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CTLA-4 and PD-L1/PD-1 Pathways: Immune Checkpoint Inhibitors and Cancer Immunotherapy

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The immune system developed certain checks and balance to control or inhibit the reactivity against normal cells of the body. Uncontrolled immune responses to the non-self entities such as bacteria, viruses, parasites, or mutated self-antigens can cause an inflammatory reaction and autoimmune diseases. To avoid an immune overreaction, the immune response is governed by a delicate balance between the expression of co-stimulatory and inhibitory signals. These signals of the immune system referred to as immune checkpoints that are crucial to maintaining the homeostasis in the body. T-cells are an important subtype of lymphocyte that plays a key role in the fighting against several diseases including cancer. Accumulation of $CD8^+$ T cells in the tumor microenvironment (TME) directly correlates with the favorable anti-tumor responses [1]. Activated T cells express several co-inhibitory receptors including programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). The interaction between PD-1 and its ligand PD-L1 and, CTLA4 and receptor B7 regulate T cell responses to self-proteins [2]. Expression of ligands for the checkpoint is one of the prominent mechanisms exploited by cancer cells to avoid the immune cell-mediated killing which helps in their unchecked growth and progression [3]. PD-L1 expressed by tumor cells to inhibit the function and activity of T cells, whereas B7 that pairs with CTLA4 is expressed by antigen-presenting cells (APCs). Immunosuppressive TME which consists complex network of cancer cells, tumor-manipulated stromal and immune cells and soluble factors affects the functions of $CD8^+$ T cells by inhibiting their activity or inducing apoptosis [4]. To keep the $CD8^+$ T cells active in TME and perform their anti-tumor function, several CTLA-4 and PD-1/PD-L1 signaling axis blocking agents were developed as new immunotherapeutic tools which demonstrated huge therapeutic potential across multiple histological tumor subtypes [4,5].

T cells require two stimulatory signals for their activity, an interaction of T cell receptor (TCR) with major histocompatibility complex (MHC) for specificity, and binding of T cells CD28 receptor with B7-1 (CD80) or B7-2 (CD86) of APCs for proliferation. CTLA-4 expressed on T cells demonstrates high structural homology to the CD28 and binds to B7 molecule with higher affinity and avidity than CD28. However, unlike CD28, binding of CTLA-4 to B7 does not produce a T cell stimulatory signal; instead, CTLA4-B7 interaction abolishes T cell expansion and differentiation. Moreover, CTLA-4: B7 binding produces inhibitory signals that counteract the stimulatory signals induced by TCR-MHC binding. Ipilimumab, a monoclonal antibody that blocks the interaction of CTLA-4 with B7 is approved by the Food and Drug Administration (FDA) for the treatment of melanoma in early 2011 [6]. Delivery of ipilimumab in patients with renal cell carcinoma who did not respond to other immunotherapeutic modalities showed reduced tumor burden [7]. Further, ipilimumab treatment showed anti-tumor activity in patients with B-cell lymphoma [8], refractory metastatic colorectal cancer [9] and hepatocellular carcinoma [10]. A combination of ipilimumab with carboplatin, etoposide, and paclitaxel chemotherapies demonstrated better clinical outcomes in advance melanoma [11] and lung cancer [12]. Also, when ipilimumab combined with anti-receptor activator of NF-κB (RANK) ligand (RANKL) denosumab, it showed positive results in metastatic melanoma [13].

Another checkpoint, PD-1 is a member of the B7/CD28 family which modulates T cell activity via its interaction with PD-L1 and PD-L2. PD-1-PD-L1 binding inhibits the production of interferon-gamma (IFN-γ) and IL-2 which reduces T-cell proliferation and survival. Overexpression of PD-L1 in melanoma and non–small cell lung cancer (NSCLC) is associated with poor prognosis. Several anti-PD-1 and anti-PD-L1 monoclonal antibodies including nivolumab, pembrolizumab, cemiplimab, atezolizumab, and avelumabwere developed to block the interaction of PD-1 with PD-L1. Impressive results obtained after nivolumab treatment in the patients with metastatic melanoma [14] and metastatic NSCLC [15] led to the FDA approval of this antibody. Also, nivolumab has been demonstrated positive results with improved survival in patients with Hodgkin's lymphoma [16] and hepatocellular carcinoma [17]. Another anti-PD-1 monoclonal antibody pembrolizumab also known as Keytruda showed positive effects in metastatic melanoma approved by the FDA [18]. Also, pembrolizumab treatment improved overall survival in metastatic urothelial carcinoma [19] and shown great potential for head and neck squamous cell carcinoma [20] and non-hodgkin's lymphoma [21]. A combination of PD-1 blockade with GM-CSF showed effective antitumor T cell responses in a murine model of melanoma, colon carcinoma, and pancreatic ductal adenocarcinoma. The success of PD-1/PD-L1 blocked in several clinical trials led FDA approval of the anti-PD-1 antibodies, pembrolizumab, and nivolumab in 2014, for patients with advanced melanoma who had not responded to anti-CTLA-4 therapy. Moreover, anti-PD-1 monoclonal antibodies are in phase III clinical trial for the treatment of head and neck cancer, lung cancer, urothelial cancer, gastric cancer, and bladder cancer. A combination of nivolumab with ipilimumab benefits the patients and improved the outcomes compared with ipilimumab alone in several malignancies including colorectal cancer [22], renal cell carcinoma [23], metastatic osteosarcoma [24] and advanced melanoma [25].

Elevated expression PD-1/PD-L1 and CTLA-4 contribute to the progression of cancer, and thus blockade of this checkpoint is a meaningful strategy to improve the clinical outcomes. CTLA-4, PD-1/PD-L1 checkpoint inhibitor will be the major anti-cancer immunotherapeutic modality in the coming few years. The data obtained from pre-clinical and clinical studies delivered anti-PD-1/PD-L1 and CTLA-4 therapy are continuously improving our understanding. CTLA-4 and PD-1/PD-L1 blockade led to the significant improvement in survival of patients with different malignancies and revolutionized the oncology care. A combination of a checkpoint inhibitor with other therapies has shown promising results, which could lead to the development of the novel therapeutic strategy for the cancer cure. However, more work is warranted to improve the efficiency and safety of these therapies. As checkpoint inhibitors modulate the overall activity of the immune system that can lead to the side effects ranging from moderate to fatal under certain circumstances. The most common side effects of checkpoint inhibitors therapy are diarrhea, headache, fatigue, nausea, insomnia, pain, weight loss, and vomiting. The checkpoint inhibition as a therapeutic approach is rapidly expanding beyond CTLA-4 and PD-1/PD-L1 blockade therapies. Several new immune checkpoint targets including T cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte activation gene-3 (LAG-3), V-domain Ig suppressor of T cell activation (VISTA), T cell immunoglobulin and ITIM domain (TIGIT), etc. are under investigation. Identification of new immune checkpoint targets, their blockade and the results obtained from the combination of different therapeutic modalities with anti-CTLA-4 and anti-PD-L1/PD-1 will provide new insights and help to advance the field of cancer immunotherapy.

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