Received: 30 August 2023 | Revised: 2 November 2023 | Accepted: 14 December 2023

DOI: 10.1111/prd.12548

Periodontology 2000 WILEY

REVIEW ARTICLE

The role of programmed death receptor (PD-)1/PD-ligand (L)1 in periodontitis and cancer

Sabine Groeger[1,2] | Joerg Meyle[1]

[1]Department of Periodontology, Dental School, Justus-Liebig-University of Giessen, Giessen, Germany

[2]Department of Orthodontics, Dental School, Justus-Liebig-University of Giessen, Giessen, Germany

Correspondence
Sabine Groeger, Departments of Periodontology and Orthodontics, Dental School, Justus-Liebig-University of Giessen, Schlangenzahl 14, Giessen 35392, Germany.
Email: sabine.e.groeger@dentist.med.uni-giessen.de

Abstract

The programmed-death-ligand-1 (PD-L1) is an immune-modulating molecule that is constitutively expressed on various immune cells, different epithelial cells and a multitude of cancer cells. It is a costimulatory molecule that may impair T-cell mediated immune response. Ligation to the programmed-death-receptor (PD)-1, on activated T-cells and further triggering of the related signaling pathways can induce T-cells apoptosis or anergy. The upregulation of PD-L1 in various cancer types, including oral squamous cell carcinomas, was demonstrated and has been linked to immune escape of tumors and poor prognosis. A bidirectional relationship exists between the increased PD-L1 expression and periodontitis as well as the epithelial–mesenchymal transition (EMT), a process of interconversion of epithelial cells to mesenchymal cells that may induce immune escape of tumors. Interaction between exosomal PD-L1 and PD-1 on T-cells may cause immunosuppression by blocking the activation and proliferation of T-cells. The efficacy and importance of treatment with PD-1/PD-L1 checkpoint inhibitors and their prognostic influence on human cancers was demonstrated. Regarding PD-1/PD-L1 checkpoint inhibitors, resistances exist or may develop, basing on various factors. Further investigations of the underlying mechanisms will help to overcome the therapeutic limitations that result from resistances and to develop new strategies for the treatment of cancer.

KEYWORDS
cancer, EMT, exosomes, immune checkpoint, immune escape, PD-L1, periodontitis

1 | INTRODUCTION

Periodontitis is characterized by a chronic inflammation that is initialized by a microbial biofilm that over the time leads to the destruction of periodontium.

Tooth-attached microbial biofilm that adhere to the teeth = tooth plaques are prerequisite but not the only cause of periodontitis. The bacterial challenge induces an inflammatory host response that induces the destructive processes of the periodontium.[1] Over 700 bacterial species were detected in the oral biofilm.[2] From this number 300 were demonstrated to administer to the periodontal pockets biofilm. The number of bacterial species that are closely associated to initiation and progression of periodontal diseases was found to be considerably smaller.[3]

Porphyromonas gingivalis (*P. gingivalis*), a gram-negative coccoid anaerobic and asaccharolytic rod, is prevalently detected in the oral cavity and regarded as one of the keystone pathogens of periodontitis.[4]

The programmed death ligand 1 (PD-L1) is known as immune-modulating molecule that is constitutively expressed on cells of the myeloid cell lineage, including macrophages and dendritic cells (DCs).[5–7] In epithelial and endothelial lineages of the lymphoid system, it is expressed after activation by interferon (INF)-γ and tumor necrosis factor (TNF)-α.[8] PD-L1 is a ligand for the programmed death receptor (PD)-1, that is described as inhibitory receptor expressed on activated $CD8^+$ cells. Originally, the PD-1 receptor was regarded as a death receptor which expression is initiated by T-cell activation.[9–12] *PD-1* gene-knockout mice exhibit excessive immune response and are drawn to the spontaneous development of autoimmune diseases, suggesting that PD-1 is a member of the mediators of inhibitory signals of immune cells including T-cells.[13,14] PD-L1 is expressed widely in B-cells, activated DCs, monocytes, T-cells, epithelial cells, and peripheral tissues.[7,9,15,16] PD-L1 was demonstrated to play an important role in the regulation of T-cell activation and function.[6,15,17,18] Although there is evidence that PD-L1 co-stimulation may increase T-cell activation during the immune response, other studies support the assumption that PD-L1 co-stimulation suppresses immune reactions.[19–22] The PD-L1 - PD-1 interaction results in PD-1-initiated opposition of downstream signaling after T-cell receptor (TCR) ligation and CD28 co-stimulation.[23] The binding of PD-L1 on PD-1 causes phosphorylation of immune-receptor tyrosine-based inhibitory motifs and immune-receptor tyrosine-based switch motifs in the intracellular domain of PD-1. This process leads to the recruitment of phosphatase sarcoma and cellular tyrosine-protein kinase (src) homology region 2 domain-containing phosphatase (SHP)-1 and SHP-2 to the intracellular PD-1 domain, which is located close to the TCR. SHP-1 and SHP-2 dephosphorylate the immune-receptor tyrosine-based activation motifs of the TCR, which suppresses downstream signaling of the TCR.[24] PD-1 impedes activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB) pathways and consequently prevents cytokine production and the survival, proliferation and production of cytokines of cytotoxic $CD8^+$ T-cells.[25] PD-L1 also interacts with the CD80 (B7-1) molecule, that is expressed on the surface of $CD8^+$ T-cells. The initiated downstream signaling of CD80 still is not completely understood but studies reported that $CD8^+$ T-cell function is similarly affected as downstream signaling of the PD-L1 and PD-1 interaction.[26–28]

It was shown that, in gastric epithelial cells (GECs), *Helicobacter pylori* (*H. pylori*) induced the expression of PD-L1, and co-incubation of these PD-L1-expressing GECs with naïve T helper cells supported the development of $CD4^+$ $CD25^+$ $FoxP3^+$ regulatory T-cells (Tregs).[29]

Using a mouse model with silenced PD-L1 the crucial importance of PD-L1 in regulating induced Treg (iTreg) development and continual induced (i) Treg function could be demonstrated. The results of this study revealed that PD-L1 itself regulates iTreg cell development, and enforces and sustains Foxp3 expression and the suppressive function of iTregs. Thus, PD-L1 is able to suppress T-cell responses by promoting the induction as well as the maintenance of iTreg cells.[30]

Since periodontitis is a prototype of a locally destructive chronic inflammatory process it has been linked to increased cancer risk. In a review by Nwizu et al.[31] this has been addressed. The authors reported that evidence provided through well-designed prospective cohort studies supports an association of periodontal disease and overall cancer risk, and risk of certain specific cancer sites, including cancers of the lung and upper digestive tract. Although head and neck cancers comprise a heterogeneous group of conditions with varying risk factors, the existent literature points to a positive association between periodontitis and head and neck cancer risk.

This review aims to shed light on what is known about the interplay between periodontitis as a disease the goes along with enhanced bacterial burden and chronic inflammation, both conditions that are known to be strongly associated with cancer, PD-L1 as one of the most important immune modulatory ligands and the development and progression of carcinomas.

2 | PD-L1 AS A MECHANISTIC LINK BETWEEN PERIODONTITIS AND ORAL CANCER

Actual studies revealed that the PD-1/PD-L1 pathway plays a role in periodontitis. PD-L1 is physiologically expressed on the oral masticatory mucosa in the oral cavity, and the expression is regulated as well on basal keratinocytes as on prickle cells. PD-L1-expressing keratinocytes are important in the regulation of $CD4^+$ T-cell-mediated local tissue inflammation and thus provide protection against exacerbated tissue damage.[32]

Results from studies that investigated the role of PD-L1 in periodontitis provided evidence that in subjects with chronic periodontitis, increased PD-L1 expression was found on leukocytes from the peripheral blood and furthermore in biopsies from gingival lesions in comparison to samples from healthy individuals.[33] In further studies, it was shown in vitro that PD-L1 expression can be induced on periodontal ligament cells (PDLCs) by inflammatory cytokines and periodontal pathogens.[34] In human gingival fibroblasts (HGFs) derived from a periodontally healthy group and a periodontal inflammatory group it was demonstrated that PD-L1 mRNA and protein levels in HGFs in the periodontal inflammatory group were significantly higher than those in the periodontal healthy group. Furthermore, stimulation with lipopolysaccharide (LPS) caused enhancement of PD-L1 mRNA levels in HGFs from both groups, with a higher peak in the periodontal inflammatory group compared to the periodontal healthy group. PD-L1 protein expression was only upregulated in the inflammatory group. Inhibition of the p38 mitogen-activated protein kinase (MAPK) pathway in HGFs diminished p38 phosphorylation in both groups but reversed the LPS-caused enhancement in PD-L1 mRNA and protein levels only in the inflammatory group.[35] In animal models, experimental periodontitis was used to demonstrate an association of lower levels of PD-L1 on cells with more severe

periodontitis, while higher PD-L1 levels on cells were linked to less severe periodontitis.[34] A direct correlation between periodontal tissue destruction and PD-L1 amounts could not be established. Nevertheless, possibly high expression of PD-L1 induce immune-suppressive processes that can limit inflammatory tissue damage. Tymkiw et al.[36] investigated the expression of 22 chemokines and cytokines in gingival crevicular fluid (GCF) from healthy in comparison to diseased sites of subjects with periodontitis and demonstrated that periodontitis patients show significantly increased cytokine and chemokine profiles. In a subsequent study, it was analyzed, if PD-L1 is detectable in archived GCF of these individuals and if a correlation of the levels of inflammatory chemokines and cytokines can be shown in diseased as well as healthy sites in periodontitis patients in comparison to sites in healthy subjects. The amount of PD-L1 correlated with 15 of 22 chemo- and cytokines. In healthy sites, PD-L1 levels were negatively correlated with 4 cytokines and chemokines; diseased sites revealed that PD-L1 values are positively correlated with 9 chemokines and cytokines and negatively correlated with 2 cytokines. The authors concluded that relationships between PD-L1 and these 15 chemokine and cytokine responses exist. In summary, this study group reported the detection of PD-L1 in GCF and furthermore that the PD-L1 amounts did not vary very much between diseased and healthy sites, and that PD-L1 levels correlated with 15 of 22 cytokine and chemokine concentrations.[37]

PD-L1 mRNA was detected in saliva from patients with periodontitis and the levels were shown to be correlated with the severity of the disease.[38] An approach was developed to detect exosomal PD-L1 in saliva of patients suffering from periodontal as well as systemic diseases.[38] A connection between the PD-1 or PD-L1 expression and periodontal diseases was also established by investigation of the expression of the checkpoint on T-lymphocytes from patients with periodontitis versus healthy controls. The expression of PD-1 and of PD-L1 was demonstrated to be significantly enhanced on $CD4^+$ and $CD8^+$ T-lymphocytes from periodontitis patients compared to controls and the level of the expression diminished after therapy.[39] The results of another study implied that expression of PD-L1 was significantly increased in periodontal tissue of rather mild chronic periodontitis versus severe periodontitis, suggesting a negative regulation of the inflammatory periodontal tissue damages by PD-L1 upregulation.[40] Lesions of apical periodontitis were shown to be more infiltrated by PD1+ and PD-L1+ lymphocytes and to express enhanced cytokine levels compared to control samples.[41] A recent study could demonstrate that mesenchymal stem/stromal cells isolated from dental pulp, gingival tissue, and periodontal ligament all exhibited upregulated PD-L1 and presented immuno-regulatory properties comparable to those from bone marrow mesenchymal stem/stromal cells.[42] The upregulation of PD-L1 in cells may be induced by pathogenic bacteria including *P. gingivalis*. This was shown in human gingival keratinocytes and using the SCC-25 and BHY oral squamous cell carcinoma (SCC) cell lines.[43] In mice that were infected with *P. gingivalis* a significant enhancement of the expression of PD-1 and PD-L1 was found in $CD4^+$ T-cells and $CD11b^+$ cells. The upregulation of PD-1 was completely dependent on interleukin (IL)-10 signaling in contrast to PD-L1, which wasn't.[44] The upregulation of PD-L1 can frequently be detected in an inflammatory state, which may lead to modifications of the immune response by down-regulating active T-cells. An increased expression of PD-L1 possibly affects the immune system and thus supports chronic bacterial infections. Investigations of the mechanism by which *P. gingivalis* causes PD-L1 expression in gingival keratinocytes revealed that the upregulation can be induced by membrane fractions of the bacteria (inner as well as outer membrane fractions), and implies that peptidoglycans attached to these fractions within the periplasm are responsible for the PD-L1 upregulating effect.[45] By this mechanism, *P. gingivalis* depletes the PD-1/PD-L1 checkpoint to enable immune evasion to the host response and to augment the infection and support development and progression of carcinomas by suppressing an adequate anti-cancer response of the host's immune system (Figure 1). This hypothesis was recently confirmed by demonstrating that the peptidoglycans were internalized into oral carcinoma cells by bacterial outer membrane vesicles which in turn triggered cytosolic nucleotide-binding oligomerization domain-containing protein receptors to induce PD-L1 expression using a receptor-interacting serine/threonine-protein kinase (RIP)2 dependent mechanism.[46]

Head and neck cancer is the eighth most common cancer worldwide, accounting for 834 000 cases and 431 000 deaths in 2018.[48] Frequently it is localized in the oral cavity and lips, but cancer also can develop in the nasopharynx, hypopharynx or oropharynx. The amount of head-and-neck squamous cell carcinomas (HNSCCs) from head-and-neck cancers is 90%, and the discovery of this malignancy occurs mostly in advanced stages.[49,50] Immune-modulation at tumor sites is a critical mechanism that allows tumor cells to evade immune response. Membrane-bound and also soluble molecules and factors are upregulated in tumor sites, and potentially affect the immune reaction.[51,52] Results of studies suggest that the PD-1/PD-L1 pathway regulates tissue/organospecific tolerance in healthy sites and may participate in the immune evasion of cancer cells.[15,53,54]

The interplay between PD-L1 and PD-1 in the tumor microenvironment supports tumor survival in various ways, i.e., ligation of PD-1 and PD-L1 on antigen-specific T-cells induces functional anergy and/or apoptosis of effector T-cells, which in turn probably promotes tolerance, and reverse signaling through PD-L1 directly protects tumors from apoptosis.[5,55–57] By upregulating PD-L1 expression following cancer-induced immune response, the PD-1/PD-L1-mediated evasion of tumor immunity can be described as an "adaptive resistance" (Figure 2).[58]

3 | PD-L1 IN HEAD-AND-NECK CANCER

In a review paper on the role of the PD-1/PD-L1 pathway in SCCs of the head and neck the authors came to the conclusion that fusion proteins and antibodies that can block PD-L1 and PD-1 interactions are promising targets for treatment of solid tumors even in advanced stages.[59] Clinical trials for PD-1 or PD-L1 blockade are ongoing and it was shown that PD-L1 blockade by a monoclonal antibody (mAb)

