REVIEW ARTICLE

Role of PD-L1 in Oral Cancer: From the Perspective of Immuno-oncology

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ABSTRACT

Oral cancers are prevalent in our region and their management requires an upgrade in terms of advanced techniques. Immunotherapy is a novel therapeutic approach across the world that has shown significance in the sphere of oncology. Tumor cells escape detection from the immune surveillance mechanism resulting in proliferation. Through cancer immunotherapy, body's own immune defense mechanism is stimulated with the aid of immunomodulating drugs. Scientists are underway studying the tumor microenvironment where immune editing takes place resulting in tumor escape and evasion. Many immune checkpoint proteins are being studied for clinical implications, however, the immune checkpoint blockade of Programmed death ligand-1(PD-L1) has proven to be successful and FDA approved in certain tumors. Role of increased expression of PD-L1 in oral cancer has been explored with variable results. Most researches have related it with tumor progression and prognosis. This review focuses on the importance of PD-L1 as an emerging immune checkpoint inhibitor, emphasizing its expression in cancers, particularly in oral cancer. The information was retrieved from reliable search engines e.g. PubMed, Medline, Google scholar and others, through original research papers and reviews published hitherto, from 2010-2019. It is essential to explore advanced treatment modalities for oral cancer especially via immunotherapy. Furthermore, additional studies on PD-L1 expression in OSCC are required including standardized protocols to reach definitive conclusions for clinical implications.

Keywords: Oral Squamous Cell Carcinoma; Programmed Death Ligand- 1(PD-L1), Immunotherapy, B7 Protein.

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INTRODUCTION

In the face of increasing diagnostic and treatment modalities, Head and Neck cancers remain to be 16th most common cancers as estimated by GLOBOCAN 2018[1]. Oral cancers is a subset of these cancers causing increased morbidity and mortality rates globally. In South Asian countries like Sri Lanka, India, Pakistan and Bangladesh there has been a dramatic increase in the prevalence of oral cancers[2]. In Pakistan, it is the second commonest cancer due to lack of awareness, diagnostic and therapeutic approaches and habits of tobacco use[3]. More cases are diagnosed with oral pre-cancerous and cancerous lesions.

Modern medicine has been exploring the roles of immune modulating therapies for cancer treatment yielding promising results. B7 protein family holds a translational significance for its role in regulating adaptive immune system either by co-stimulation or co-inhibition[4,5]. PD-L1 (B7- H1), is an immune checkpoint inhibitor that negatively modulates immune responses. In 2018, two scientists from Physiology and Medicine received a Nobel Prize for their work related to cancer immunotherapy, particularly, PD-L1. This biomarker has shown a remarkable potential in cancer therapeutics overtime. Despite myriads of studies, conclusions remain to be elusivefor successful immunotherapy in oral cancers. In this review article, we focus on PD-L1, emphasizing its expression levels in cancers, particularly in oral cancer.

DISCUSSION

Tumor microenvironment (TME) is a term given to complex form of tissue, which includes tumor cells

with surrounding stroma and different kinds of mesenchymal cells along with extracellular matrix (ECM)[6]. Tumors build their own microenvironment during the course of tumorigenesis. The cellular component of TME is comprised of Cancer associated fibroblasts (CAFs), Endothelial cells (EC), Pericytes and cells derived from myeloid and lymphoid lineage e.g., Neutrophils, Macrophages, Natural killer (NK) cells, Dendritic cells and Lymphocytes[7]. The interaction between these components through cell surface molecules or cellular mediators results in growth of tumor and protection from the host. Tumor cells over express the inhibitory checkpoint proteins, such as PD-L1 which has been causing T cell exhaustion (Figure 1 and 2)[8]. This has led to development of immunotherapy through which normal immune surveillance mechanism could be restored.

