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Mini Review

T cell Immune Pathways Current and Future Implementation in Cancer Immunotherapy

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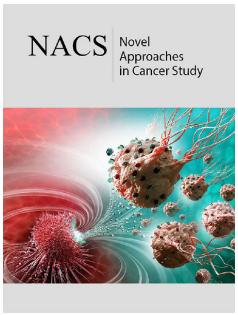

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Abstract

T cells are central players in cancer immune response. The discovery of T cell immune pathways has revealed several inhibitory and stimulatory pathways that affect the differentiation and activation of T cell. Theses pathways represent ideal candidates that can be targeted to augment *in-vivo*. T cell immune response against tumors. In this mini review we will try to reveal some inhibitory and stimulatory T cell immune pathways to which efforts of those interested in cancer immunotherapy can be directed.

Keywords: Immunotherapy; T cell; Immune pathways

Background

Tumor immunotherapy exceeds radiotherapy and chemotherapy in the fact that it considered the most tumor-specific therapy; it is characteristically effective in metastatic tumors, which is a real challenge facing current tumor therapies. Additionally, it confers long-lasting memory, which cannot by induce by other therapeutic approaches [1]. T cell is the major cell orchestrating the anti-tumor immune response. For a T cell to be activated and differentiated, it should receive activating signal not only from the T cell receptor but also from other co-stimulatory molecules [2]. On the other hand, to maintain a balanced immune system other molecule are involved in the inhibition of the activated T cell after the end of an immune response. Understanding these pathways can help in influencing the activity of T cell and thus provide other options for cancer immunotherapy [3].

Inhibition of the Inhibitory Pathways (Check Point Inhibitors)

Programmed Death-1 (PD-1) pathway blockade

Programmed death-1 (PD-1) is an important immune checkpoint receptor on cytotoxic T cells. The PD-1 receptor has two ligands, programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2). Upregulation of the PD-1 receptor plays a key role in T-cell exhaustion [4]. T-cell exhaustion occurs as a result of repeated exposure to tumor antigen, this repeated exposure steadily increases the activity of PD-1 [5] and hence decrease the ability of T cells to respond and eventually T cell survival is affected [6]. Exhausted Tumor-infiltrating T cells are characterized by up-regulation of PD-1 and other inhibitors of immune function, decreased production of cytokines, decreased cell-signaling molecules that help guide the immune response and impaired ability to kill tumor [7].

Available anti-PD-1 checkpoint inhibitors include Pembrolizumab, Nivolumab, and Atezolizumab, are currently licensed for use in advanced melanoma, renal cell carcinoma, Hodgkin lymphoma, and bladder cancer [1]. Preclinical studies suggest that complete inhibition of PD-1 signaling through both PD-L1 and PD-L2 is more effective in restimulating T-cell exhaustion than inhibiting PD-L1 alone [8].

Cytotoxic T-lymphocyte Antigen 4 (CTLA-4 pathway) blockade

Under normal conditions, activation of T-cells requires two signals; the first is the binding of the T-cell receptor (TCR) to the major histocompatibility complex (MHC) on antigen-pre-

senting cells (APCs). And the second is the interaction between CD28, the primary costimulatory receptor on T cells, binds and CD80, and CD86 on APCs [9]. Inhibition of T-cell occurs when Cytotoxic T-lymphocyte antigen 4 (CTLA-4), an immune checkpoint receptor, is expressed on the surface of activated T cells. It competes with CD28 and has a greater affinity for CD80/86. Binding of CTLA-4 to CD80/86 inhibits T-cell activation and preserve immune balance to avoid the immune system overactivity, CTLA-4 can also be found on regulatory T cells (Tregs), the key drivers for T-cell activity suppression [10].

In the tumor microenvironment, tumor cells utilize the CTLA-4 pathway to suppress the initiation of an immune response. Therefore, it inhibits T-cell activation and a causes reduced ability to proliferate into memory T cells. CTLA-4 signaling decreases the ability of memory T-cells to sustain a response, damaging a key element of durable immunity [11]. Additionally, T-cell activity is suppressed by the continuous expression of CTLA-4 on Tregs. Inhibition of CTLA-4 restores antitumor immunity and restore the immune response through the increased accumulation, function, and survival of not only T- cells, but also memory T-cells, as well as the depletion of Tregs [12]. A novel approach to regulate the degree of immune activity is to increase the depletion of Tregs. A CTLA-4 antibody with a modified Fc region can bind to Tregs, therefore, identify them for elimination by other immune cells. As shown in mouse models, the increased depletion of Tregs can improve cytotoxic T-cell activation and antitumor activity [12].

