

Generation and Immuno-inflammatory Checkpoints in Oral Cavity Cancers

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Abstract

Oral malignancies are responsible for a considerable portion of cancer-related deaths worldwide. Even though survival rates have increased recently, new treatments are being explored to slow the advancement of the disease and enhance outcomes, especially in cases of oral cavity squamous cell carcinoma (OSCC) and oral potentially malignant diseases (OPMDs). Immunotherapy is a novel therapeutic approach that targets immune checkpoint molecules such as programmed cell death protein-1 (PD-1) and its ligand programmed death-ligand 1 (PD-L1), cytotoxic T-lymphocyte antigen 4, lymphocyte-activated gene 3, and T cell immunoglobulin mucin 3 in order to enhance the host's immune response against malignancies and impede the growth and metastasis of cancer cells. Accordingly, a systematic review was performed by scanning five databases for keywords related to immune checkpoint inhibitors, along with oral malignancies, oral pathologies, and OPMDs, in order to describe the current state of their use and efficacy in these disorders. For this purpose, 644 unique publications published between 2004 and 2019 were found, 76 of which were judged to be appropriate for the study and produced 8826 samples. PD-1 and PD-L1 are expressed in most OPMD and OSCC samples, and their expression is associated with worse survival rates and greater rates of progression. Two immunotherapy drugs targeting PD-1, namely, pembrolizumab and nivolumab, have been demonstrated to enhance disease outcomes and increase survival rates, especially when combined with radiation or chemotherapy. Despite the equivocal nature of the available data, there is support for the prognostic and predictive usefulness of immune checkpoint molecules, notably PD-L1, and multiple studies support the useful use of immune checkpoint inhibitors in the management of OSCC.

Keywords: Generation, Oral cancer, Immune-check point

Introduction

The oral cavity extends from the vermilion border of the lips to the superior junction of the hard and soft palates, as well as the inferior circumvallate papillae of the tongue.¹ The lip, oral tongue, floor of the mouth, buccal mucosa, upper and lower gums, retromolar trigone, and hard palate are the anatomical subsites that together comprise the oral cavity. Despite their proximity, these subsites have unique anatomical features that should be taken into account when designing oncologic therapy.² The fifth decade of life is when oral cancer usually manifests itself in most men. About 1.5% of individuals will experience another synchronous primary in the lung, esophagus, or oral cavity of the aero-digestive tract. Nearly 10%–40% of metachronous cancers arise in the first ten years after the treatment of the index primary.^{3,4} Regular post-therapy surveillance and lifestyle adjustments are therefore crucial secondary preventive measures. Squamous cell carcinomas account for more than 90% of all oral cancer cases. Other malignant tumors can also arise from the epithelium, connective tissue,

small salivary glands, lymphoid tissue, melanocytes, and metastasis of a distant tumor. Numerous premalignant lesions have been connected to squamous cell carcinoma (SCC). Among the most common premalignant lesions, leukoplakia, erythroplakia, oral lichen planus, and oral submucous fibrosis all have different degrees of risk for developing into malignant transformation⁵. Based on the degree of dysplasia, premalignant lesions are classified as carcinoma in situ, mild, moderate, severe, and severe, according to the World Health Organization.

T Cell Activation and Regulation

Signals that are produced when the T cell receptor identifies the major histocompatibility complex (MHC) antigen are responsible for T cell activation. As stimulatory factors, the B molecule on the surface of the antigen-presenting cell (APC) and the CD28 molecule on the surface of the T cell carry out these signals. Checkpoints both centrally and peripherally control T lymphocytes. Bidirectional T cell activation generates an inhibitory pathway that ultimately reduces the potency of the T cell response.⁶