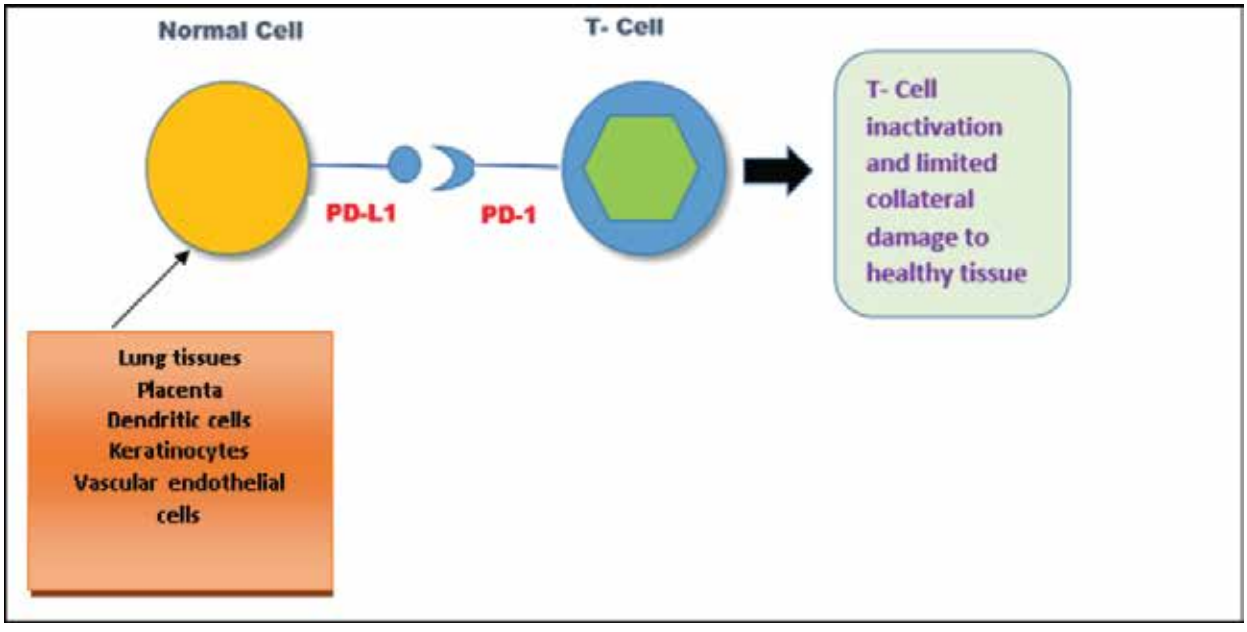

Figure 1: Physiological interaction between normal Cell expressing PD-L1 and T- cell receptor PD-1.