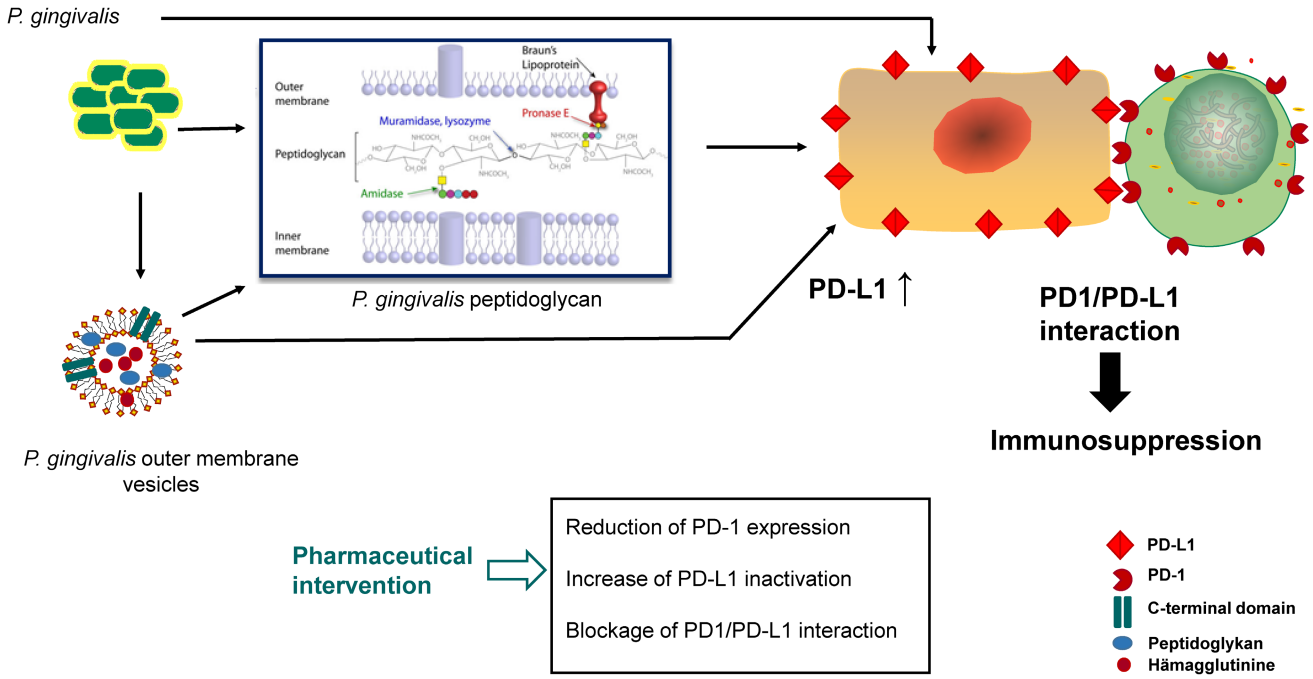

FIGURE 1 PD-L1 as mechanistic link between periodontitis and cancer. The PD-1/PD-L1 checkpoint in periodontitis: Bacterial peptidoglycans (i.e. *P. gingivalis*, *F. nucleatum*) may induce the upregulation of PD-L1 and PD-1 expressed on gingival keratinocytes and lymphocytes T-cells. The PD-1/PD-L1 interaction causes immune suppressive effects that contribute to the process of periodontitis. PD-L1- expression inhibiting drugs or PD-L1 functional blockage could be useful to revers immune escape and inflammation linked with periodontitis. Modified after Bailly et al.[47]

efficiently reinforced the outcome of adaptive T-cell immunotherapy in a murine model of PD-L1-transfected SCC and inhibited the de novo growth of induced PD-L1-positive SCC.[60,61] These results indicate a potential therapeutic usability of PD-L1-blockade in clinical settings. In esophageal SCC, PD-L1 and PD-L2 expression levels were closely correlated, and it was shown that PD-L1- and PD-L2-positive patients encountered significantly poorer prognoses than patients who expressed neither PD-L1 nor PD-L2, although no significant evidence for a correlation between PD-L1 expression and the number of tumor-infiltrating lymphocytes could be detected.[62]

The upregulation of PD-L1 in host cells may contribute to the chronicity of inflammatory disorders that frequently precedes the development of cancers.[63] In cells originating from cancers of the lungs, ovary, colon, skin, the brain, kidneys, esophagus, stomach, and the breast, the expression of PD-L1 was demonstrated to be upregulated.[5,61,62,64–67] These types of cancers are usually accompanied by chronic inflammation. Oral cancers belong to the 10 most common neoplasms.[68] In addition to tobacco and alcohol, other risk factors such as infections and poor oral hygiene were shown to be relevant.[68–71]

Oral SCC tissue samples showed enhanced PD-L1 expression compared to oral mucosa of noncancerous controls, and an association of the increased expression of PD-L1 messenger ribonucleic acid (mRNA) in tissue of the malignancy was found. Oral SCC (OSCC) patients with advanced tumor grades and patients exhibiting lymph node metastases were also demonstrated to be linked to the increased PD-L1 mRNA expression in peripheral blood cells. This led to the conclusion that the PD-L1 expression in OSCC possibly supports the immunosuppressive properties in the local tumor microenvironment and that the enhanced malignant behavior might be associated with PD-L1-mediated systemic immune tolerance, which indicates that PD-L1 expression in peripheral blood is a promising marker that a metastatic OSCC is existent.[72] Individuals which express raised membranous PD-L1 positivity and the presence of tumor-infiltrating lymphocytes, were shown to have a decreased risk of tumor recurrence.

It has been shown that stromal and immune cells in the microenvironment of human cancers upregulate the expression of inhibitory B7 molecules such as PD-L1, and that this supports tumor immune evasion.[73]

Together with tobacco and/or alcohol (ab-)use oral infections and poor oral hygiene are classical risk factors for head-and-neck cancer.[68,70,71] In over 50% of patients with HNSCC tumor metastasis and recurrence were observed within 3 years. Options for the treatment of recurrent or metastatic (R/M) HNSCC are rare, causing the poor prognosis of patients with R/M HNSCC as a consequence. Additionally, a higher number of patients with R/M HNSCC exhibit symptoms that are related to tumors, such as pain, respiratory or nutritional disorders and hemorrhage, which severely worsen the quality of life and limit the possibilities for follow-up treatments.

The 3-year survival rates of patients with renal carcinomas after surgery are 71.5% and 69.1% in case of positive PD-L1 expression

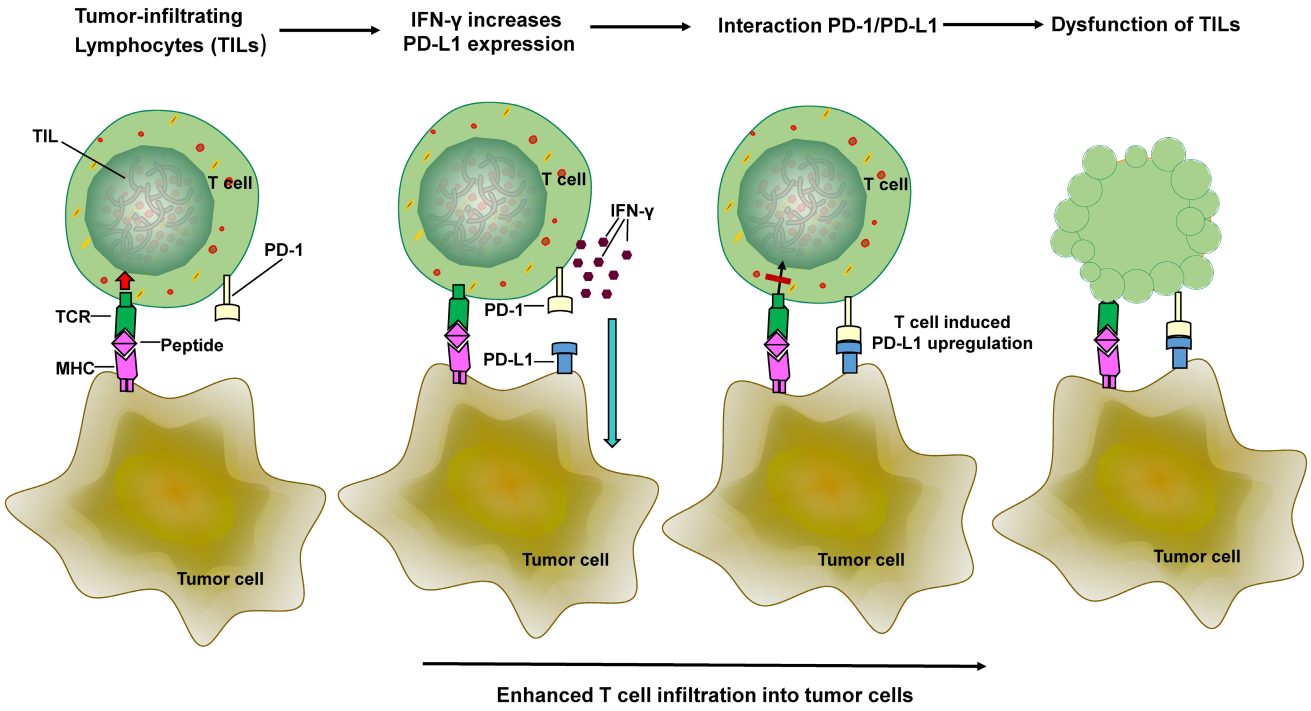

FIGURE 2 PD-L1 as mechanistic link between periodontitis and cancer. Adaptive resistance to tumor immunity mediated by PD-1/PD-L1: After activation in lymphoid organs, tumorspecific T effector cells (Teffs) migrate into the tumor site and then develop tumor-infiltrating lymphocytes (TILs). Following recognition of tumor antigens, TILs release cytokines including IFN-γ, which induces the expression of PD-L1 in the tumor microenvironment. Binding to PD1, PD-L1 provides a suppressive signal to T-cells and an anti-apoptotic signal to tumor cells, causing dysfunction of T-cells and tumor survival. Modified after Ghosh et al.[58]

while it was 84.9% and 91.8% for patients showing negative PD-L1 expression.[74,75] Less than 80% of patients with high-PD-L1-expressing urothelial carcinomas survived 36 months after surgical treatment, in comparison to patients with low-PD-L1-expressing urothelial carcinomas.[76] The results of the study from Groeger et al.[77] support the conclusion that the expression level of PD-L1 may serve as prognostic marker for patients with oral SCCs. The extend of PD-L1 and PD-L2 expression was investigated in 52 surgically resected nonsmall cell lung carcinoma (NSCLC) patients, including squamous cell and adenocarcinoma patients. The findings suggest no existent correlation between the expression levels of PD-L1 and PD-L2 and the pathological or clinical variables or with the postoperative survival rate. In PD-L1-positive tumor sites significantly lesser tumor-infiltrating lymphocytes (TILs) were detected and the counts of PD-1+ TILs also were significantly lower in these locations.[78]

3.1 | Therapeutic aspects

Therapeutic attempts to inhibit the interactions between PD-1 and PD-L1 provided promising clinical results for a number of different tumor types. The anti-tumor effect of monoclonal PD-L1 antibodies in a HNSCC dose-expansion cohort could be proven. One prerequisite for inclusion in the study was the exhibition of at least 1% PD-L1 expression in the tumor samples. Sixty patients were identified and treated with the antibody. The highest response rate was 19.6% (95% CI, 10.2–32.4).[78] In human OSCC cell lines the expression of PD-L1 was also shown in vitro.[61] Furthermore PD-L1 upregulation upon infection with the periodontal pathogen *P. gingivalis* was detected in two OSCC cell lines and in primary and immortalized human gingival keratinocytes in vitro.[43] Groeger et al.[77] clearly revealed the expression of PD-L1 in oral SCCs investigating cancerous tissues that originated from various areas of the oral cavity. These results provide evidence for in vivo expression of PD-L1 in OSCC at different locations in the oral cavity.

3.2 | Inflammation and cancer

It was demonstrated that inflammation plays a critical role in cancer development and progression.[79] A variety of different cancers originate from infected or inflamed localizations.[80] Possibly the development of malign tumors may be provoked by inflammatory cells, an effect that similarly is started by various chemical mediators.[79–82] Chronic inflammatory conditions can cause damage of tissues that in turn induces specific inflammatory cytokines. Expression of anti-inflammatory or pro-inflammatory cytokines including IL-10, IL-4, transforming growth factor (TGF)-β1, IFN-γ or monocyte chemoattractant protein-1 (MCP-1), was demonstrated to be specifically regulated during formation of premalignant lesions in OSCC tissue.[83] T helper (Th) cells, which are mainly involved in cancer immunology,

can be functionally categorized into Th1, Th2, and Th17 cells, depending on the secreted cytokines and their immunological profiles.[84] Th2 cytokines (IL-4, IL-5, and IL-10) are regarded as anti-inflammatory and have been linked to tumor-promotional effects. The majority of Th1 cytokines, represented by IFN-γ, are classified as pro-inflammatory cytokines that are associated with good prognosis.[85] Serum levels of IL-17A, TGF-β1, IL-4 and IL-10 were investigated and it was shown that these levels were significantly elevated in OSCC patients, while IL-2 and IFN-γ levels were demonstrated to be lower in OSCC patients in comparison to those of the controls.[86] In OSCC patients, increased IL-10 and TGF-β1 and suppressed IFN-γ concentrations are related to the negative regulation of natural killer (NK) cells.[87]

Inflammatory cells combined with cytokines are responsible for an inflammatory microenvironment in tumor tissue, which is of major importance for all tumors and participates in tumor progression by promoting tumor cell survival, migration, proliferation and immune evasion.[79,88,89] Immune cells and their expressed molecules localized in the tumor microenvironment, play essential dual roles in anti-tumor immunity and immune evasion, since malignant tumors express phenotypes that indicate inflammatory response. Inflammatory pathways are involved in the transformation, proliferation, angiogenesis, invasion, survival, metastasis, radio- and chemoresistance of cancers, providing evidence that the blockage of inflammatory biomarkers may be useful for the prevention and treatment of cancers.[90–92] Inflammatory processes possibly suppresses tumors, but it also may promote development of cancers and activation of immune evasive mechanisms by various signaling pathways.[92,93]

It was established that the immune system plays an essential role in tumor growth and progression control. Increasing evidence indicates that *P. gingivalis* is involved in the etiology of oral but also of pancreatic and gastrointestinal cancers.[94] The mortality of orodigestive cancers was shown to be related to periodontitis and to the levels of *P. gingivalis* immunoglobulin G (IgG) in serum, which is an independent marker of the severity of periodontitis. This finding indicates that *P. gingivalis* possibly plays an important role in oral or gastro-intestinal carcinogenesis.[95]

A number of epidemiological and clinical studies demonstrated a positive relationship between periodontal disease or tooth loss and the progression of cancers including oral cancer, gastric cancer and pancreatic cancer.[96–103] The results of a meta-analysis revealed that patients with periodontitis exhibit a 2.66-fold higher risk for the development of oral cancer, and periodontitis was found to be an independent risk factor for this malignancy.[104]

It was also reported that the serum levels of IgG and IgA for *P. gingivalis* are significantly elevated in esophageal squamous cell carcinoma (ESCC) patients compared to those of non-ESCC controls. ESCC patients in which high levels of IgG as well as IgA were detected exhibited the worst prognosis. A multivariate analysis identified IgG and IgA as independent prognostic factors, leading to the conclusion of the authors that IgG and IgA against *P. gingivalis* may be potential serum biomarkers for ESCC.[98]

Recently a study showed significantly elevated serum levels of *P. gingivalis* IgG and IL-6 in OSCC patients compared to non-OSCC controls. High IL-6 serum levels were demonstrated to be associated with a worse prognosis for OSCC patients. This suggested the conclusion that *P. gingivalis* IgG and IL-6 may serve as potential serum biomarkers for the diagnosis of OSCC and that the serum level of IL-6 may provide to the enhancement of prognostic accuracy.[105]

Geng et al.[106] aimed to analyze host genes that change the expression as the reaction to chronic *P. gingivalis* infection and thus possibly contribute to the development of oral cancer. A comprehensive analysis of microarray data obtained from a chronic infection model of immortalized oral epithelial cells that were persistently exposed to *P. gingivalis* for 15 weeks was performed. Protein–protein interactions (PPIs) and network assays as well as an ingenuity pathway analysis (IPA) were used to identify genes, hub genes, upstream regulators and major biological processes that potentially participate in tumor initiation and progression. Gene expression was validated, and genetic alterations of hub genes in clinical samples from head and neck cancer tissues were shown. Concha-Benavente et al.[107] investigated intrinsic and extrinsic cellular pathways downstream of epidermal growth factor receptor (ERGF) and IFN-γ. The results demonstrated a mechanism inducing the upregulation of PD-L1 expression in head and neck cancer cells in the context of Janus kinase (JAK)/signaling transductors and activators of transcription (STAT) signaling pathway activation, Th1 inflammatory response and human papilloma virus (HPV) status. In a large cohort of head and neck cancer samples, it was shown that highly expressed WT EGFR was significantly correlated with JAK2 and PD-L1 expression. Furthermore, PD-L1 expression was induced in an EGFR- and JAK2/STAT1-dependent manner, and specific inhibition of JAK2 suppressed PD-L1 upregulation in tumor cells and increased their immunogenicity. These results provide evidence that JAK2/STAT1 plays a role in EGFR-mediated immune evasion. Possible therapeutic approaches targeting this signaling axis may be effective to inhibit PD-L1 upregulation, which was shown in a large subset of head and neck cancers.