Cytotoxic T Lymphocyte Antigen 4

CTLA-4, or cytotoxic T lymphocyte antigen 4, which is mostly expressed in T cells, was identified as the first immune checkpoint receptor to be targeted. Activated B cells, monocytes, granulocytes, and dendritic cells (DCs) express these factors at lower levels. Inducing T cell malfunction and contributing to the negative regulation of the immune response, CTLA-4 can bind the B7 protein. CTLA-4 has an inhibitory effect on normal tissues without causing undue harm, and cancer cells release transforming growth factor-beta (TGF-β), which can stimulate CTLA-4 expression and cause T cell exhaustion, which impairs T cell activity and suppresses the immune system. T cell function is lost as a result of CD28's greater affinity for CTLA-4 on T cell surfaces than for CD80 or CD86.⁷⁻⁹

Two ligands expressed on the surface of APC, CD80 and CD86, are bound by both CTLA-4 and CD28. Furthermore, CTLA-4 expression rises in response to T cell activation to the point where it finally blocks co-stimulation and deactivates T cells. Tregs express CTLA-4 as well. Some of the characteristics of CTLA-4 make it occasionally localize to the plasma membrane. About 90% of CTLA-4 is found inside cells. CTLA-4 induces endocytosis as well. Research indicates that lysosomal blockage has the ability to prevent CTLA-4 degradation¹⁰ (Figure 1).

Programmed Death Ligand 1/Programmed Cell Death Protein-1

Activated T cells and B cells express PD-1, a member of the CD28 receptor family. Monocytes and a tiny portion of thymocytes also contain this protein. Activated lymphocytes, endothelium, and epithelial APCs express PD-L1 and PD-L2, two ligands for PD-1, although PD-L1 is highly induced in hematological and solid cancers. The tumor cell overexpression of PD-L1 can encourage the growth of new tumors. Patients with poor prognoses and high tumor grades are closely correlated with high expression of PD-L1 in tumor cells. PD-1/PD-L1 signaling is triggered during inflammatory responses. Although Tregs' capacity to mediate immunological tolerance is hindered when PD-1 is inhibited, this does

not imply that PD-1 can directly control Treg function. In addition to diminishing antitumor T cell function, PD-L1 modifies the relationship between DCs, myeloid-derived suppressor cells, and Tregs. PD-1 and CTLA-4 share structural similarities and are members of the same protein family. DCs and activated macrophages both express the PD-L2 molecule. Cytokine production is suppressed, and lymphocyte proliferation is reduced by binding PD-L1 to PD-1. T cells become phosphorylated when PD1 binds to PDL-1, which in turn induces downstream kinase proteins to become dephosphorylated.^{11,12}

T Cell Immunoglobulin Mucin 3

Th2 cells do not express TIM-3; only cluster of differentiation 4 (CD4)+T helper 1 (Th1) lymphocytes express it. Tregs, DCs, monocytes, mast cells, natural killer (NK) cells, and tumor-infiltrating lymphocytes express it as well. Additionally, tumor cells, including melanoma and B-cell lymphoma cells, have TIM-3 on them. Research has indicated that T cell tolerance can be regulated by TIM-3 and its ligands. Galectin-9, a member of the galectin family, is the primary ligand for TIM-3. It has the ability to control a variety of biological processes in tumor cells, including adhesion, apoptosis, and aggregation. Moreover, it can impair Th1 and Th17 cell function while ultimately speeding up the Th1 cell apoptotic process. By secreting interferon-gamma (IFN-γ), TIM-3 + CD4 + cells exert anti-tumor actions in the early phases of tumor growth. Though research indicates that TIM-3 expression is not correlated with metastasis—which is not the case in lymph nodes—it is elevated in carcinomas and adenocarcinomas. Excessive production of TIM-3 leads to effector T cell fatigue, which can impede the antitumor immune response and tumor clearance. Tumorigenesis is dramatically reduced, and antitumor immune responses are enhanced when CD4 + and CD8 + T cell function is increased and suppressor cell activity is decreased.¹³⁻¹⁵