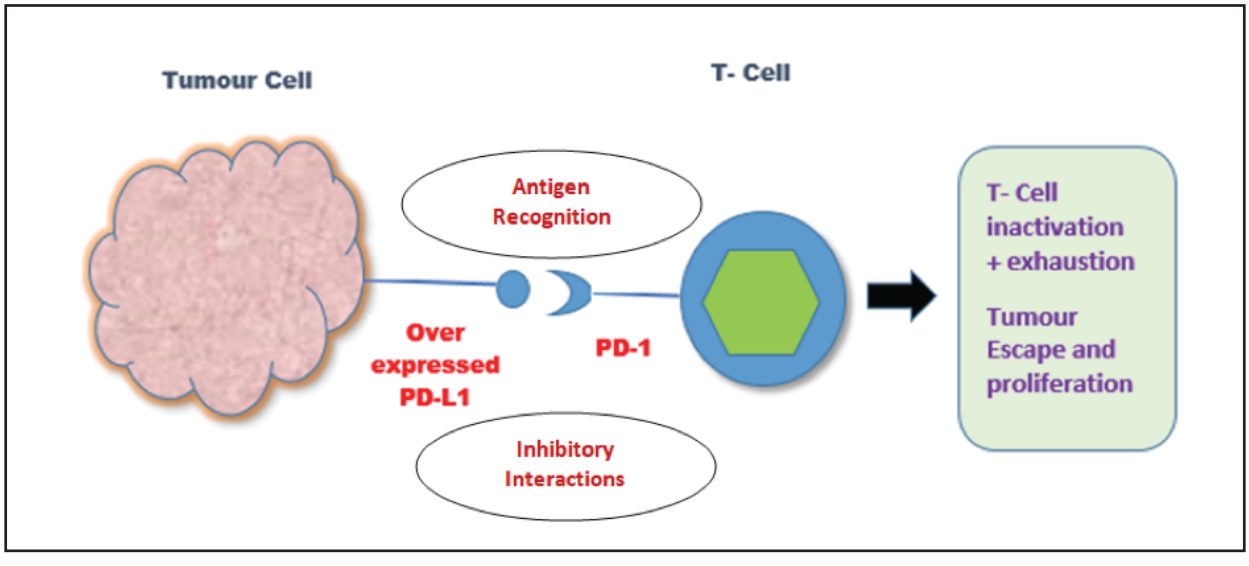

Figure 2: Interaction between tumor Cell Over expressing PD-L1 and T- cell receptor PD-1.

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Immune Checkpoint Proteins

Immune checkpoint proteins refer to a plethora of inhibitory mechanisms as a component of immune system that maintain self-tolerance and control immune responses to minimalize collateral damage to the healthy tissues. Over the last two decades, progress has been made in identifying novel agents in cancer treatment. Immune checkpoint proteins have been investigated and some been selected as therapeutic targets by pharmaceutical industries.

Antibodies to block PD-1/PD-L1 pathway, have shown success in cancer therapy. Apart from this, there are emerging immune checkpoint therapeutic targets that are currently under clinical trials and developmental process[9]. Despite the ongoing clinical trials, such as that of LAG-3 or TIM-3 antibodies, no pharmaceutical agents have shown clinical success. In addition, studies are underway investigating ligands for some immune checkpoint proteins such as VISTA or B7-H3. In this scenario, the immune checkpoint protein that has shown successful therapeutic potential remains to be PD-L1.

PD-L1

PD-L1 is a transmembrane proteinthat is speculated to play an essential role in immune suppression. It is a member of B7 protein family, which comprised of ligands that are structurally related. These ligands regulate responses of immune system by inhibition or stimulation after binding to receptors present on lymphocytes. PD-L1 is programmed by gene CD274 present on 9p24.1 chromosome and is composed of 290 amino acids. PD-L1 is not present in naïve T cells in humans, but on activated T cells it can be induced and has been found in lung tissues, placenta, monocytes, dendritic cells, keratinocytes and vascular endothelial cells[1, 10].

In healthy tissues, the presence of PD-L1 is suggestive of its role in prevention of auto immune reactions and regulating immune responses in chronic conditions due to exhaustion of T cells. This is featured by reduced cytokine production, proliferation andcytotoxic action, preventing damage to the tissues. PD-L1 results in Co inhibition of T cells by binding to cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and its receptor programmed cell death-1 (PD-1)[4,5]. CTLA-4 is a co-inhibitory receptor expressed on T cells. Antibodies to target CTLA-4 were the initial class of immune therapeutic targets that received approval by FDA. However, the emergence of PD-L1 has indicated wide and versatile therapeutic opportunities[9].

PD-L1 is a negative regulator of cellular and humoral immune responses by engaging PD-1 receptor. PD-1 receptor was identified within cells experiencing programmed cell death where it was exclusively expressed. Activation of T-cell causes the up regulation of PD-1[8].

Role of PD-L1 in Human Cancers

PD-L1 is established as a novel biomarker and in certain solid tumors, it is over expressed where it stifles T-cell activation and anti tumoral immune responses, creating a protective niche for nurturing cancer cells.[11-13]. Most studies have documented its immunohistochemical expression, though; its soluble forms and gene expression have also been studied[14].

Role of PD-L1 in Oral Squamous Cell Carcinoma (OSCC)

As the growing literature has signified the value of PD-L1 in various carcinomas, studies on its expression in OSCC have shown conflicting outcomes. Few studies have also attempted to explore their role in oral pre cursor lesions. Majority of studies are on immunohistchemical expression but the results have shown disparities overtime. Earlier, Malaspina et al. observed increased PD-L1expression in tissue samples and blood of patients with Actinic Chelitits (AC) and OSCC showing CD4+ PD-L1, CD8+ PD-L1expression increased in moderate levels in AC lesion sites as compared to OSCC sites[15].