The investigation of the mechanism of PD-L1 upregulation provides further interesting insights. First, it could be demonstrated that viable and heat-killed bacteria were able to induce PD-L1 upregulation, suggesting that the bacterial component responsible for this induction does not depend on the viability of the bacteria. These findings were the base for further attempts to identify the responsible components by preparing bacterial fractions. Preparation of the bacteria into a cytosolic, total membrane and separate outer and inner membrane fractions increased the ability to differentiate between different bacterial components. The results of these experiments showing stimulation of primary and malignant oral epithelial cells with the different components revealed that the causal agent is localized in the total membrane fraction.[45]

Under noninfected, physiological conditions, co-inhibitory pathways such as the PD-L1 pathway, play an essential role in the maintenance of self-tolerance, and they protect against excessive tissue

damage caused by the immune response. These pathways function as immune checkpoints that protect against possible unsolicited and harmful self-directed responses, an essential function that supports the prevention of autoimmunity.[108,109]

It was demonstrated that additionally to immune-suppressive cytokines such as IL-10, IL-13 and TGF-β, PD-L1 levels are elevated in saliva from patients with oral cancer or salivary gland carcinoma.[110,111] Saliva-derived exosome containing samples have been analyzed as a possible source of biomarkers for periodontitis.[112,113] Exosomes are 30–100-nm membrane-encapsulated vesicles that contain nucleic acid and protein loads. Eukaryotic cells are able to secrete these vesicles.[114]

The content of cell-derived exosomes may include cargos that possibly can be used as biomarkers. The exosomal content in saliva was investigated for its use as a diagnostic and/or prognostic tool in various diseases, including oral cancer, oral lichen planus, Sjögren's syndrome and inflammatory bowel disease.[115–118]

The presence of PD-L1 mRNA has been demonstrated in periodontitis.[34,40] Yu et al.[38] investigated if PD-L1 mRNA is detectable in salivary exosomes of periodontitis patients and to what extend the level of exosomal PD-L1 mRNA correlates with the state of the disease. This research group succeeded in isolating exosomal RNAs from the saliva of periodontitis patients and compared them to those from healthy controls. The results revealed higher levels of PD-L1 mRNA in patients than in controls. Furthermore, significant differences between the stages of periodontitis could be demonstrated. These results suggest that analysis of exosome-derived PD-L1 mRNAs in saliva may possibly be used to distinguish individuals with periodontitis from healthy individuals, with the levels correlating with stage or severity of the disease.

The upregulation of PD-L1 on tumors is of clinical relevance for the progression of the disease.[119] The effects of *P. gingivalis* PGN on tumor cells, especially the upregulation of receptors, make this gram-negative anaerobic rod a pathogen comparable to *H. pylori*. Since this mechanism is abundant in periodontitis and periodontal diseases, antimicrobial therapy possibly is not only useful for improvement of oral health but can also enhance general health, especially in patients suffering from oral cancer. The formation and function of osteoclasts induced by PGN of another periodontal pathogen, *Actinomyces (A.) naeslundii* and inflammatory cytokine gene expression (IL-1β, IL-6, and TNF-α) were investigated by Sato et al.[120] The results revealed increased bone resorption and elevated expression levels of IL-1β, IL-6, and TNF-α. In experimental periodontitis, the bone loss caused by *A. naeslundii* was similar to *P. gingivalis* induced bone loss. These results support the hypothesis that the PDG of *A. naeslundii* may be an important virulence factor in the development and progression of periodontitis.

An actual study addresses the role of further oral bacteria in oral SCC. Paired tumor and adjacent normal tissues from 37 oral tongue SCC patients were used for 16S rRNA gene sequencing and whole exome sequencing (WES). Additionally, RNA sequencing was performed in tumor samples. *Fusobacterium* was significantly enriched in oral tongue cancer while *Streptococcus* and *Rothia* were accumulated in adjacent normal tissues. Decreased alpha diversity was demonstrated in tumors in comparison to the neighboring normal tissues. The increased load of *Fusobacterium* in tumor samples was found not to be associated with alterations in the infiltration with immune cells, but it was associated with enhanced PD-L1 mRNA expression, so the effects of *Fusobacterium* on the PD-L1 expression in head-and-neck SCC cell lines was further investigated. The results showed that infection with *Fusobacterium* species are able to upregulate as well PD-L1 mRNA as surface PD-L1 protein expression on the used head and neck cancer cell lines. The relation between *Fusobacterium* and the PD-L1 expression in oral tongue SCC, combined with the capability of the germ to increase the PD-L1 expression in vitro suggests a potential importance of *Fusobacterium* on regulation of the tumor immune microenvironment in head and neck cancer.[121]

4 | PD-L1 AND EPITHELIAL–MESENCHYMAL TRANSITION (EMT) AS A FACTOR IN TUMOR PROGRESSION AND METASTATIC EXPANSION

The EMT is a highly dynamic process of interconversion of epithelial cells to quasi- mesenchymal cells that demonstrate increased motility, invasive capacity and stem cell- like properties and express resistance to several treatment strategies and immune-evasive and immunosuppressive characteristics.[122] The EMT is a reversible cellular programme that transiently transforms epithelial cells into a mesenchymal-like cell state.[123–126] During this process, epithelial cells proceed to lose their cobble-like typical epithelial aspect in monolayer cultures to change into a spindle-shaped, mesenchymal appearance. The developed quasi mesenchymal cells can revert back to an epithelial morphology in the reverse process, named mesenchymal–epithelial transition (MET) (Figure 3). The EMT plays important roles in distinct states of embryogenesis such as gastrulation, tissue morphogenesis during development and wound healing in the adult.[123,124,126] Furthermore, the malignant progression of many carcinoma types, most likely all of them, depends on activation of EMT in neoplastic cells.[127]

Scientific advances found out that the EMT process induces upregulation of PD-L1 expression. Interestingly, the results of several other studies also suggested that PD-L1 signaling plays is of importance for the maintenance of the EMT status in breast cancer, renal cell carcinoma, glioblastoma, esophageal cancer and hepatocellular carcinoma (HCC).[128–130]

Recently, it was demonstrated that the EMT enriches PD-L1 in cancer stem-like cells (CSCs) using the EMT/β-catenin/staurosporine way and temperature-sensitive dolichyl-diphosphooligosaccharide–protein glycosyltransferase (STT)3 catalytic subunits of the oligosaccharyltransferase complex/PD-L1 signaling axis, by that EMT transcriptionally induces the N-glycosyltransferase STT3 through β-catenin activation, and the subsequent STT3-dependent PD-L1 N-glycosylation stabilizes and upregulates PD-L1.[131]

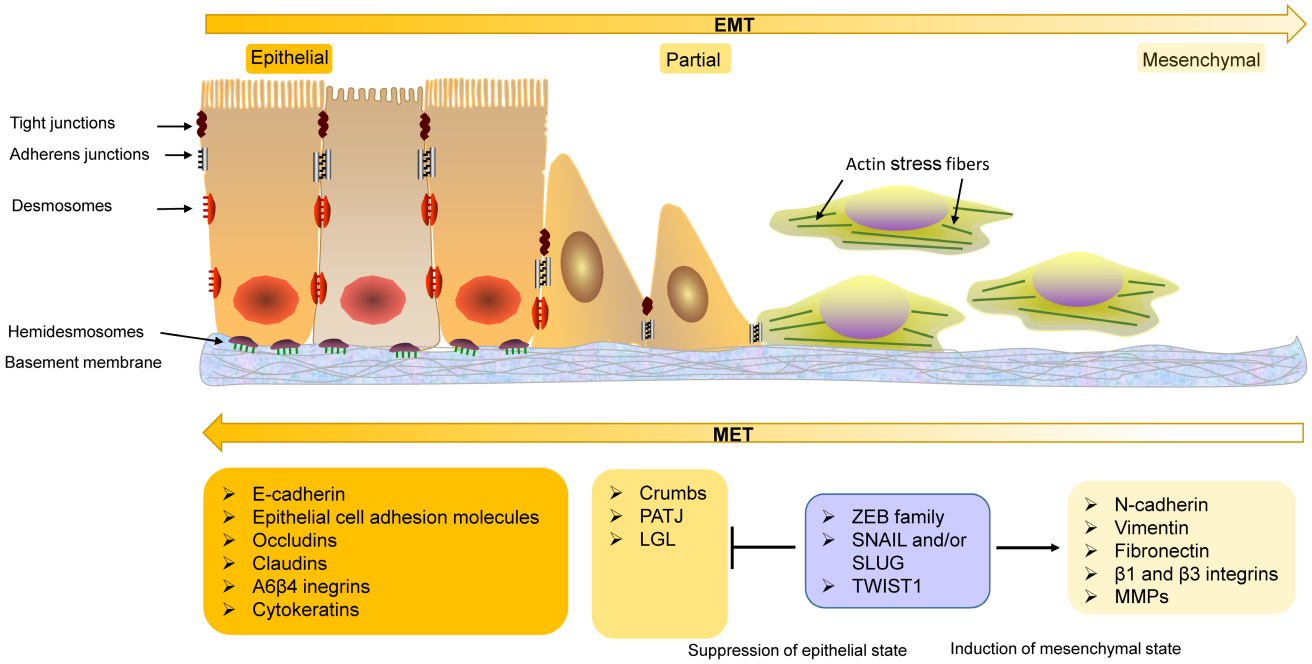

FIGURE 3 Epithelial–mesenchymal transition (EMT) as factor in tumor progression and metastatic expansion. Outline of a typical EMT programme: Epithelial cells showing apical–basal polarity are connected by tight junctions, adherens junctions and desmosomes and are attached to the underlying basement membrane by hemidesmosomes. Molecules associated with epithelial state and cell polarity: E-cadherin, epithelial cell adhesion molecules, occludins, claudins, A6β4 inegrins, cytokeratins. The induction of EMT results in the expression of the EMT-maintaining transcription factors (EMT-TFs) ZEB, SNAIL and TWIST that inhibit the expression of genes associated with the epithelial state, coming along with activation of the expression of genes associated with the mesenchymal state: N-cadherin, Vimentin, Fibronectin, β1 and β3 integrins, MMPs. Changed gene expression lead to cellular modifications including disassembly of epithelial cell–cell junctions and the dissolution of apical–basal cell polarity by the downregulation of crumbs, PALS1-associated tight junction protein (PATJ) and lethal giant larvae (LGL), all proteins that specifically maintain tight junction formation and apical–basal polarity. The process of EMT leads to enhanced cellular motility and the cells derive invasive capabilities. The process of EMT is reversible, and mesenchymal cells can go back to the epithelial morphology by undergoing mesenchymal–epithelial transition (MET). Both, EMT and MET, take place during normal development as well as cancer progression. E-cadherin, epithelial cadherin; MMP, matrix metalloproteinase; N-cadherin, neural cadherin. Modified after Dongre et al.[122]

Cancer stem-like cells are known to be tumor-initiating cells and represent a small subpopulation of tumor cells that play an essential role in the initiation, progression and drug resistance of tumors because of their ability for extensive proliferation that enables them to develop into new tumors. Evidence suggests the existence of dysregulated signaling pathways in the regulation of normal stem cell self-renewal in CSCs, which leads to the continuous spreading of self-renewing cancer cells and tumor development.[132,133] CSCs are more resistant to immune surveillance than non-CSCs, and cancer control by the immune response causes enrichment of a subpopulation of cancer cells with stem-like properties.

The capability to escape the immune surveillance is essential for tumorigenesis by CSCs since they subvert host response to inflammation-induced tumors, in which inflammatory regulators and cells promote angiogenesis and can support growth, invasion, and metastasis of tumor cells. Additionally, immune-altered tumor cells undergo EMT that is accompanied by an upregulation of invasion factors that in turn enhance the invasiveness of mesenchymal tumor cells.[134,135]

Zhao et al.[136] assessed the role of the MAPK signaling pathway in the development of the EMT in oral SCC induced by the inflammatory cytokine TNF-α. After stimulation with TNF-α, the expression of JNK, extracellular-signal regulated kinases (ERK), and p38 in the MAPK signaling pathway raised, while the expression of E-cadherin and Claudin1 declined compared to the concentrations in the non-stimulated control group. These results suggest that TNF-α regulated the EMT process by promoting the invasion and metastasis of oral squamous carcinoma cells via the MAPK signaling pathway.

Wu et al.[137] aimed to characterize the essential links among PD-L1, tumor microenvironment of oral SCCs and EMT process and to investigate the sensitivity of different chemical agents to different PD-L1 expression groups. A bioinformatical analysis revealed that PD-L1 was highly expressed in OSCC and that this higher PD-L1 expression is correlated with poorer survival in patients. PD-L1 was also positively correlated with macrophages infiltration and gene expression of EMT markers. Furthermore, patients in the PD-L1 high expressing group possibly have a greater benefit from immune checkpoint inhibition treatment and they also showed higher sensitivity to

chemical drugs such as olaparib, paclitaxel, docetaxel, and pazopanib as well. The authors concluded that PD-L1 may serve as a novel target for prognostic and therapeutic approaches in OSCC patients. PD-L1-mediated immune evasion might play a role in the infiltration of macrophages and the resulting EMT progress. Chemical agents in combination with PD-L1 inhibitors may be useful for personalized treatment plans for OSCC patients, which enable a maximum benefit for the patients. In esophageal SCC cells it was found, that tumor necrosis factor-associated apoptosis-inducing ligand (TRAIL), that was initially regarded as immunity guard but with remaining controversial functions, promotes EMT by the induction of PD-L1 over a p-ERK/signal transducer and activator of transcription (STAT)3 dependent signaling pathway.[138] Many studies indicated a solid correlation between EMT state and immune checkpoints, particularly PD-L1, in a multitude of cancers including head and neck SCCs, nonsmall-cell lung cancer (NSCLC), esophageal squamous cancer breast cancer and extrahepatic cholangiocarcinoma. In pulmonary adenocarcinoma, investigating EMT markers and PD-L1 expression, it was shown that that zinc finger protein SNAI1 (Snail) and vimentin H levels were positively correlated with PD-L1 expression. The rate of PD-L1 positivity was clearly elevated in patients with mesenchymal phenotypes in comparison to those with epithelial phenotypes, especially in EGFR-mutated cancers.[139] Significantly increased PD-L1 expression was also established in mesenchymal compared to epithelial lung adenocarcinoma with a strong negative correlation of E-cadherin with PD-L1 protein expression.[140] Expression of PD-L1 in head and neck SCCs were shown to be significantly linked to EMT status as analyzed by low E-cadherin and high vimentin expression. Furthermore, the PD-L1+/EMT+ cohort exhibited poorer prognosis compared to the PD-L1+/EMT- group.[141] In patients with extrahepatic cholangiocarcinoma the expression of PD-L1 was correlated with high expression of vimentin, N-cadherin and zinc finger e-box binding homeobox (ZEB)1, and low E-cadherin expression. In breast cancer, mesenchymal cell lines sustain higher percentages of PD-L1 positive cells and enhanced activation of Snail or ZEB1, inducing increased PD-L1 expression.[142] The same effect was found in tissues from esophageal squamous cancer, exhibiting high expression of ZEB1 that in combination with PD-L1 high expression leading to the worst prognosis for these patients.[143]

These data suggest that the EMT status together with PD-L1 may be a combined biomarker to predict more suitably the prognosis of cancer and may be a potential predictive biomarker to guide selection of patients who more likely will obtain benefit from a checkpoint blockade. Even if high PD-L1 expression does not guarantee an efficient reaction to PD-1 inhibitors, low or missing PD-L1 expression does not mean that a positive response to PD-1/PD-L1 antibodies is impossible.[144,145]

A bidirectional relationship seems to exist between PD-L1 expression and EMT status that eventually causes immune escape of tumors (Figure 4).

