L1	YES	3/23/2017	In a phase III study, eligible patients were divided into avelumab plus radiotherapy and placebo plus radiotherapy groups. Median progression-free survival was not reached in the avelumab group and not reached (23-0 months-not estimable) in the placebo group. In patients with locally advanced HNSCC, progression-free survival was not prolonged after the combination of avelumab and radiotherapy.	[113]

5.3. Chemotherapy in combination with anti-PD-1/PD-L1 therapy

The cytotoxic effects of conventional chemotherapeutic agents against cancer cells are accompanied by the modulation of the body's immune response [98]. After conventional chemotherapy, tumor cells become susceptible to chemotherapeutic resistance owing to immune escape mechanisms. Some chemotherapeutic drugs can cause the overexpression of PD-1/PD-L1 in OSCC patients through the MAPK pathway, thus promoting tumor immune escape. This discovery has made PD-1/PD-L1 blockade combined treatment a research hotspot. Numerous clinical studies have confirmed that combination therapy shows excellent performance in controlling tumor growth and prolonging patient survival durations [99].

Recent studies have shown that the blocking effect of PD-1 can be enhanced with chemotherapy [100]. Drugs enhance binding to PD-1/PD-L1 by stimulating the release of neoantigens on cancer cells, upregulating MHC class I molecules, which may promote antigen presentation by antigen-presenting cells (APCs) [101]. In the study by Dong et al. a mouse OSCC model was constructed and the results showed that PD-1 blockers alone could retard tumor growth in OSCC. In the cisplatin group, altered PD-1 expression suggested that the mechanism of cisplatin-mediated tumor cell death may involve the PD-1/PD-L1 pathway, while local immunosuppression of drug-resistant tumors could be achieved via PD-L1 upregulation [102]. Hence, chemotherapy combined with PD-1 blockade may improve anti-tumor responses. In Tran et al.'s study on a mouse model of HNSCC, combined therapy with anti-PD-L1/PD-1 agents and cisplatin reduced tumor growth rates and improved survival. Notably, the regimen did not significantly reduce the number or inhibit the function of tumor-infiltrating immune cells, while not increasing cisplatin-induced toxicity. This suggests that appropriate doses of cisplatin may prevent tumor immune escape through mechanisms other than direct tumor cell killing, and that anti-PD-L1/PD-1 combination therapy may further enhance this effect [103].

Since the first PD-1 Opdivo monoclonal antibody was approved by the FDA in 2014, tumor immunotherapy, including anti-PD-1/PD-L1 agents, has become one of the greatest areas of research and development due to its broad spectrum of tumor types and higher clinical efficacy [104]. All current PD-1/PD-L1 inhibitors are large-molecule antibody drugs. Monoclonal antibodies have many inherent disadvantages, including poor oral bioavailability, extended tissue retention time and half-life, poor membrane permeability, and transport storage. In addition, antibody drugs are also expensive. Hence, researchers are increasingly exploring small molecule drugs as PD-1/PD-L1 inhibitors to circumvent some disadvantages of therapeutic antibodies [105]. By 2022, the United States and European Union had approved 11 antibody therapy drugs. At present, there is only chemotherapy combination PD-1/PD-L1, CTLA-4 and angiogenesis inhibitors, namely cysteine protease inhibitors, have been approved by FDA and the National Medical Product Administration (NMPA). The anti-tumor activity of most other combination regimens is limited in animal tumor models. In addition, combination therapy also increases the risk of therapeutic injury and medical costs, and incorrect combination treatment can lead to adverse events. Therefore, the formulation of optimal combination treatment plans and the comprehensive optimization of drug administration plans — including the dose, timing, and order of administration — are the current challenges in the development of combination therapy. In the future, tumor immunotherapy will be geared toward integrating individual patient differences, tumor heterogeneity, and tumor evolution and providing individualized combination therapies for patients based on an immune analysis and other predictive biomarkers [106]. Table 2 summarizes the recent research advances in the use of anti-PD-1/PD-L1 antibodies against OSCC.

6. Exosomes in OSCC with PD-1/PD-L1 expression

Human blood contains multiple forms of PD-L1 in soluble or extracellular exosomes and microvesicles, in addition to some free forms of PD-L1. According to the latest research, these different forms of PD-L1 produce different outcomes for PD-1/PD-L1 immunotherapy [114]. Exosomal PD-L1 (exoPD-L1) is an important form of PD-L1 that directly and systemically inhibits anti-tumor immune

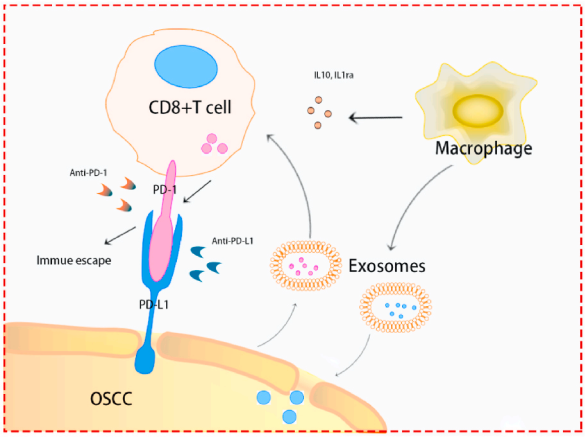

Fig. 3. Immunomodulatory mechanisms of exosomes in OSCC. PD-1 expression in $CD8^+$ T cells is promoted by serum-derived exosomes, promoting immune escape in OSCC and inducing a pro-inflammatory macrophage phenotype and $CD8^+$ T cell dysfunction.

responses. ExoPD-L1 mediates PD-1 cross-linking and immunosuppression, and multiple PD-L1 molecules and proteins essential for T cell signaling — such as MHC molecules — can be simultaneously expressed on the surface of exosomes. Hence, exosomal PD-L1 may provide more potent immunosuppression than other extracellular forms of this protein. Mouse experiments demonstrate that exoPD-L1 can act as a systemic immunosuppressant in vivo and inactivate TILs and T cells. However, if exoPD-L1 levels are suppressed locally, anti-tumor immune responses may be generated [115]. Therefore, finding ways to target exoPD-L1 to enhance antitumor memory responses and overcome resistance to PD-1 blockade has gained immense attention.