Cho et al in 2011 did not report a significant correlation of PD-L1 expression with clinic-pathological parameters but mentioned that tumors with well differentiation had low expression of PD-L1 than tumors with moderate differentiation[16]. In oral lichen planus (OLP), studies indicated that the pathway, PD-1/B7-H1, may be vital in negative modulation of T cell immune responses and recommended to consider its expression on peripheral blood T lymphocytes as an indicator of severe OLP cases[17]. Lin et al. correlated higher PD-L1 expression with a poor prognosis in smoker male subjects who had OSCC18. Data also suggested that PD-L1 expression is more likely positive in HPV positive tumors than HPV negative in Oropharyngeal cancers. A previous study suggested that PD-L1expression in OSCC is associated with an inflammatory phenotype and can be heterogeneous and frequently observed in females and tumors with high lymphocytic infiltrate[11].

A study on protein expression and gene amplification of PD-L1 stated that these events are commonly observed in OSCC and suggested to consider PD-L1 protein status and copy number status in screening strategies as a future prospect[19]. A cohort study of Japanese patients diagnosed with OSCC and precancerous lesions concluded

that the immunohistochemical status of PD-L1 and PD-1 maybe related to carcinogenesis. This study also associated PD-L1 expression with poorly differentiated carcinoma but not with other clinic-pathological parameters such as site. It also reported higher PDL1 expression with tumor progression and prognosis in epithelial lesions and recommended to further explore the treatment via immunotherapy[5].

Weber in 2017 investigated PD-L1 expression in 45 blood and tissue specimens of OSCC and reported that PD-L1 expression may contribute to immune suppression and might be indicative of a metastatic disease[20]. Expression of PD-L1 in high grade OSCC cell line is reported to be lower than in low grade carcinoma as reported by Hirai et al. This study also showed a close relation between PD-L1 expression and epithelial mesenchymal transition[21]. Another study demonstrated that PD-L1 positivity was associated with better survival and frequency of tumor infiltrating lymphocytes[22]. A study by Yagyuu on epithelial dysplastic lesions reported that PD-L1 expression in oral sub epithelial and epithelial cells may be related to their transformation to malignancy. The precancerous lesions evade the host's immune system leading to invasive oral carcinoma[23, 24].

Hanna et al. further reported thatexpression of PD-L1 was related with better survival rates and low recurrent risk in females in younger age groups. However, the study had its limitations such as study design and small sample size that included a subset of young females' only[25]. Recently, Maruse reported that PD-L1 positivity was related topoor prognosis and lymph node metastasis but did not correlate with histopathological grade. This study recommended to further explore the expression of PD-L1 with uniform assays in larger cohort sizes to resolve incongruity amongst studies and for understanding the role of PD-L1 in oral cancer in a better way[26]. Ahn et al. showed an inverse relationship of PD-L1 expression with miR-197 and concluded that it is an independent favorable prognostic factor for overall survival[27]. Likewise, Vicente et al also reported PD-L1 as an independent prognostic element in OSCC patients[28].

Statiskowska and Chen associated the PD-L1 expression levels with disease progression in oral pre cursor and tumor lesions and reported a significant association with tumor grade[29,30]. Troeltzsch observed significant relationship of PD-L1 with tumor site and cervical metastases in a study and Schneider et al. reported similar finding on the significance of PD-L1 with nodal metastases in Head and Neck malignancies[31, 32]. Currently in 2019, Weber compared PD-L1and PD-L2 levels in OSCC and reported that PD-L1 in peripheral blood may serve as prognostic marker in order to monitor immune dysfunction as compared to PD-L2. Another recent study by Moratin also associated PD-L1 expression levels in OSCC with tumor size and regional metastases[34]. Takahashi demonstrated that Lower PD-L1 expression correlated with vascular invasion and recommended to evaluate its status with other markers for future clinical implications[35]. In a multitude of researches, an updated meta-analysis by Trojano focused on the existing disparity in associating PD-L1 with various clinic-pathological parameters of OSCC and most importantly difference in scoring methods for PD-L1 assays using Immunohistochemistry as a tool for evaluation[36]. This has caused uncertainty in deriving substantial conclusions.