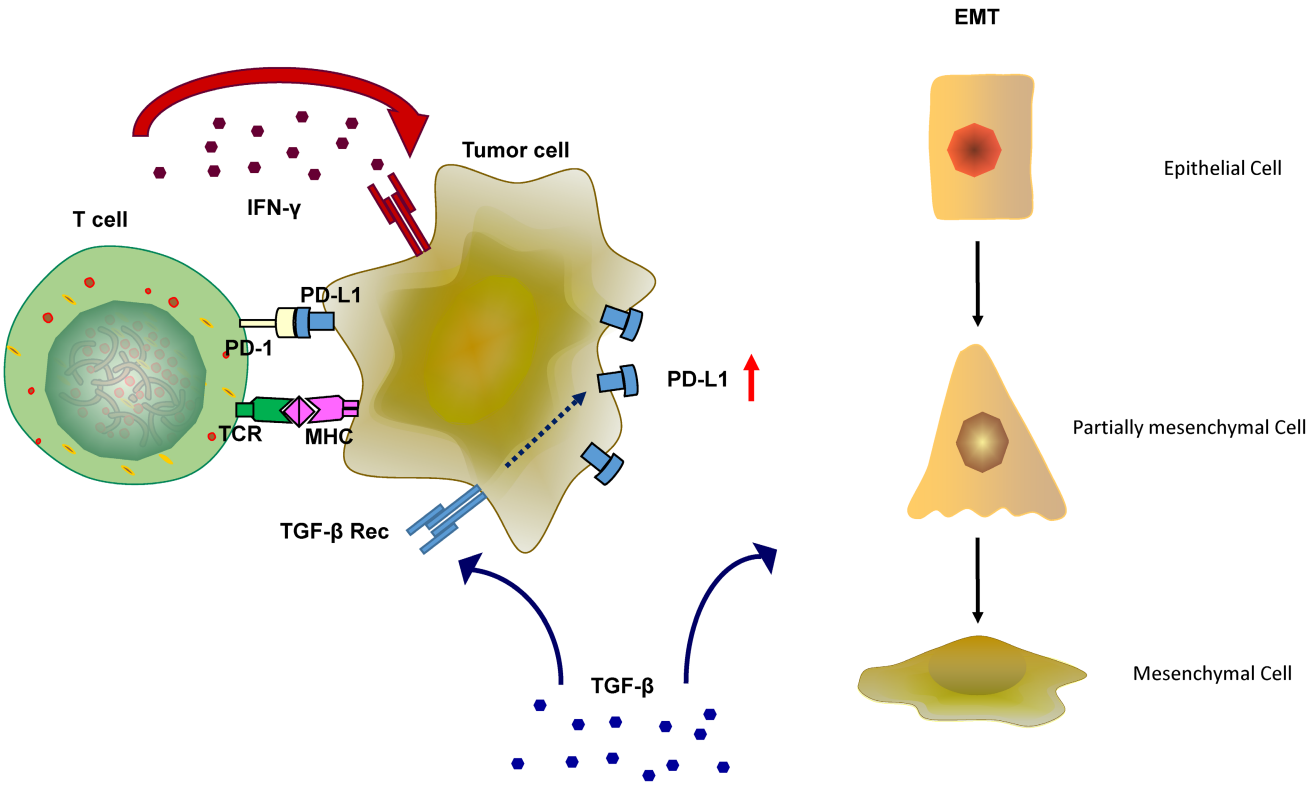

FIGURE 4 Epithelial–mesenchymal transition (EMT) as factor in tumor progression and metastatic expansion. Schematic overview of the crosstalk between EMT and IFNγ-induced PD-L1 expression: IFNγ-induced PD-L1 upregulation supports the processes of EMT. EMT can also be induced by, i.e.TGF-β, enhanced PD-L1 expression levels, promoting tumor immunoevasion. Modified after Burger et al.[146]

5 | ROLE OF PD-L1 IN TUMOR-DERIVED EXOSOMES (TEXs)

Studies on extracellular vesicles revealed that they can serve as mediators of signal communication between the cells.[147–149] The exosomal content is mainly consists of microRNAs, cytosolic proteins, lipids, circular RNAs, cytokines, long noncoding RNAs, transcription factor receptors, DNA and other molecules.[114] It was demonstrated that normal or diseased cells are able to secrete exosomal miRNAs, which may affect neighboring and also distant target cells.[150] Noncoding RNAs in exosomes possibly have an effect on the expression of tumor-related genes and can provide in the cancer-causing process.[151] A number of studies demonstrated the participation of exosomes in a multitude of physiological and pathological processes, particularly the development of cancers. Exosomes can widely be detected in body fluids such as plasma, saliva, breast milk, amniotic fluid and urine as well in cancer as in noncancerous cells from tumor patients.[152] In the tumor microenvironment, exosomes possible participate in the mediation of immune regulation and intracellular communication.

Tumor-derived exosomes (TEXs) and immune cell-derived exosomes (IEXs) were shown to activate immune reactions by transporting antigens to antigen presenting cells (APCs), which induces the activation of $CD4^+$ T-cells and $CD8^+$ T-cells, which in turn increases the anti-tumor responses and cause inhibition of tumor progression.[153] A further possible way of action has also been described that includes apoptosis induction tumor cells.[154] A study found that exosomes derived from heat-stressed tumor cells are able to induce the production of IL-6 by DCs and macrophages. This leads to a heat-shock protein (HSP)-70 dependent switch of Tregs into Th17 in the tumor microenvironment.[155] It was proven that, when DCs are targeted by TEXs, it results in increased antitumor responses.[156] Exosomes from T lymphoblast derived EG7 tumor cells are able to transfer the cell-associated antigen ovalbumin (OVA) and the parental major histocompatibility complex (pMHC)-I into DCs, which induce an increased proliferation and differentiation of cytotoxic T-lymphocytes (CTL) and create a more robust OVA-specific antitumor immunity compared to controls.[156] Comparable results were detected in HCC models and in other studies.[157] TGF-β-silenced leukemia cells derived exosomes diminish the production of TGF-β by DCs and effectively support their maturation and function. Furthermore, exosome-bearing DCs promoted the proliferation of $CD4^+$ T-cells and augmented the antigen-specific CTL responses.[158,159] The reason why TEXs exhibiting stable antitumor responses are mostly because they target DCs. It has been reported as well that IEXs also promote increase of the anti-tumor response. Furthermore, IEXs are able to change the microenvironment to a more suitable so the tumor growth is suppressed. Lu et al.[160] reported that exosomes derived from α-fetoprotein (AFP)-expressing DCs were able to support the antigen-specific immune response over enhancement of the IFN-γ and interleukin-2 levels and reduced expression of interleukin-10 and TGF-β. Extracellular vesicles that originate from activated $CD8^+$ T-cells could directly target mesenchymal tumor stromal cells and prevent by this effect tumor invasion and metastasis.[161] Using in vitro as well as in vivo experiments it was demonstrated that NK cell-derived exosomes could inhibit the development of melanomas by their amounts of perforin, TNF-α and Fas ligand (FasL).[162] Besides the antitumor effects of exosomes, a number of studies investigated their activity in promoting tumor progression.[163] The growth of tumors is linked to a variety of growth factor receptors and signaling pathways. These receptors activate downstream signaling pathways including protein kinase B (Akt), protein kinase (PK)C/PKB and ERK kinase pathways by activating or phosphorylating of intracellular kinase domains which maintains tumor cell proliferation and migration. TEXs originating from lung cancer and breast cancer models suppressed the differentiation of myeloid precursors into DCs and their maturation by enhancing the expression of the immunosuppressive molecule PD-L1 to induce inhibiting signals.[164] Gastric cancer-derived exosomes were demonstrated to stimulate monocytes to differentiate into PD-1+ tumor-associated macrophages (TAMs), which robustly can inhibit anti-tumor responses by activation of the PD-1/ PD-Ls interaction and signaling.[165] Exosomes that originated from oral SCCs upregulated the expression of PD-L1 on myeloid-derived suppressor cells (MDSCs) to further cause γδ T-cell exhaustion by an exosome micro RNA (miR)-21/ phosphatase and tensin homolog (PTEN)/PD-L1 pathway which similarly has been shown for HCC cells.[166] Liu et al.[167] revealed that exosomes released from HCC cells upregulated the expression of PD-L1 in macrophages that in turn suppressed T-cell function by a miR-23a/PTEN/AKT Signaling pathway. Additionally, exosomes derived from melatonin-treated HCC cells downregulated the expression of PD-L1 and the release of cytokines including IL-6, IL-1β, IL-10, and TNF-α in macrophages.[168] All these data indicate that miRNAs enclosed in tumor-derived exosomes may promote the growth and metastasis of tumors.[169]

One essential mechanism of tumor immune evasion is the binding of PD-L1 expressed on the surface of tumor cells, to PD-1 on T-cells. PD-L1-overexpressing tumor cells show the exceeding capability to survive, escape the surveillance of the host immune reaction and thus have the possibility to invade adjacent tissues.[170] IFN-γ, that is secreted by inflammatory cells including NK cells and macrophages, can induce upregulation of PD-L1 expression on tumor cells.[171,172] This upregulated expression of PD-L1 enables tumor cells to acquire adaptive resistance against the IFN-γ released by CTL, generating a vicious circle that leads to exacerbation of the disease.[172] The results of studies show that the infiltration of immune cells in the tumor microenvironment is possibly linked to the expression of PD-L1 on their surface.[173] PD-L1 overexpressing TAMs can inhibit the function of CTL. The results of investigations using a breast cancer cell line have also implicated that the TAM receptors Tyro3, Axl, and Mertk may cause an upregulated expression of PD-L1.[174]

Evidence demonstrates that exosomes from tumor cells contain bioactive PD-L1 on their surface which subsequently may suppress the immune response.[175] Exosomes derived from metastatic melanoma, which can be stimulated by IFN-γ, expressed higher amounts of PD-L1 on these vesicles and impeded antitumor responses.[176] It is known that the microenvironment of HNSCCs has highly

immunosuppressive properties. HNSCCs expressing increased levels of PD-L1 show particularly poor outcomes. It was found that high expression of exosomal PD-L1 is able to inhibit T-cell activation (Figure 5).[177]

Exosomes loaded with PD-L1 could be isolated from plasma of patients with HNSCC and were shown to be correlated with enhanced disease activity caused by suppression of lymphocyte activity.[178] A study that aimed to reveal the contribution of PD-L1 containing exosomes to immune suppression and disease activity of HNSCC patients found that the levels of PD-L1 loaded in exosomes correlated with patients' disease activity, the UICC stage and the lymph node status. In contrast, the plasma levels of soluble (s)PD-L1 or exosome PD-1 levels did not correlate with any clinicopathological parameter.[179]

PD-L1 protein can be expressed at the cell plasma membrane (mPD-L1), in cell nuclei (nPD-L1), at the surface of exosomes (exo-PD-L1) and as a soluble circulating protein (sPD-L1). Bailly et al.[180] aimed to highlight the different variants of sPD-L1 produced either over proteolytic cleavage of m/exoPD-L1 or by alternative splicing of PD-L1 pre-mRNA. The aim was also to point out the presence and role of circulating sPD-L1 isoforms in various cancer manifestations and multiple other diseases, such as chronic inflammatory and viral diseases. sPD-L1 possibly represents a general marker of inflammatory conditions. The stock of sPD-L1 proteins is an essential part of the greatly dynamic PD-1/PD-L1 signaling pathway. The diversity of the circulating soluble PD-L1 forms can be produced via different proteolytic or splicing processes. Enhanced sPD-L1 protein levels were detected in a multitude of cancer types and many inflammatory conditions beyond cancer. sPD-L1 can prevalently be found in the plasma or serum, but its exact biochemical nature and functions are not well understood. More scientific activities are necessary to enable a better characterization of the contribution of sPD-L1 to the function and activity of the PD-L1/PD-1 checkpoint, and to provide a better understanding of the dynamic interplay between the different PD-L1 species of PD-L1, cytoplasmic, nuclear, membrane, soluble and exosomal. However, sPD-L1 is an important multi-faceted systemic circulating protein that is linked to a big diversity of diseases with a still partly unclear contribution to the disease progression.