Tumor-derived exosomes (TEXs) interact with a variety of tumor cells, leading to cellular reprogramming and promoting disease progression. They can also serve as non-invasive biomarkers of cancer progression. In a study by Razzo et al. a single intravenous dose of PD-L1-bearing TEXs given to mice with precancerous OSCC lesions accelerated tumorigenic progression while reducing the migration of immune cells to the tumor [116]. Immunocaptured CD44v3(+) exosomes in the plasma of OSCC patients showed higher levels of EGFR, TGF-β1, and PD-L1 than did CD44v3(-) exosomes, and this was correlated with clinicopathological parameters. Similarly, PD-L1 levels were higher in CD3(+) and CD3(-) exosomes from HNSCC patients than in exosomes from healthy donors [117]. The resistance of tumor cells is caused by the failure of ICB therapy due to genetic transcription profiles, and cytotoxic T lymphocytes, such as $CD8^+$ T cells, also play a significant role. Some circular RNAs can induce M2 polarization, remodeling the TME and limiting the sensitivity of anti-PD-1 therapy, both in vivo and in vitro [118, Fig. 3]. In the TME, anti-γδ cell and pre-γδ cell homeostasis is regulated by oxygen pressure via changes in TEX content. The TEX content in turn affects the function of bone marrow-derived inhibitory cells, which mainly depends on the miR-21/PTEN/PD-l1 signal axis. These findings have facilitated further investigation into exosome-integrated inhibition and ICIs for the treatment of OSCC. Yuan et al. described a novel exosome regulatory mechanism for OSCC-macrophage crosstalk-driven tumor development. They demonstrated that endoplasmic reticulum stress leads to the secretion of exosomal PD-L1 by OSCC cells and the upregulation of PD-L1 expression in macrophages, promoting tumor escape from immune surveillance, although the underlying mechanism remains unclear [119].

7. Pathology is closely related to the PD-1/PD-L1 pathway

From a pathological perspective, providing useful information to assist the decision-making process is not simple, but there are still valuable research results. ICI represents an emerging treatment option. It is now necessary to develop a coordinated approach to address the variability between cloning, scoring, and observers, in order to ultimately enable patients to obtain the most appropriate, effective, and safe diagnostic and treatment measures. New tools have emerged, such as digital pathology. In fact, in a series of studies by Albino Eccher and his team, the disruptive advances in these technologies have recently completely changed many fields of surgical pathology, and computer-based automatic learning algorithms are now widely available [120,121]. For HNSCC, the immunohistochemical platform can evaluate the combined positive score of PD-L1 expression, making commercial pathological in vitro diagnosis feasible [122]. The pathological expression of PD-L1 may also reflect the balance between host immune response and cancer escape ability [123]. However, this diagnostic approach also faces some difficulties, such as a small portion of studies involving HNSCC cases, and incorporating different positive cutoff values in the presence or absence of evaluation of immune and tumor cells. This is also a key point that requires more work in the future to clarify the definition of precancerous lesion subgroups. This will help to better estimate the prevalence of PD-L1 expression in the head and neck, thus helping to better determine the potential application of immunotherapy as a preventive treatment in this situation [124].

8. Perspectives and conclusions

The clonotypic amplification gene signature of effector-like T cells in different tissues may influence the response to anti-PD-L1 therapy. Strategies to personalize combination treatment plans based on this signature should be part of future plans. More importantly, the amplified clonotypes found in tumors or normal adjacent tissues can often also be detected in peripheral blood. Hence, more convenient predictive methods may be possible and warrant further research.

Although numerous scholars have proposed criteria for the therapeutic classification of ICB and elucidated the clinical and immunological features of OSCC from different perspectives, how OSCC subtypes are generated and the roles and specific details of the genes involved remain unclear. Moreover, the clinical translation of this information remains a distant frontier. These challenges must be addressed in the future. The degree of PD-1/PD-L1 interaction determines the degree of T-cell activation and peripheral tolerance. The expression of PD-1/PD-L1 has been described in many tumors, such as esophageal, gastric, and breast cancer. In recent years, PD-1/PD-L1 inhibitors have shown clinical efficacy against many cancers, and anti-PD-1/PD-L1 therapy has become a hotspot for solid tumor immunotherapy. However, in OSCC, more studies are still needed to identify specific mechanisms and thereby develop new therapeutic strategies. Nevertheless, PD-1/PD-L1 blockade therapy shows great potential as a novel approach for combination treatment in OSCC patients.

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Yuxi Cheng: Writing – original draft, Writing – review & editing. **Zhengzheng Song:** Resources, Software, Writing – original draft, Writing – review & editing. **Juan Chen:** Data curation, Methodology, Software. **Zhangui Tang:** Project administration, Resources. **Baisheng Wang:** Funding acquisition, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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