Lymphocyte-activated Gene 3

The immunoglobulin (Ig) superfamily, which includes this protein, is mostly expressed on activated T cells, while it can also be expressed on B cells, NK cells, and plasmacytoid DCs. LAG-3 acts similarly to CTLA-4 and PD-1.¹⁷, negatively modulating T cell proliferation, activation, and homeostasis. LAG-3 is essential to Tregs' ability to serve as inhibitors. LAG-3 has a higher affinity for MHC-II and shares the same protein sequence as the CD4 receptor. The connection between LAG-3 and MHC-II is not necessary for its effect on CD8 + T cell activity. Another ligand for LAG-3 is thought to be liver and lymph node sinusoidal endothelial cell C-type lectin (LSECTin), which is a member of the DC signaling family. LSECTin inhibits the anti-tumor immune response by binding to LAG-3 and reducing IFN-γ production in cancer. LAG-3 is essential for maintaining T cell homeostasis and is mostly expressed in Tregs. According to research, fibrinogen-like protein 1 (FGL1), a new

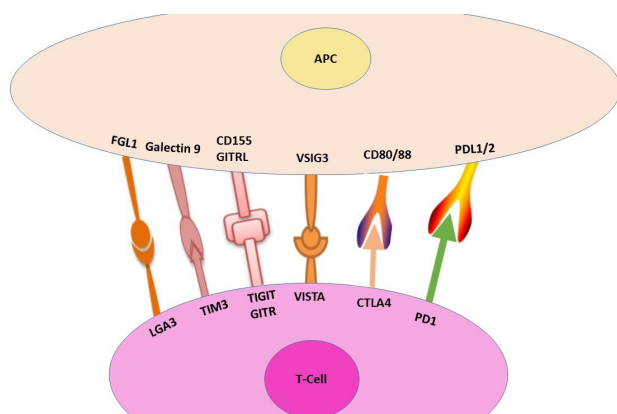


Figure 1. A Summary of Immune-check Points

ligand for LAG-3, functions as MHC-II independently as the primary functional ligand for LAG-3. FGL1 enhances T cell activity, inhibits antigen-specific T cell activation, and fortifies anti-tumor immunity.¹⁶⁻¹⁸

T Cell Immunoglobulin and Receptor Tyrosine-based Inhibitory Motif

TIGIT belongs to the family of poliovirus receptor/nectin, which is made up of four domains, including the type 1 transmembrane domain, the extracellular Ig (IgV) variable region domain, the classical ITIM, and the Ig tyrosine d motif. TIGIT lymphocytes express this immunoglobulin, particularly NK cells, follicular helper CD4+T cells, effector CD8+T cells, and regulatory and effector CD4+T cells. Moreover, endothelial cells, fibroblasts, DCs, and tumor cells all have high expression levels of this cell surface receptor.^{19,20}

Glucocorticoid-Induced Tumor Necrosis Factor Receptor Family Gene

Effector T cells, NK cells, and CD25+CD4+Tregs all express GITR, a new member of the TNFR superfamily. Treg recruitment is inhibited when GITR binds to its ligand. It reduces their inhibitory capacity and increases Nuclear factor kappa B (NF- κ B) signaling and the mitogen-activated protein kinase/signal-regulated kinase pathway. This gene triggers the release of pro-inflammatory cytokines, boosts T cell proliferation, and improves anti-tumor activity.²¹⁻²⁴

Immunoglobulin Domain V Suppressor of T Cell Activation

This molecule is known as Gi24, or embryonic stem cell differentiation 1, and functions similarly to PD-L1 in terms of function and potency in suppressing T cell activation. Numerous tumor models show that VISTA enhances antitumor immune blockade and is strongly expressed on tumor-infiltrating leukocytes.²⁵

V Suppressor of T Cell Activation and Programmed Cell Death Protein-1 Inhibit T Cells and Modulate T Cell Responses