6 | PD1/PD-L1 CHECKPOINT TREATMENT AS A THERAPEUTIC OPTION FOR CANCER

A number of studies has affirmed the clinical importance of PD-1/PD-L1 antibodies and their prognostic influence on human cancers.[181,182] However, it is not clear how these biomarkers and its clinical significance are related since it shows diversity in different types of human cancers.[183]

Generally, PD-1/PD-L1 inhibitory checkpoints inhibit TCR-mediated cytotoxicity and $CD8^+$ T-cell proliferation over interaction with the ligand PD-L1, resulting in evasion of the killing function of the immune response to tumor cells and immune surveillance.[184–186] Immune checkpoint antibodies are promising approaches for cancer therapy which base on their physiological function as T-cell-activated co-inhibitory receptors that plays an important role in the treatment of PD-1/PD-L1 immune checkpoint inhibitors.[187] Expression of PD-L1 in tumor cells or tumor-associated stromal cells can possibly serve as predictive marker for outcome of and response to anti-PD-1/PD-L1 immunotherapy.[188,189]

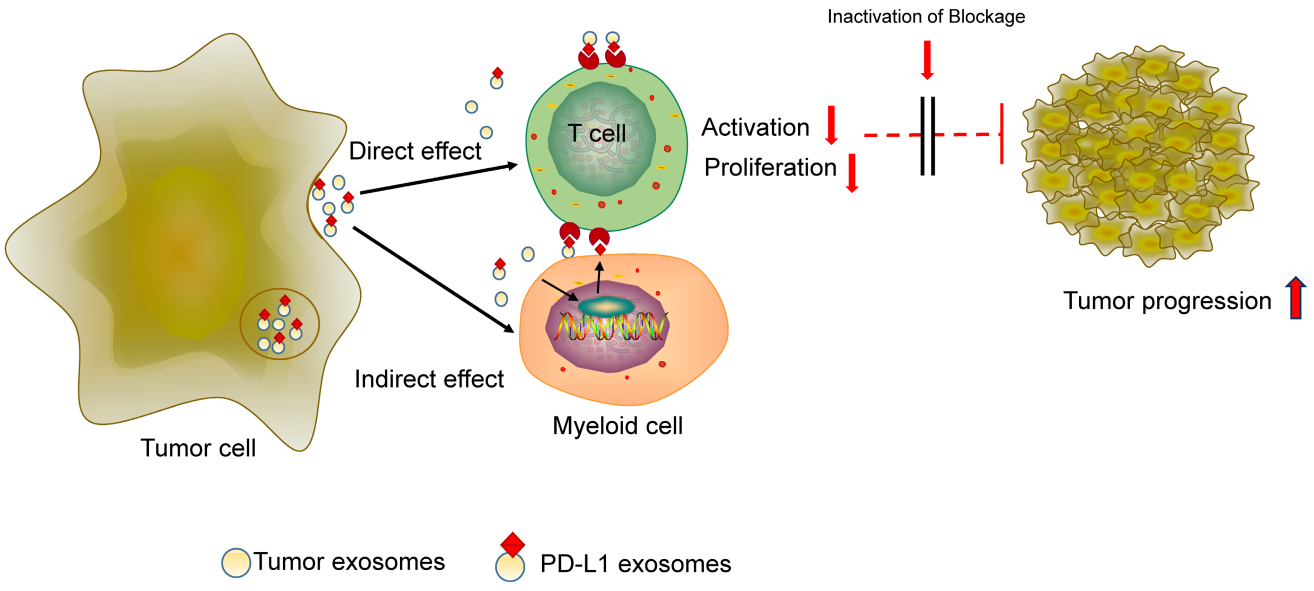

FIGURE 5 Mechanisms of exosomal PD-L1 induced immunosuppression. Interaction between exosomal PD-L1 and PD-1 on T-cells may directly cause immunosuppression. Additionally, exosomal PD-L1 upregulates the expression of PD-L1 in myeloid cells via the NF-κB pathway, induces their transformation into myeloid immune cells, and indirectly suppresses the activation and proliferation of T-cells. The final result of these processes is T-cell inactivation and tumor progression. Modfied after Ye et al.[177]

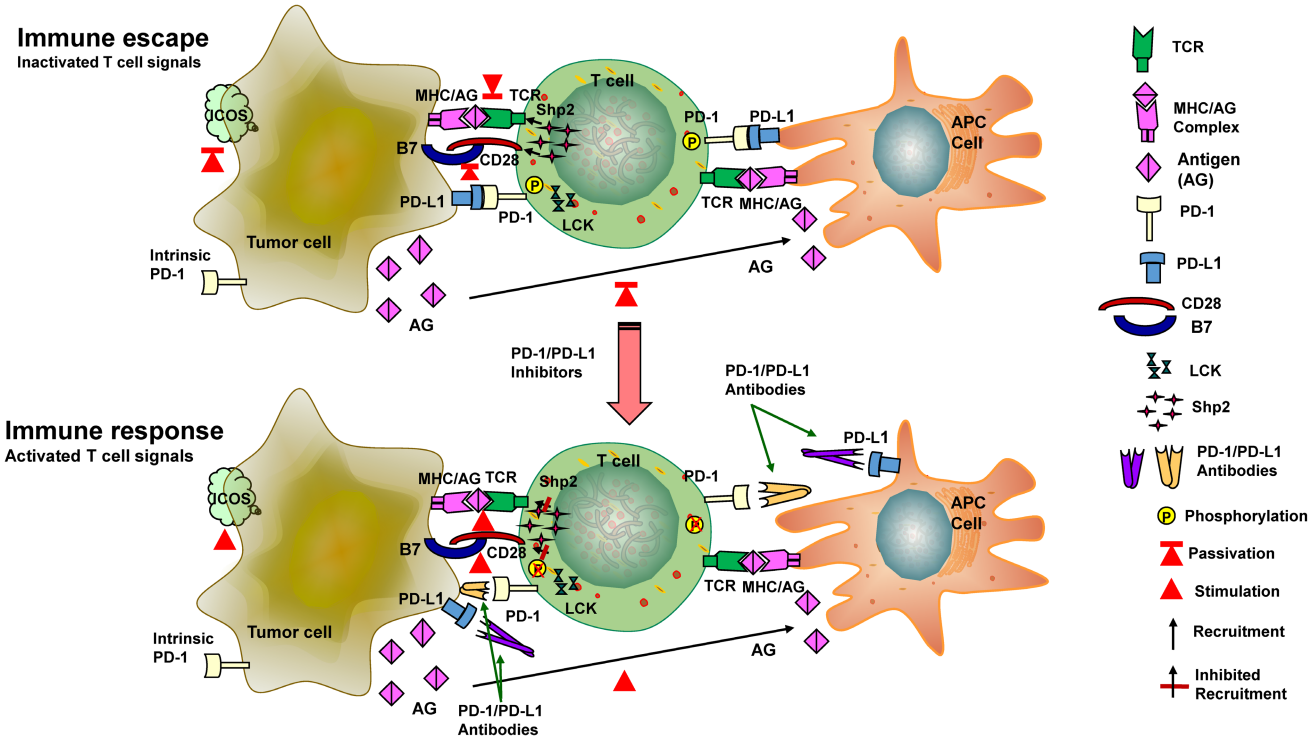

FIGURE 6 PD-L1 as therapeutic target in cancer. Mechanisms of PD-1/PD-L1 inhibitor treatment response: PD-1 mainly is expressed in T-cells and PD-L1 in tumor cells and antigen presenting (APC) cells. Some tumor cells can also express intrinsic PD-1. After PD-1 – PD-L1 ligation immune escape is enabled. PD-1 can be phosphorylated by LCK to further recruit tyrosine phosphatase Src homologous phosphatase 2 (Shp2), resulting in inactivation of CD28 and TCR function and signaling pathway. This leads to attenuation of the T-cell activating signal that causes immune escape. Lymphocyte-specific protein tyrosine kinase (LCK) kinase activity is needed to mediate PD-1/SHP-2-maintained inhibiting signaling. The interaction of PD-1/PD-L1 immunocheckpoint inhibitors with its targets can effectively block the binding between PD-L1 and PD-1, which in turn inhibits the recruitment of SHP-2 and can reactivate T-cells signaling and their immunologic function. Modified after Tang et al.[202]

There is no doubt about efficacy of PD-1/PD-L1 immunocheckpoint inhibitors in the therapy of cancer, but some issues are existent including adverse effects and drug resistance that may significantly affect the outcome of anti-PD-1/PD-L1 immunotherapy. The immunotherapy mechanisms of anti-PD-1/PD-L1 antibodies are revealed to some extend. It is know that for the activation of T-cells dual signals are necessary. The first signaling step is the binding of MHC-presenting antigen to the TCR. The second signal is proceeded by interaction co-stimulatory and co-inhibitory molecules.[190] The binding of PD-1 on T-cells to PD-L1 on tumor cells or APCs can effectively suppress T-cell activation and induce T-cell apoptosis, diminished cytokine production, T-cell lysis and furthermore trigger tolerance to antigens, which enables the tumor to evade immune surveillance.[191] The function of PD-1/PD-L1 inhibitors is to bind to PD-1 or PD-L1 to impede the interaction between PD-1 and PD-L1, PD-1 activation efficiently suppresses TCR signaling, CD28 co-stimulatory signaling and inducible T-cell co-stimulator (ICOS) signaling.[192–194] The results of studies suggested the following process: after PD-1 was activated by its ligand PD-L1, PD-1 is phosphorylated by protein tyrosine kinase Lck phosphorylates PD-1 which in turn recruits tyrosine phosphatase Src homologous phosphatase 2 (Shp2), leading to dephosphorylation of TCR and CD28, followed by inhibition of T-cell-linked signaling (Figure 6).[195–198] The intervention of PD-1/PD-L1 immune checkpoint inhibitors disable the phosphorylation of the intramembrane PD-1 motif of by the lymphocyte-specific protein tyrosine kinase (LCK), causing failed cell recruitment to SHP-2. TCR and CD28 inhibited the dephosphorylation of CD28 and TCR causes successful transfer of activation signals to downstream proteins and signaling pathways, this finally stimulates T-cell differentiation and proliferation and the immune function of the T-cells can proceed effectively (Figure 6).[199] It has been shown that tumor cells can express intrinsic PD-1 too to support the formation of tumors that can escape the adaptive immunity. PD-1 checkpoint inhibitors are able to inhibit the binding of intrinsic PD-1 and PD-L1, which blocks the tumor growth (Figure 6).[200,201]

Tumor cells lose the capability to express tumor antigens in order to evade the recognition by APCs and cytotoxic T-cells.[203] It was demonstrated that major histocompatibility complex class-I and -II (MHC-I and MHC-II) are necessary for effective tumor antigen presentation and immune-surveillance.[204–206] In a number of malignancies, the downregulation of MHC-I/II is linked to immunosuppression, metastatic progression and poor prognosis, and it is a predictive factor for the response to anti-PD-1/PD-L1 therapy.[207] Aiming to amend the response rate to PD-1/PD-L1 immunotherapy, researches tried to find ways to upregulate MCH-II expression in tumor cells. It was revealed that epigenetic and ERK signaling

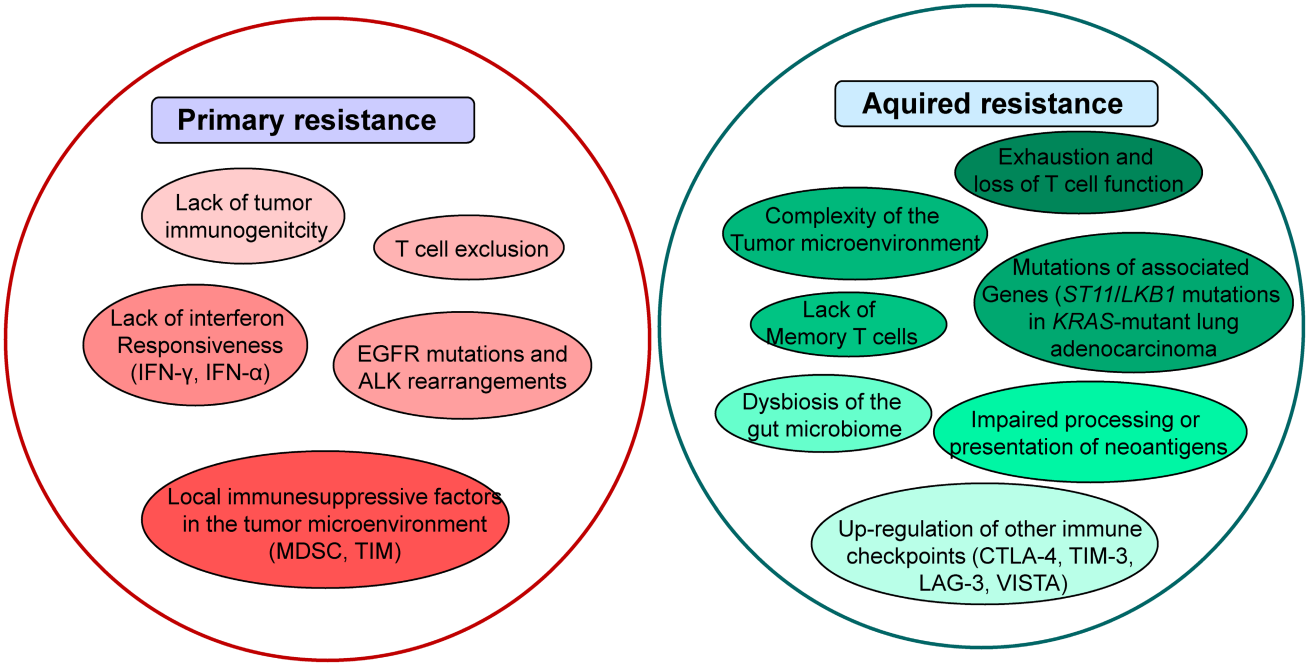

FIGURE 7 PD-L1 as therapeutic target in cancer. Mechanisms of PD-1/PD-L1 inhibitors resistance: PD-1/PD-L1 inhibitor resistance is classified as primary resistance and acquired resistance. Mechanisms of primary resistance include lack of tumor immunogenicity; T-cell rejection; lack of interferon responsiveness, such as IFNg (interferon-γ) and IFN-α (interferon-α); EGFR (epidermal growth factor receptor) mutations and ALK rearrangements; local immunosuppressive factors within the tumor microenvironment, such as MDSC (myeloid-derived suppressor cell) and TIM (tumorinfiltrating myeloid cell). The mechanisms of acquired resistance are attributed to exhaustion and loss of T-cell function; impaired processing or presentation of neoantigens; complexity of the tumor microenvironment; mutations in associated genes, such as STK11/LKB1; dysbiosis of the gut microbiome; lack of Memory T-cells and upregulation of other Immune Checkpoints, such as CTLA-4 (cytotoxic T-lymphocyte antigen-4), TIM-3 (T-cell immunoglobulin and mucin domain-containing molecule-3), LAG-3 (lymphocyte activation gene-3) and VISTA (V-domain Ig suppressor of T-cell activation). Modified after Tang et al.[202]

cascades were involved in inhibiting the expression of intrinsic MHC II in nonsmall cell lung cancer.[208] This led to the development of combined blocking strategies for these pathways attempting a more positive response to PD-1/PD-L1 immune checkpoint therapy in human cancers. A study showed furthermore, that in lung epithelial MHC-II is necessary for surface expression of PD-L1.[209] In a clinical study treatment of recurrent or metastatic nasopharyngeal carcinoma with an anti-PD-1 antibody (camrelizumab) was investigated and it was shown that patients with a high expression of both MHC-II and PD-L1 responded better to this treatment.[210] All these results lead to the conclusion that MHC-II and PD-L1 affect each other as well in expression as in function for the treatment of PD-1/PD-L1 immune-checkpoint blockers in human cancer. Immune checkpoints blockade therapy targeting the PD-1/PD-L1 axis provided a novel summit in tumor immunotherapy in the last years, showing convincing therapeutic success in various malignancies. Nevertheless, many of the patients developed resistance to PD-1/PD-L1 inhibitors that gravely limits its usage and grows to a severe clinical problem that has to be addressed. For this reason it is needed to investigate and identify the molecular mechanism of immune checkpoint inhibitor resistance and enhance the response rate of patients to PD-1/PD-L1 immunotherapy. The resistance to PD-1/PD-L1 inhibitors consist of primary and acquired resistance. The definition of primary resistance is if patients never have demonstrated clinical response or stable disease when PD-1/PD-L1 blockade was utilized. To the mechanisms of primary resistance belong deficient immunogenicity of the tumor,[211] T-cell exclusion,[212] deficient responsiveness to IFN,[213] epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements[214] and local immunosuppressive factors in tumor microenvironment (Figure 7).[215] Acquired drug resistance indicates at the beginning of the therapy PD-1/PD-L1 inhibitors show an effective and solid response, but in some patients during the treatment the therapeutic efficacy of inhibitors is significantly impaired or they develop a nonresponsiveness.[216] Probably the underlying mechanisms are closely linked to T-cell exhaustion and loss of function,[217–219] diminished processing or presentation of neoantigens,[220] mutations in associated genes,[221] complex composition of the tumor microenvironment,[222] defectiveness of memory T-cells,[223] dysbiosis of the gastro-intestinal microbiome[224] and upregulation of further immune checkpoint molecules (Figure 7).[225]

Tumor cells are capable of close interactions with immune cells, stromal cells, environmental cytokines or further suppressive acting immune checkpoints. This protects them from detection and elimination by the immune surveillance system.[222] T-lymphocytes gain immunological clearance of tumors by recognition of specific

tumor-antigens on the surface of the cell membranes, they are able to kill tumor cells. Thus, the expression of tumor-specific antigens is essential for an effective function of the immune response. If the composition of the specific antigen is alike to autoantigens or antigens linked to immune tolerance, disability of APCs to recognize antigens and to trigger T-cell activation may occur. This possibly represents the initiation of acquired resistance.[226,227] Furthermore, some tumors secrete suppressors, including IL-10 and VEGF, which may induce a reduction of functional mature DCs and an increase in the amount of immature DCs. Recruitment of these immature DCs by tumor cells cause an ineffective activation of effector T-cells during antigen presentation.[199,228] Patients suffering from these tumors will fail to maintain an efficient immune response with PD-1/PD-L1 blockers, leading to drug resistance and following immune escape.