Other Cancers

In 2013, Velcheti et al. reported 35 % of PD-L1 expression in a large cohort of non-small cell lung carcinoma (NSCLC) patients, suggesting a significant relationship[37]. Tuobe et al. also reported a significant expression of PD-L1 in tumors including Melanoma, Renal cell carcinoma (RCC), NSCLC, Prostate Adenocarcinoma and Colorectal Carcinoma[38]. As PD-L1 has proved to be a potential biomarker in different entities of tumor, different approaches that disrupt the pathway of PD-1/ PD-L1, have been evaluated in clinical settings with promising outcomes.

Antibodies to PD-L1

The efficacy of PD-1 antibodies has been tested in some clinical trials. Studies including patients of advanced Melanoma revealed effective treatment with Pembrolizumab, an anti-PD-1 antibody[39],[40]. Its importance has also been determined in lymphomas, hepatocellular carcinoma, gastric carcinomas, breast carcinoma, head, and neck cancer (HNC) [14, 41]. Treatment by Pembrolizumab in patients with positive PD-L1 expression in NSCLC prolonged the overall survival and future studies are being conducted to improve the efficacy of PD-L1 therapy in these patients[42, 43]. Clinical trials testing antibodies to PD-L1 for NSCLC showed prolonged survival of patients with Atezolizumab in comparison to treatment with docetaxel[44]. Treatment of metastatic renal cell carcinoma and ovarian cancer by different anti-PD-1 antibody, Nivolumab, has also shown clinical effectiveness[45,46]. Another study also demonstrated significant clinical responses in patients with metastatic urothelial cancers[47].

In these clinical trials, multiple antibodies, which include Pembrolizumab, Nivolumab and Atezolizumab, have been implicated and shown prolonged overall survival in tumors. Immunotherapies with these monoclonal antibodies are recently FDA approved for treatment of NSCLC; whereas, there are ongoing phase III clinical trials for Melano-

ma, Breast carcinoma, Head and Neck cancers and Urothelial cancers[42-50]. In a trial involving patients with metastatic or recurrent HNC, Pembrolizumab was noticeably tolerated and showed clinical effectiveness, mostly in tumors with PD-L1-positivity[48,51]. Much recent studies have shown the value of Pembrolizumab in HNC as an important domain of current research and have hypothesized that hindering CTLA-4 and PD-1 pathways in combination should provide a robust tumor response. Moreover, the reduced response rate of PD-1 inhibitors, which are approved by FDA in some cases, highlights the significance of investigating basic immune evasion mechanisms and immunotherapy resistance, along with developing novel curative strategies to combine immunotherapy with chemotherapy and radiotherapy[48, 52].

Animal Studies

In animal subjects, studies report that blockade of PD-1 potentiates immune response against tumors[53]. According to these reports, there is a direct association between PD-1/PD-L1and tumor escape mechanisms[15]. Studies have reported the use of monoclonal antibodies in mice models bearing oral precancerous lesions and given ambivalent findings; Animal studies to test the efficacy of anti-PD-L1 treatment have also been conducted in Melanoma[54-56].

In a study by Levingston and Young, anti PD-1 was used to treat mice induced with oral precancerous lesions. The overall results reported a favorable response to treatment by PD-1 antibody early on, which failed with progression of the lesion and continuous treatment. However, definitive conclusions could not be drawn because of lack of clinical studies in human/animal subjects bearing oral pre malignant and malignant lesions[54].

CONCLUSION

Studies on the expressions of PD-L1 in OSCC have so far shown inconsistent results as it has demonstrated a complex pattern of expression. Its significance with clinico-pathological parameters has shown discrepancy as well, however, majority of studies report it as a marker of tumor progression, metastases andworsening prognosis. Factors such as non-validated and varying tests, lack of uniform immune assays and different patient population may contribute to such disparity in results. Scientists must explore the value of PD-L1 in combination therapies to achieve successful results. Throughinterventions like these, there is hope to harness the effects of immune checkpoint inhibition in oral tumors that have otherwise life debilitating consequences.

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CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Both the authors contributed equally in this review article write up.

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