On activated T cells, the interaction between ligand and VISTA suppresses T cell growth and chemokine and cytokine production. Blocking the VSIG3 pathway and its ligand may be a novel approach to cancer immunotherapy, as evidenced by the inhibition of ligands on activated T cells and the high expression of ligand in colorectal adenocarcinoma, hepatocellular carcinoma, and intestinal-type gastric cancer.²⁶⁻²⁸

Anti-inflammatory Function

Research has demonstrated that inflammation, which results in tissue damage and the release of particular inflammatory cytokines, raises the aggressiveness of oral malignancies. According to previous research, oral cavity squamous cell carcinoma (OSCC) can prevent cancer

from becoming malignant by expressing pro- or anti-inflammatory cytokines (TGF- β 1, interleukin [IL-10], IL-4, or IFN- γ , monocyte chemoattractant protein 1). Th cells, or Th cells, are functionally categorized as Th1, Th2, and Th17 cells and are mostly involved in tumor immunology.²⁹ While most Th1 cytokines, including IFN- γ , are classified as protumors, Th2 cytokines (IL-4, IL-5, and IL-10) are considered anti-inflammatory and are frequently linked to protumor activity. Patients with OSCC had significantly greater serum levels of IL-17A, TGF- β 1, IL-4, and IL-10 than the control group, but comparatively lower levels of IL-2 and IFN- γ . In patients with OSCC, the negative regulation of NK cells is linked to the increased production of IL-10 and TGF- β 1, as well as reduced IFN- γ .^{30,31}

Anti-inflammatory and Anti-tumor Cytokines

TGF- β and IL-10 are anti-inflammatory and immunosuppressive cytokines that lead to immunological suppression of neoplastic cells. They are also anti-tumor cytokines. The overexpression of IL-10 and TGF- β 2 is, in fact, linked to a worse prognosis for OSCCs. It suppresses dendritic and macrophage cells, controls regulatory T cell development, and builds tumor cells' resistance to the effects of cytotoxic T lymphocytes. IL-4, an additional anti-inflammatory cytokine, is regarded as proinflammatory as well.^{32,33} IL-17 is an inflammatory cytokine that is mostly released by neutrophils and type 17 T-helper cells. In OSCC, there has also been evidence of increased IL-17 expression. The advancement of tongue cancer is linked to IL-17 overexpression. The expression of IL-17 protein in the OSCC tissue is linked to a worse prognosis, including metastasis, recurrence, clinical stages, and T classification.³³

Therapeutic Approaches

A humanized IL-1 α neutralizing antibody called MABp1 (XBiotech Inc.) has been shown to enhance clinical outcomes and survival rates in patients with advanced non-small cell lung cancer, ovarian cancer, and other resistant malignancies.³⁴⁻³⁶

Targeting Tumor-Associated Macrophages

A novel treatment method is provided by manipulating protumorigenic M2 polarization to the anticancer M1 macrophage phenotype. Using poly (I:C) to stimulate TLR3/Toll-IL-1 receptor domain-containing adapter molecule 1, many proinflammatory cytokines, including IL-1 β , are secreted more quickly, and M1 macrophage polarization is accelerated.³⁷ Tumor-conditioned macrophages can be effectively stimulated to produce cytotoxic activity against cancer cells by the TLR3 agonist poly (I:C).³⁸

Conclusion

The tumor microenvironment (TME) of OSCC contains a variety of immune modulators, such as cytokines,

immune checkpoint inhibitors, and cellular elements. Within the TME, extrinsic and internal processes regulate these substances and cellular constituents. Targeting these processes with particular antibodies, miRNAs, and extracellular vesicles produced from T cells are some of the treatments available. Bisphosphonates can be used to stimulate alternate TAM differentiation as a novel treatment strategy. However, when it comes to optimizing treatment strategies, the elements of pre-tumor immunity remain incompletely known. Immunology and anesthesia transplantation may provide novel therapeutic benefits.

Competing Interests

None.

Ethical Approval

Not applicable.

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