Increased knowledge about the resistance against PD-1/PD-L1 immunocheckpoint inhibitors will support the development of new immunotherapeutic strategies to control the process of disease progression and to improve survival of patients.[229] It is essential to discover mechanisms of immune-related adverse events of PD-1/PD-L1 immunocheckpoint inhibitors in human cancer therapy so that the risk for patients can be reduced and the outcome of therapeutic interventions can be further improved.[202]

7 | CONCLUSIONS

The immunomodulatory role of PD-L1 in a variety of carcinomas, including oral carcinomas, has widely been established. There is also evidence about the important role of PD-L1, not only in oral carcinomas but also in periodontitis. PD-L1 levels in GCF of periodontitis patients could be correlated with a set of inflammatory cytokines and increased PD-L1 was found in periodontal lesions and in leukocytes from patients with periodontitis. A bidirectional relationship may be evident between PD-L1 expression and EMT status that eventually induces immune evasion and escape of tumors. EMT, this strongly dynamic interconversion of epithelial to mesenchymal cells induces upregulation of PD-L1 expression. Furthermore, in EMT, PD-L1 could be shown to be enriched in cancer stem-like cells. PD-L1 can be present in cancer-derived exosomes as well and it was demonstrated, that PD-L1 loaded exosomes are able to suppress T-cell functions.

Tumor-derived exosomes have been demonstrated to promote tumor growth and metastasis in a multitude of cancers. Exosomes from metastatic tumor cells exhibit enhanced PD-L1 expression compared with nonmetastatic cells. Additionally, the amount of PD-L1 expression in exosomes is often positively correlated with the severity of cancer staging and negatively connected to survival in a multitude of primary cancers. This strongly supports the prospect that PD-L1+ exosomes particularly are of great importance in regulating tumor progression.

Immune checkpoint antibodies are promising approaches for cancer therapy and their efficacy has been affirmed by a numerous clinical studies. Nevertheless a number of patients show primary or develop secondary resistance against this treatment. More insights about resistance to PD-1/PD-L1 immunocheckpoint inhibitors will support the development of new immunotherapeutic strategies.

PD-L1 can act as mechanistic interlink between periodontitis and cancer since it can be upregulated by periodontopathogenic bacteria and its components. Over its immune-suppressive properties it supports immune-evasion that in turn helps to generate and sustain chronic inflammatory conditions. Both, immune evasive mechanisms and chronic inflammation can support the development and progression of cancers.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

PERMISSION STATEMENT FOR PICTURES

All pictures are prepared by the authors or modified after a source that was cited correctly.

ORCID

Joerg Meyle https://orcid.org/0000-0003-0495-6926

REFERENCES

1. Darveau RP. Periodontitis: a polymicrobial disruption of host homeostasis. *Nat Rev Microbiol*. 2010;8:481-490.
2. Larsen T, Fiehn NE. Dental biofilm infections—an update. *APMIS*. 2017;125:376-384.
3. Picolos DK, Lerche-Sehm J, Abron A, Fine JB, Papapanou PN. Infection patterns in chronic and aggressive periodontitis. *J Clin Periodontol*. 2005;32:1055-1061.
4. Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. *Nat Rev Microbiol*. 2012;10:717-725.
5. Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med*. 2002;8:793-800.
6. Dong H, Zhu G, Tamada K, Chen L. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. *Nat Med*. 1999;5:1365-1369.
7. Yamazaki T, Akiba H, Iwai H, et al. Expression of programmed death 1 ligands by murine T cells and APC. *J Immunol*. 2002;169:5538-5545.
8. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol*. 2008;26:677-704.
9. Agata Y, Kawasaki A, Nishimura H, et al. Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes. *Int Immunol*. 1996;8:765-772.
10. Carreno BM, Collins M. The B7 family of ligands and its receptors: new pathways for costimulation and inhibition of immune responses. *Annu Rev Immunol*. 2002;20:29-53.
11. Greenwald RJ, Latchman YE, Sharpe AH. Negative co-receptors on lymphocytes. *Curr Opin Immunol*. 2002;14:391-396.
12. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J*. 1992;11:3887-3895.

13. Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity*. 1999;11:141-151.
14. Nishimura H, Okazaki T, Tanaka Y, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. *Science*. 2001;291:319-322.
15. Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med*. 2000;192:1027-1034.
16. Mazanet MM, Hughes CC. B7-H1 is expressed by human endothelial cells and suppresses T cell cytokine synthesis. *J Immunol*. 2002;169:3581-3588.
17. Latchman Y, Wood CR, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nat Immunol*. 2001;2:261-268.
18. Tamura H, Dong H, Zhu G, et al. B7-H1 costimulation preferentially enhances CD28-independent T-helper cell function. *Blood*. 2001;97:1809-1816.
19. Carter L, Fouser LA, Jussif J, et al. PD-1:PD-L inhibitory pathway affects both CD4(+) and CD8(+) T cells and is overcome by IL-2. *Eur J Immunol*. 2002;32:634-643.
20. Dong H, Chen L. B7-H1 pathway and its role in the evasion of tumor immunity. *J Mol Med*. 2003;81:281-287.
21. Iwai H, Kozono Y, Hirose S, et al. Amelioration of collagen-induced arthritis by blockade of inducible costimulator-B7 homologous protein costimulation. *J Immunol*. 2002;169:4332-4339.
22. Kanai T, Totsuka T, Uraushihara K, et al. Blockade of B7-H1 suppresses the development of chronic intestinal inflammation. *J Immunol*. 2003;171:4156-4163.
23. Riley JL. PD-1 signaling in primary T cells. *Immunol Rev*. 2009;229:114-125.
24. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. *J Immunol*. 2004;173:945-954.
25. Parry RV, Chemnitz JM, Frauwirth KA, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Mol Cell Biol*. 2005;25:9543-9553.
26. Butte MJ, Keir ME, Phamduy TB, Sharpe AH, Freeman GJ. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. *Immunity*. 2007;27:111-122.
27. Gibbons RM, Liu X, Pulko V, et al. B7-H1 limits the entry of effector CD8(+) T cells to the memory pool by upregulating Bim. *Onco Targets Ther*. 2012;1:1061-1073.
28. Park JJ, Omiya R, Matsumura Y, et al. B7-H1/CD80 interaction is required for the induction and maintenance of peripheral T-cell tolerance. *Blood*. 2010;116:1291-1298.
29. Beswick EJ, Pinchuk IV, Das S, Powell DW, Reyes VE. Expression of the programmed death ligand 1, B7-H1, on gastric epithelial cells after *Helicobacter pylori* exposure promotes development of $CD4^{+}$ $CD25^{+}$ $FoxP^{3+}$ regulatory T cells. *Infect Immun*. 2007;75:4334-4341.
30. Francisco LM, Salinas VH, Brown KE, et al. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. *J Exp Med*. 2009;206:3015-3029.
31. Nwizu N, Wactawski-Wende J, Genco RJ. Periodontal disease and cancer: epidemiologic studies and possible mechanisms. *Periodontol 2000*. 2020;83:213-233.
32. Kang S, Zhang C, Ohno T, Azuma M. Unique B7-H1 expression on masticatory mucosae in the oral cavity and trans-coinhibition by B7-H1-expressing keratinocytes regulating $CD4^{(+)}$ T cell-mediated mucosal tissue inflammation. *Mucosal Immunol*. 2017;10:650-660.
33. Figueira EA, de Rezende ML, Torres SA, et al. Inhibitory signals mediated by programmed death-1 are involved with T-cell function in chronic periodontitis. *J Periodontol*. 2009;80:1833-1844.
34. Zhang J, Wang CM, Zhang P, et al. Expression of programmed death 1 ligand 1 on periodontal tissue cells as a possible protective feedback mechanism against periodontal tissue destruction. *Mol Med Rep*. 2016;13:2423-2430.
35. Zhou K, Sun M, Xia Y, Xie Y, Shu R. LPS stimulates gingival fibroblasts to express PD-L1 via the p38 pathway under periodontal inflammatory conditions. *Arch Oral Biol*. 2021;129:105161.
36. Tymkiw KD, Thunell DH, Johnson GK, et al. Influence of smoking on gingival crevicular fluid cytokines in severe chronic periodontitis. *J Clin Periodontol*. 2011;38:219-228.
37. Shelby A, Pendleton C, Thayer E, Johnson GK, Xie XJ, Brogden KA. PD-L1 correlates with chemokines and cytokines in gingival crevicular fluid from healthy and diseased sites in subjects with periodontitis. *BMC Res Notes*. 2020;13:532.
38. Yu J, Lin Y, Xiong X, et al. Detection of exosomal PD-L1 RNA in saliva of patients with periodontitis. *Front Genet*. 2019;10:202.
39. Zhu D, Liu F, Dai F, Luo X, Hong B. Expression of programmed death-1 and programmed death ligand-1 in the peripheral T-lymphocytes from patients with chronic periodontitis. *Zhonghua Kou Qiang Yi Xue Za Zhi*. 2014;49:216-219.
40. Yuan W, Wang X, Zhang J, et al. Programmed death ligand 1 negatively regulates inflammatory response of chronic periodontitis. *Hua Xi Kou Qiang Yi Xue Za Zhi*. 2015;33:366-369.
41. Delgado RJR, Pinheiro CR, Gasparoto TH, et al. CAMPANELLIProgrammed death 1 (PD-1) and PD-1 ligand (PD-L1) expression in chronic apical periodontitis. *Eur Endod J*. 2019;4:3-8.
42. De la Rosa-Ruiz MDP, Alvarez-Perez MA, Cortes-Morales VA, et al. Mesenchymal stem/stromal cells derived from dental tissues: a comparative in vitro evaluation of their immunoregulatory properties against T cells. *Cells*. 2019;8:1491.
43. Groeger S, Domann E, Gonzales JR, Chakraborty T, Meyle J. B7-H1 and B7-DC receptors of oral squamous carcinoma cells are upregulated by *Porphyromonas gingivalis*. *Immunobiology*. 2011;216:1302-1310.
44. Gaddis DE, Maynard CL, Weaver CT, Michalek SM, Katz J. Role of TLR2-dependent IL-10 production in the inhibition of the initial IFN-gamma T cell response to *Porphyromonas gingivalis*. *J Leukoc Biol*. 2013;93:21-31.
45. Groeger S, Jarzina F, Mamat U, Meyle J. Induction of B7-H1 receptor by bacterial cells fractions of *Porphyromonas gingivalis* on human oral epithelial cells: B7-H1 induction by *Porphyromonas gingivalis* fractions. *Immunobiology*. 2017;222:137-147.
46. Groeger S, Denter F, Lochnit G, Schmitz ML, Meyle J. *Porphyromonas gingivalis* cell wall components induce PD-L1 expression on human oral carcinoma cells by a RIP2-dependent mechanism. *Infect Immun*. 2020;88:e00051–20.
47. Bailly C. The implication of the PD-1/PD-L1 checkpoint in chronic periodontitis suggests novel therapeutic opportunities with natural products. *Jpn Dent Sci Rev*. 2020;56:90-96.
48. Bray VJ, Dhillon HM, Vardy JL. Systematic review of self-reported cognitive function in cancer patients following chemotherapy treatment. *J Cancer Surviv*. 2018;12:537-559.
49. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. *Mayo Clin Proc*. 2008;83:489-501.
50. Sacco AG, Cohen EE. Current treatment options for recurrent or metastatic head and neck squamous cell carcinoma. *J Clin Oncol*. 2015;33:3305-3313.
51. Gyrd-Hansen M, Meier P. IAPs: from caspase inhibitors to modulators of NF-kappaB, inflammation and cancer. *Nat Rev Cancer*. 2010;10:561-574.
52. Uppaluri R, Dunn GP, Lewis JS Jr. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in head and neck cancers. *Cancer Immun*. 2008;8:16.

53. Okazaki T, Honjo T. The PD-1-PD-L pathway in immunological tolerance. *Trends Immunol*. 2006;27:195-201.
54. Tsushima F, Yao S, Shin T, et al. Interaction between B7-H1 and PD-1 determines initiation and reversal of T-cell anergy. *Blood*. 2007;110:180-185.
55. Azuma T, Yao S, Zhu G, Flies AS, Flies SJ, Chen L. B7-H1 is a ubiquitous antiapoptotic receptor on cancer cells. *Blood*. 2008;111:3635-3643.
56. Duraiswamy J, Kaluza KM, Freeman GJ, Coukos G. Dual blockade of PD-1 and CTLA-4 combined with tumor vaccine effectively restores T-cell rejection function in tumors. *Cancer Res*. 2013;73:3591-3603.
57. Wang W, Lau R, Yu D, Zhu W, Korman A, Weber J. PD1 blockade reverses the suppression of melanoma antigen-specific CTL by CD4+ CD25(Hi) regulatory T cells. *Int Immunol*. 2009;21:1065-1077.
58. Ghosh C, Luong G, Sun Y. A snapshot of the PD-1/PD-L1 pathway. *J Cancer*. 2021;12:2735-2746.
59. Zandberg DP, Strome SE. The role of the PD-L1:PD-1 pathway in squamous cell carcinoma of the head and neck. *Oral Oncol*. 2014;50:627-632.
60. Strome SE, Dong H, Tamura H, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. *Cancer Res*. 2003;63:6501-6505.
61. Tsushima F, Tanaka K, Otsuki N, et al. Predominant expression of B7-H1 and its immunoregulatory roles in oral squamous cell carcinoma. *Oral Oncol*. 2006;42:268-274.
62. Ohigashi Y, Sho M, Yamada Y, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. *Clin Cancer Res*. 2005;11:2947-2953.
63. Vakkila J, Lotze MT. Inflammation and necrosis promote tumour growth. *Nat Rev Immunol*. 2004;4:641-648.
64. Ghebeh H, Mohammed S, Al-Omair A, et al. The B7-H1 (PD-L1) T lymphocyte-inhibitory molecule is expressed in breast cancer patients with infiltrating ductal carcinoma: correlation with important high-risk prognostic factors. *Neoplasia*. 2006;8:190-198.
65. Thompson RH, Kwon ED. Significance of B7-H1 overexpression in kidney cancer. *Clin Genitourin Cancer*. 2006;5:206-211.
66. Wintterle S, Schreiner B, Mitsdoerffer M, et al. Expression of the B7-related molecule B7-H1 by glioma cells: a potential mechanism of immune paralysis. *Cancer Res*. 2003;63:7462-7467.
67. Wu CP, Jiang JT, Tan M, et al. Relationship between co-stimulatory molecule B7-H3 expression and gastric carcinoma histology and prognosis. *World J Gastroenterol*. 2006;12:457-459.
68. Gupta PC, Murti PR, Bhonsle RB. Epidemiology of cancer by tobacco products and the significance of TSNA. *Crit Rev Toxicol*. 1996;26:183-198.
69. Moreno-Lopez LA, Esparza-Gomez GC, Gonzalez-Navarro A, Cerero-Lapiedra R, Gonzalez-Hernandez MJ, Dominguez-Rojas V. Risk of oral cancer associated with tobacco smoking, alcohol consumption and oral hygiene: a case-control study in Madrid, Spain. *Oral Oncol*. 2000;36:170-174.
70. Reichart PA. Oral mucosal lesions in a representative cross-sectional study of aging Germans. *Community Dent Oral Epidemiol*. 2000;28:390-398.
71. Zheng TZ, Boyle P, Hu HF, et al. Dentition, oral hygiene, and risk of oral cancer: a case-control study in Beijing, People's Republic of China. *Cancer Causes Control*. 1990;1:235-241.
72. Weber M, Wehrhan F, Baran C, et al. PD-L1 expression in tumor tissue and peripheral blood of patients with oral squamous cell carcinoma. *Oncotarget*. 2017;8:112584-112597.
73. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. *Nat Rev Immunol*. 2008;8:467-477.
74. Thompson RH, Dong H, Kwon ED. Implications of B7-H1 expression in clear cell carcinoma of the kidney for prognostication and therapy. *Clin Cancer Res*. 2007;13:709s-715s.
75. Thompson RH, Gillett MD, Cheville JC, et al. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. *Cancers*. 2005;104:2084-2091.
76. Nakanishi J, Wada Y, Matsumoto K, Azuma M, Kikuchi K, Ueda S. Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. *Cancer Immunol Immunother*. 2007;56:1173-1182.
77. Groeger S, Howaldt HP, Raifer H, Gattenloehner S, Chakraborty T, Meyle J. Oral squamous carcinoma cells express B7-H1 and B7-DC receptors in vivo. *Pathol Oncol Res*. 2017;23:99-110.
78. Seiwert TYBB, Weiss J. A phase Ib study of MK-3475 in patients with human papillomavirus (HPV)-associated and non-HPV–associated head and neck (H/N) cancer. *J Clin Oncol*. 2014;32(Suppl 5S):6011.
79. Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G. Inflammation and cancer: how hot is the link? *Biochem Pharmacol*. 2006;72:1605-1621.
80. Grange JM, Krone B, Mastrangelo G. Infection, inflammation and cancer. *Int J Cancer*. 2011;128:2240-2241.
81. Eiro N, Vizoso FJ. Inflammation and cancer. *World J Gastrointest Surg*. 2012;4:62-72.
82. Mantovani A, Pierotti MA. Cancer and inflammation: a complex relationship. *Cancer Lett*. 2008;267:180-181.
83. Sun Y, Liu N, Guan X, Wu H, Sun Z, Zeng H. Immunosuppression induced by chronic inflammation and the progression to oral squamous cell carcinoma. *Mediators Inflamm*. 2016;2016:5715719.
84. Zhou L, Chong MM, Littman DR. Plasticity of CD4+ T cell lineage differentiation. *Immunity*. 2009;30:646-655.
85. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454:436-444.
86. Gaur P, Singh AK, Shukla NK, Das SN. Inter-relation of Th1, Th2, Th17 and Treg cytokines in oral cancer patients and their clinical significance. *Hum Immunol*. 2014;75:330-337.
87. Dutta A, Banerjee A, Saikia N, Phookan J, Baruah MN, Baruah S. Negative regulation of natural killer cell in tumor tissue and peripheral blood of oral squamous cell carcinoma. *Cytokine*. 2015;76:123-130.
88. Tan TT, Coussens LM. Humoral immunity, inflammation and cancer. *Curr Opin Immunol*. 2007;19:209-216.
89. Whiteside TL. The tumor microenvironment and its role in promoting tumor growth. *Oncogene*. 2008;27:5904-5912.
90. Aggarwal BB, Gehlot P. Inflammation and cancer: how friendly is the relationship for cancer patients? *Curr Opin Pharmacol*. 2009;9:351-369.
91. Arias JI, Aller MA, Arias J. Cancer cell: using inflammation to invade the host. *Mol Cancer*. 2007;6:29.
92. Moore MM, Chua W, Charles KA, Clarke SJ. Inflammation and cancer: causes and consequences. *Clin Pharmacol Ther*. 2010;87:504-508.
93. Alexandrescu DT, Riordan NH, Ichim TE, et al. On the missing link between inflammation and cancer. *Dermatol Online J*. 2011;17:10.
94. Atanasova KR, Yilmaz O. Looking in the *Porphyromonas gingivalis* cabinet of curiosities: the microbium, the host and cancer association. *Mol Oral Microbiol*. 2014;29:55-66.
95. Ahn J, Segers S, Hayes RB. Periodontal disease, *Porphyromonas gingivalis* serum antibody levels and orodigestive cancer mortality. *Carcinogenesis*. 2012;33:1055-1058.
96. Fan X, Alekseyenko AV, Wu J, et al. Human oral microbiome and prospective risk for pancreatic cancer: a population-based nested case-control study. *Gut*. 2018;67:120-127.
97. Fitzpatrick SG, Katz J. The association between periodontal disease and cancer: a review of the literature. *J Dent*. 2010;38:83-95.
98. Gao SG, Yang JQ, Ma ZK, et al. Preoperative serum immunoglobulin G and A antibodies to *Porphyromonas gingivalis* are potential serum biomarkers for the diagnosis and prognosis of esophageal squamous cell carcinoma. *BMC Cancer*. 2018;18:17.

99. Gholizadeh P, Eslami H, Yousefi M, Asgharzadeh M, Aghazadeh M, Kafil HS. Role of oral microbiome on oral cancers, a review. *Biomed Pharmacother*. 2016;84:552-558.
100. Meyer MS, Joshipura K, Giovannucci E, Michaud DS. A review of the relationship between tooth loss, periodontal disease, and cancer. *Cancer Causes Control*. 2008;19:895-907.
101. Tezal M, Sullivan MA, Hyland A, et al. Chronic periodontitis and the incidence of head and neck squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev*. 2009;18:2406-2412.
102. Wu-chao W, Yafei W, Lei Z. Research progress on the relationship between *Porphyromonas gingivalis* and oral squamous cell carcinoma. *Hua Xi Kou Qiang Yi Xue Za Zhi*. 2015;33:651-655.
103. Yao QW, Zhou DS, Peng HJ, Ji P, Liu DS. Association of periodontal disease with oral cancer: a meta-analysis. *Tumour Biol*. 2014;35:7073-7077.
104. Sayehmiri F, Sayehmiri K, Asadollahi K, et al. The prevalence rate of *Porphyromonas gingivalis* and its association with cancer: a systematic review and meta-analysis. *Int J Immunopathol Pharmacol*. 2015;28:160-167.
105. Park DG, Woo BH, Lee BJ, et al. Serum levels of interleukin-6 and titers of antibodies against *Porphyromonas gingivalis* could Be potential biomarkers for the diagnosis of oral squamous cell carcinoma. *Int J Mol Sci*. 2019;20:2749.
106. Geng F, Wang Q, Li C, et al. Identification of potential candidate genes of Oral cancer in response to chronic infection with *Porphyromonas gingivalis* using bioinformatical analyses. *Front Oncol*. 2019;9:91.
107. Concha-Benavente F, Srivastava RM, Trivedi S, et al. Identification of the cell-intrinsic and -extrinsic pathways downstream of EGFR and IFNgamma that induce PD-L1 expression in head and neck cancer. *Cancer Res*. 2016;76:1031-1043.
108. Korman AJ, Peggs KS, Allison JP. Checkpoint blockade in cancer immunotherapy. *Adv Immunol*. 2006;90:297-339.
109. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12:252-264.
110. Aziz S, Ahmed SS, Ali A, et al. Salivary immunosuppressive cytokines IL-10 and IL-13 are significantly elevated in oral squamous cell carcinoma patients. *Cancer Invest*. 2015;33:318-328.
111. Goncalves AS, Arantes DA, Bernardes VF, et al. Immunosuppressive mediators of oral squamous cell carcinoma in tumour samples and saliva. *Hum Immunol*. 2015;76:52-58.
112. Baltacioglu E, Yuva P, Aydin G, et al. Lipid peroxidation levels and total oxidant/antioxidant status in serum and saliva from patients with chronic and aggressive periodontitis. Oxidative stress index: a new biomarker for periodontal disease? *J Periodontol*. 2014;85:1432-1441.
113. Recker EN, Brogden KA, Avila-Ortiz G, et al. Novel biomarkers of periodontitis and/or obesity in saliva-an exploratory analysis. *Arch Oral Biol*. 2015;60:1503-1509.
114. Tkach M, Thery C. Communication by extracellular vesicles: where we are and where we need to go. *Cell*. 2016;164:1226-1232.
115. Byun JS, Hong SH, Choi JK, Jung JK, Lee HJ. Diagnostic profiling of salivary exosomal microRNAs in oral lichen planus patients. *Oral Dis*. 2015;21:987-993.
116. Michael A, Bajracharya SD, Yuen PS, et al. Exosomes from human saliva as a source of microRNA biomarkers. *Oral Dis*. 2010;16:34-38.
117. Sivadasan P, Gupta MK, Sathe GJ, et al. Human salivary proteome—a resource of potential biomarkers for oral cancer. *J Proteomics*. 2015;127:89-95.
118. Zheng X, Chen F, Zhang Q, et al. Salivary exosomal PSMA7: a promising biomarker of inflammatory bowel disease. *Protein Cell*. 2017;8:686-695.
119. Takahashi H, Sakakura K, Arisaka Y, et al. Clinical and biological significance of PD-L1 expression within the tumor microenvironment of oral squamous cell carcinoma. *Anticancer Res*. 2019;39:3039-3046.
120. Sato T, Watanabe K, Kumada H, Toyama T, Tani-Ishii N, Hamada N. Peptidoglycan of *Actinomyces naeslundii* induces inflammatory cytokine production and stimulates osteoclastogenesis in alveolar bone resorption. *Arch Oral Biol*. 2012;57:1522-1528.
121. Michikawa C, Gopalakrishnan V, Harrandah AM, et al. Fusobacterium is enriched in oral cancer and promotes induction of programmed death-ligand 1 (PD-L1). *Neoplasia*. 2022;31:100813.
122. Dongre A, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. *Nat Rev Mol Cell Biol*. 2019;20:69-84.
123. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. *J Clin Invest*. 2009;119:1420-1428.
124. Nieto MA. Epithelial-mesenchymal transitions in development and disease: old views and new perspectives. *Int J Dev Biol*. 2009;53:1541-1547.
125. Nieto MA, Huang RY, Jackson RA, Thiery JP. Emt: 2016. *Cell*. 2016;166:21-45.
126. Thiery JP, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. *Cell*. 2009;139:871-890.
127. Ye X, Tam WL, Shibue T, et al. Distinct EMT programs control normal mammary stem cells and tumour-initiating cells. *Nature*. 2015;525:256-260.
128. Alsuliman A, Colak D, Al-Harazi O, et al. Bidirectional crosstalk between PD-L1 expression and epithelial to mesenchymal transition: significance in claudin-low breast cancer cells. *Mol Cancer*. 2015;14:149.
129. Qiu XY, Hu DX, Chen WQ, et al. PD-L1 confers glioblastoma multiforme malignancy via Ras binding and Ras/Erk/EMT activation. *Biochim Biophys Acta Mol Basis Dis*. 2018;1864:1754-1769.
130. Wang Y, Wang H, Zhao Q, Xia Y, Hu X, Guo J. PD-L1 induces epithelial-to-mesenchymal transition via activating SREBP-1c in renal cell carcinoma. *Med Oncol*. 2015;32:212.
131. Hsu JM, Xia W, Hsu YH, et al. STT3-dependent PD-L1 accumulation on cancer stem cells promotes immune evasion. *Nat Commun*. 2018;9:1908.
132. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. *Annu Rev Immunol*. 2004;22:329-360.
133. Reiman JM, Kmieciak M, Manjili MH, Knutson KL. Tumor immunoediting and immunosculpting pathways to cancer progression. *Semin Cancer Biol*. 2007;17:275-287.
134. Knutson KL, Lu H, Stone B, et al. Immunoediting of cancers may lead to epithelial to mesenchymal transition. *J Immunol*. 2006;177:1526-1533.
135. Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. *Mol Cancer Res*. 2006;4:221-233.
136. Zhao XW, Zhou JP, Bi YL, et al. The role of MAPK signaling pathway in formation of EMT in oral squamous carcinoma cells induced by TNF-alpha. *Mol Biol Rep*. 2019;46:3149-3156.
137. Wu T, Tang C, Tao R, Yong X, Jiang Q, Feng C. PD-L1-mediated immunosuppression in oral squamous cell carcinoma: relationship with macrophage infiltration and epithelial to mesenchymal transition markers. *Front Immunol*. 2021;12:693881.
138. Zhang H, Qin G, Zhang C, et al. TRAIL promotes epithelial-to-mesenchymal transition by inducing PD-L1 expression in esophageal squamous cell carcinomas. *J Exp Clin Cancer Res*. 2021;40:209.
139. Kim S, Koh J, Kim MY, et al. PD-L1 expression is associated with epithelial-to-mesenchymal transition in adenocarcinoma of the lung. *Hum Pathol*. 2016;58:7-14.
140. Lou Y, Diao L, Cuentas ER, et al. Epithelial-mesenchymal transition is associated with a distinct tumor microenvironment including elevation of inflammatory signals and multiple immune checkpoints in lung adenocarcinoma. *Clin Cancer Res*. 2016;22:3630-3642.

141. Ock CY, Kim S, Keam B, et al. PD-L1 expression is associated with epithelial-mesenchymal transition in head and neck squamous cell carcinoma. *Oncotarget*. 2016;7:15901-15914.
142. Dongre A, Rashidian M, Reinhardt F, et al. Epithelial-to-mesenchymal transition contributes to immunosuppression in breast carcinomas. *Cancer Res*. 2017;77:3982-3989.
143. Tsutsumi S, Saeki H, Nakashima Y, et al. Programmed death-ligand 1 expression at tumor invasive front is associated with epithelial-mesenchymal transition and poor prognosis in esophageal squamous cell carcinoma. *Cancer Sci*. 2017;108:1119-1127.
144. Henriksen A, Dyhl-Polk A, Chen I, Nielsen D. Checkpoint inhibitors in pancreatic cancer. *Cancer Treat Rev*. 2019;78:17-30.
145. Zheng L. PD-L1 expression in pancreatic cancer. *J Natl Cancer Inst*. 2017;109:djw304.
146. Burger GA, Nesenberend DN, Lems CM, Hille SC, Beltman JB. Bidirectional crosstalk between epithelial-mesenchymal plasticity and IFNgamma-induced PD-L1 expression promotes tumour progression. *R Soc Open Sci*. 2022;9:220186.
147. Cai Z, Yang F, Yu L, et al. Activated T cell exosomes promote tumor invasion via Fas signaling pathway. *J Immunol*. 2012;188:5954-5961.
148. Kalluri R. The biology and function of exosomes in cancer. *J Clin Invest*. 2016;126:1208-1215.
149. Zhang L, Yu D. Exosomes in cancer development, metastasis, and immunity. *Biochim Biophys Acta Rev Cancer*. 2019;1871:455-468.
150. Yang F, Ning Z, Ma L, et al. Exosomal miRNAs and miRNA dysregulation in cancer-associated fibroblasts. *Mol Cancer*. 2017;16:148.
151. Ma P, Pan Y, Li W, et al. Extracellular vesicles-mediated noncoding RNAs transfer in cancer. *J Hematol Oncol*. 2017;10:57.
152. Kim SH, Bianco NR, Shufesky WJ, Morelli AE, Robbins PD. MHC class II+ exosomes in plasma suppress inflammation in an antigen-specific and Fas ligand/Fas-dependent manner. *J Immunol*. 2007;179:2235-2241.
153. Greening DW, Gopal SK, Xu R, Simpson RJ, Chen W. Exosomes and their roles in immune regulation and cancer. *Semin Cell Dev Biol*. 2015;40:72-81.
154. Ristorcelli E, Beraud E, Verrando P, et al. Human tumor nanoparticles induce apoptosis of pancreatic cancer cells. *FASEB J*. 2008;22:3358-3369.
155. Guo D, Chen Y, Wang S, et al. Exosomes from heat-stressed tumour cells inhibit tumour growth by converting regulatory T cells to Th17 cells via IL-6. *Immunology*. 2018;154:132-143.
156. Yao Y, Chen L, Wei W, Deng X, Ma L, Hao S. Tumor cell-derived exosome-targeted dendritic cells stimulate stronger CD8 + CTL responses and antitumor immunities. *Biochem Biophys Res Commun*. 2013;436:60-65.
157. Rao Q, Zuo B, Lu Z, et al. Tumor-derived exosomes elicit tumor suppression in murine hepatocellular carcinoma models and humans in vitro. *Hepatology*. 2016;64:456-472.
158. Huang F, Wan J, Hao S, Deng X, Chen L, Ma L. TGF-beta1-silenced leukemia cell-derived exosomes target dendritic cells to induce potent anti-leukemic immunity in a mouse model. *Cancer Immunol Immunother*. 2017;66:1321-1331.
159. Huang F, Wan J, Hu W, Hao S. Enhancement of anti-leukemia immunity by leukemia-derived exosomes via downregulation of TGF-beta1 expression. *Cell Physiol Biochem*. 2017;44:240-254.
160. Lu Z, Zuo B, Jing R, et al. Dendritic cell-derived exosomes elicit tumor regression in autochthonous hepatocellular carcinoma mouse models. *J Hepatol*. 2017;67:739-748.
161. Seo N, Shirakura Y, Tahara Y, et al. Activated CD8(+) T cell extracellular vesicles prevent tumour progression by targeting of lesional mesenchymal cells. *Nat Commun*. 2018;9:435.
162. Zhu L, Kalimuthu S, Gangadaran P, et al. Exosomes derived from natural killer cells exert therapeutic effect in melanoma. *Theranostics*. 2017;7:2732-2745.
163. Tung KH, Ernstoff MS, Allen C, Shu S. A review of exosomes and their role in the tumor microenvironment and host-tumor "Macroenvironment". *J Immunol Sci*. 2019;3:4-8.
164. Ning Y, Shen K, Wu Q, et al. Tumor exosomes block dendritic cells maturation to decrease the T cell immune response. *Immunol Lett*. 2018;199:36-43.
165. Harada K, Dong X, Estrella JS, et al. Tumor-associated macrophage infiltration is highly associated with PD-L1 expression in gastric adenocarcinoma. *Gastric Cancer*. 2018;21:31-40.
166. Li L, Cao B, Liang X, et al. Microenvironmental oxygen pressure orchestrates an anti- and pro-tumoral gammadelta T cell equilibrium via tumor-derived exosomes. *Oncogene*. 2019;38:2830-2843.
167. Liu J, Fan L, Yu H, et al. Endoplasmic reticulum stress causes liver cancer cells to release exosomal miR-23a-3p and up-regulate programmed death ligand 1 expression in macrophages. *Hepatology*. 2019;70:241-258.
168. Cheng L, Liu J, Liu Q, et al. Exosomes from melatonin treated hepatocellularcarcinoma cells Alter the immunosupression status through STAT3 pathway in macrophages. *Int J Biol Sci*. 2017;13:723-734.
169. Haderk F, Schulz R, Iskar M, et al. Tumor-derived exosomes modulate PD-L1 expression in monocytes. *Sci Immunol*. 2017;2:eaah5509.
170. Wei Y, Zhao Q, Gao Z, et al. The local immune landscape determines tumor PD-L1 heterogeneity and sensitivity to therapy. *J Clin Invest*. 2019;129:3347-3360.
171. Abiko K, Matsumura N, Hamanishi J, et al. IFN-gamma from lymphocytes induces PD-L1 expression and promotes progression of ovarian cancer. *Br J Cancer*. 2015;112:1501-1509.
172. Garcia-Diaz A, Shin DS, Moreno BH, et al. Interferon receptor signaling pathways regulating PD-L1 and PD-L2 expression. *Cell Rep*. 2017;19:1189-1201.
173. Ruffell B, Coussens LM. Macrophages and therapeutic resistance in cancer. *Cancer Cell*. 2015;27:462-472.
174. Kasikara C, Kumar S, Kimani S, et al. Phosphatidylserine sensing by TAM receptors regulates AKT-dependent chemoresistance and PD-L1 expression. *Mol Cancer Res*. 2017;15:753-764.
175. Seo N, Akiyoshi K, Shiku H. Exosome-mediated regulation of tumor immunology. *Cancer Sci*. 2018;109:2998-3004.
176. Chen G, Huang AC, Zhang W, et al. Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. *Nature*. 2018;560:382-386.
177. Ye L, Zhu Z, Chen X, et al. The importance of exosomal PD-L1 in cancer progression and its potential as a therapeutic target. *Cells*. 2021;10:3247.
178. Ludwig S, Floros T, Theodoraki MN, et al. Suppression of lymphocyte functions by plasma exosomes correlates with disease activity in patients with head and neck cancer. *Clin Cancer Res*. 2017;23:4843-4854.
179. Theodoraki MN, Yerneni SS, Hoffmann TK, Gooding WE, Whiteside TL. Clinical significance of PD-L1(+) exosomes in plasma of head and neck cancer patients. *Clin Cancer Res*. 2018;24:896-905.
180. Bailly C, Thuru X, Quesnel B. Soluble programmed death ligand-1 (sPD-L1): a pool of circulating proteins implicated in health and diseases. *Cancers*. 2021;13:3034.
181. Chen L, Mo DC, Hu M, Zhao SJ, Yang QW, Huang ZL. PD-1/PD-L1 inhibitor monotherapy in recurrent or metastatic squamous cell carcinoma of the head and neck: a meta-analysis. *Am J Otolaryngol*. 2022;43:103324.
182. Luke JJ, Rutkowski P, Queirolo P, et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial. *Lancet*. 2022;399:1718-1729.
183. Saito Y, Fujiwara Y, Shinchi Y, et al. Classification of PD-L1 expression in various cancers and macrophages based on immunohistocytological analysis. *Cancer Sci*. 2022;113:3255-3266.

184. Banchereau R, Chitre AS, Scherl A, et al. Intratumoral CD103+ CD8+ T cells predict response to PD-L1 blockade. *J Immunother Cancer*. 2021;9:e002231.
185. Pena-Asensio J, Calvo H, Torralba M, Miquel J, Sanz-de-Villalobos E, Larrubia JR. Anti-PD-1/PD-L1 based combination immunotherapy to boost antigen-specific CD8(+) T cell response in hepatocellular carcinoma. *Cancers*. 2021;13:1922.
186. Song D, Powles T, Shi L, Zhang L, Ingersoll MA, Lu YJ. Bladder cancer, a unique model to understand cancer immunity and develop immunotherapy approaches. *J Pathol*. 2019;249:151-165.
187. Zhu HH, Feng Y, Hu XS. Emerging immunotherapy targets in lung cancer. *Chin Med J*. 2020;133:2456-2465.
188. Daud AI, Wolchok JD, Robert C, et al. Programmed death-ligand 1 expression and response to the anti-programmed death 1 antibody pembrolizumab in melanoma. *J Clin Oncol*. 2016;34:4102-4109.
189. Zandberg DP, Algazi AP, Jimeno A, et al. Durvalumab for recurrent or metastatic head and neck squamous cell carcinoma: results from a single-arm, phase II study in patients with >/=25% tumour cell PD-L1 expression who have progressed on platinum-based chemotherapy. *Eur J Cancer*. 2019;107:142-152.
190. O'Neill RE, Cao X. Co-stimulatory and co-inhibitory pathways in cancer immunotherapy. *Adv Cancer Res*. 2019;143:145-194.
191. Schutz F, Stefanovic S, Mayer L, von Au A, Domschke C, Sohn C. PD-1/PD-L1 pathway in breast cancer. *Oncol Res Treat*. 2017;40:294-297.
192. Ai L, Xu A, Xu J. Roles of PD-1/PD-L1 pathway: signaling, cancer, and beyond. *Adv Exp Med Biol*. 2020;1248:33-59.
193. Duhen R, Fesneau O, Samson KA, et al. PD-1 and ICOS coexpression identifies tumor-reactive CD4+ T cells in human solid tumors. *J Clin Invest*. 2022;132:e156821.
194. Sun L, Li CW, Chung EM, et al. Targeting glycosylated PD-1 induces potent antitumor immunity. *Cancer Res*. 2020;80:2298-2310.
195. Hui E, Cheung J, Zhu J, et al. T cell costimulatory receptor CD28 is a primary target for PD-1-mediated inhibition. *Science*. 2017;355:1428-1433.
196. Kamphorst AO, Wieland A, Nasti T, et al. Rescue of exhausted CD8 T cells by PD-1-targeted therapies is CD28-dependent. *Science*. 2017;355:1423-1427.
197. Liu Y, Wu L, Tong R, et al. PD-1/PD-L1 inhibitors in cervical cancer. *Front Pharmacol*. 2019;10:65.
198. Xia L, Liu Y, Wang Y. PD-1/PD-L1 blockade therapy in advanced non-small-cell lung cancer: current status and future directions. *Oncologist*. 2019;24:S31-S41.
199. Wang Z, Wu X. Study and analysis of antitumor resistance mechanism of PD1/PD-L1 immune checkpoint blocker. *Cancer Med*. 2020;9:8086-8121.
200. Cao Z, Kon N, Liu Y, et al. An unexpected role for p53 in regulating cancer cell-intrinsic PD-1 by acetylation. *Sci Adv*. 2021;7:eabf4148.
201. Yao H, Wang H, Li C, Fang JY, Xu J. Cancer cell-intrinsic PD-1 and implications in combinatorial immunotherapy. *Front Immunol*. 2018;9:1774.
202. Tang Q, Chen Y, Li X, et al. The role of PD-1/PD-L1 and application of immune-checkpoint inhibitors in human cancers. *Front Immunol*. 2022;13:964442.
203. Leko V, Rosenberg SA. Identifying and targeting human tumor antigens for T cell-based immunotherapy of solid tumors. *Cancer Cell*. 2020;38:454-472.
204. Burr ML, Sparbier CE, Chan KL, et al. An evolutionarily conserved function of Polycomb silences the MHC class I antigen presentation pathway and enables immune evasion in cancer. *Cancer Cell*. 2019;36:385-401.e8.
205. Dersh D, Phelan JD, Gumina ME, et al. Genome-wide screens identify lineage- and tumor-specific genes modulating MHC-I- and MHC-II-restricted immunosurveillance of human lymphomas. *Immunity*. 2021;54:116-131.e10.
206. Ghasemi F, Tessier TM, Gameiro SF, Maciver AH, Cecchini MJ, Mymryk JS. High MHC-II expression in Epstein-Barr virus-associated gastric cancers suggests that tumor cells serve an important role in antigen presentation. *Sci Rep*. 2020;10:14786.
207. Tu K, Yu Y, Wang Y, et al. Combination of chidamide-mediated epigenetic modulation with immunotherapy: boosting tumor immunogenicity and response to PD-1/PD-L1 blockade. *ACS Appl Mater Interfaces*. 2021;13:39003-39017.
208. Neuwelt AJ, Kimball AK, Johnson AM, et al. Cancer cell-intrinsic expression of MHC II in lung cancer cell lines is actively restricted by MEK/ERK signaling and epigenetic mechanisms. *J Immunother Cancer*. 2020;8:e000441.
209. Shenoy AT, Lyon De Ana C, Arafa EI, et al. Antigen presentation by lung epithelial cells directs CD4(+) T(RM) cell function and regulates barrier immunity. *Nat Commun*. 2021;12:5834.
210. Yang Y, Zhou T, Chen X, et al. Efficacy, safety, and biomarker analysis of camrelizumab in previously treated recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN study). *J Immunother Cancer*. 2021;9:e003790.
211. Kawakami Y, Ohta S, Sayem MA, Tsukamoto N, Yaguchi T. Immune-resistant mechanisms in cancer immunotherapy. *Int J Clin Oncol*. 2020;25:810-817.
212. Mariathasan S, Turley SJ, Nickles D, et al. TGFbeta attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. *Nature*. 2018;554:544-548.
213. Bullock BL, Kimball AK, Poczobutt JM, et al. Tumor-intrinsic response to IFNgamma shapes the tumor microenvironment and anti-PD-1 response in NSCLC. *Life Sci Alliance*. 2019;2:e201900328.
214. Gainor JF, Shaw AT, Sequist LV, et al. EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer: a retrospective analysis. *Clin Cancer Res*. 2016;22:4585-4593.
215. Antonios JP, Soto H, Everson RG, et al. Immunosuppressive tumor-infiltrating myeloid cells mediate adaptive immune resistance via a PD-1/PD-L1 mechanism in glioblastoma. *Neuro Oncol*. 2017;19:796-807.
216. Nowicki TS, Hu-Lieskovan S, Ribas A. Mechanisms of resistance to PD-1 and PD-L1 blockade. *Cancer J*. 2018;24:47-53.
217. Huang AC, Postow MA, Orlowski RJ, et al. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. *Nature*. 2017;545:60-65.
218. Koyama S, Akbay EA, Li YY, et al. Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. *Nat Commun*. 2016;7:10501.
219. Peng DH, Rodriguez BL, Diao L, et al. Collagen promotes anti-PD-1/PD-L1 resistance in cancer through LAIR1-dependent CD8(+) T cell exhaustion. *Nat Commun*. 2020;11:4520.
220. Veldman J, Visser L, Berg AVD, Diepstra A. Primary and acquired resistance mechanisms to immune checkpoint inhibition in Hodgkin lymphoma. *Cancer Treat Rev*. 2020;82:101931.
221. Skoulidis F, Goldberg ME, Greenawalt DM, et al. STK11/LKB1 mutations and PD-1 inhibitor resistance in KRAS-mutant lung adenocarcinoma. *Cancer Discov*. 2018;8:822-835.
222. Bai J, Gao Z, Li X, Dong L, Han W, Nie J. Regulation of PD-1/PD-L1 pathway and resistance to PD-1/PD-L1 blockade. *Oncotarget*. 2017;8:110693-110707.
223. Ribas A, Shin DS, Zaretsky J, et al. PD-1 blockade expands Intratumoral memory T cells. *Cancer Immunol Res*. 2016;4:194-203.
224. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science*. 2018;359:91-97.
225. Pathak R, Pharaon RR, Mohanty A, Villaflor VM, Salgia R, Massarelli E. Acquired resistance to PD-1/PD-L1 blockade in lung cancer: mechanisms and patterns of failure. *Cancers*. 2020;12:3851.

226. Patel SA, Minn AJ. Combination cancer therapy with immune checkpoint blockade: mechanisms and strategies. *Immunity*. 2018;48:417-433.
227. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;348:124-128.
228. Martin-Gayo E, Sierra-Filardi E, Corbi AL, Toribio ML. Plasmacytoid dendritic cells resident in human thymus drive natural Treg cell development. *Blood*. 2010;115:5366-5375.
229. Zhuang Y, Liu C, Liu J, Li G. Resistance mechanism of PD-1/PD-L1 blockade in the cancer-immunity cycle. *Onco Targets Ther*. 2020;13:83-94.

How to cite this article: Groeger S, Meyle J. The role of programmed death receptor (PD-)1/PD-ligand (L)1 in periodontitis and cancer. *Periodontol 2000*. 2024;96:150-169. doi:10.1111/prd.12548