An approach aims to improve the specificity of CTLA-4 blockade is by reducing antibody binding outside of the tumor microenvironment. This includes the use of pro-antibodies (anti-CTLA-4 that have been masked with a protein) the masking protein can be removed by enzymes that are either highly expressed by or only present on tumor cells. Pro-antibodies are, therefore, active primarily at the tumor site [13]. Currently, available anti-CTLA-4 include Ipilimumab, Combination of ipilimumab, and nivolumab [1]. Major adverse effects of using check point inhibitors are autoimmunity: for example, acute-onset type 1 diabetes, lesions in pituitary and inflammatory reactions, especially in the colon, lung, and liver. PD-L1blockers exhibit fewer side effects than CTLA4 blockers. Side effects can be controlled by anti-inflammatory and hormonal replacement if needed. Non-response to check point inhibitors can occur as a result of: tumors which have relatively few somatic mutations encoding neoantigens because fewer tumor-specific T-cells will respond, tumors with sparse inflammatory cell infiltration, down-regulation of PD- L1 receptor, selective growth of tumor clons that express other inhibitory check points [14]. Preclinical data indicate that limiting antibody binding to the tumor microenvironment may prevent an immune attack of healthy cells, yet still enable an antitumor response [13].

Lymphocyte-Activation Gene 3 (LAG-3) blockade

Lymphocyte-activation gene 3 (LAG-3) is an immune checkpoint receptor expressed on the surface of both activated cytotoxic T cells and regulatory T cells (Tregs) as a result of repeated exposure to tumor antigen [15]. LAG-3 binds MHC on APC, activation of LAG-3 negatively regulate T-cell proliferation and the development of lasting memory T cells and lead to cell exhaustion. Exhausted T cells have an impaired ability to fight tumor cells, which may result in tumor growth. T cells co-expressing both LAG-3 and PD-1 may show an even greater degree of exhaustion compared with those expressing LAG-3 alone [16]. LAG-3 can also trigger the immunosuppressive activity of Tregs. In cancer, Tregs expressing LAG-3 gather at tumor sites and show potent suppression of cytotoxic T cells. Increased LAG-3 expression has been associated with poorer prognosis in multiple tumor types [17]. In preclinical studies, when the PD-1 pathway is blocked, LAG-3 may be upregulated to maintain tumor growth. Inhibition of both LAG-3 and other checkpoint pathways may synergistically increase T-cell antitumor activity compared with inhibition of either pathway alone [15].

T-cell Immunoreceptor with Immunoglobulin and ITIM domains (TIGIT) blockade

T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) is an immune checkpoint receptor expressed on the surface of cytotoxic, memory, and regulatory T cells (Tregs), as well as natural killer (NK) cells. TIGIT has two ligands: CD155 (PVR) and CD112 (Nectin2). On cytotoxic T-cells and NK cells, the interaction of TIGIT with either of its ligands suppresses immune activation [18]. When TIGIT is expressed on Tregs, this interaction enhances their ability to suppress the immune response [19]. Experimental data showed that inhibition of TIGIT signaling increases the proliferation and function of cytotoxic T-cells [20].

T-cell Immunoglobulin and Mucin-3 (TIM-3) blockade

T-cell immunoglobulin and mucin-3 (TIM-3) are immune checkpoint receptor involved in the suppression of both innate and adaptive immune cells. It is expressed on a wide range of immune cells, including cytotoxic T cells, Tregs, NK cells, APC like DCs. TIM-3 can suppress effector cells through the interaction with a broad array of ligands: carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), galectin-9, phosphatidylserine (PS), and high mobility group box 1 (HMGB1) [21]. Experimental data suggest that the blockade of TIM-3 may rescue NK-cell activity, stimulates tumor antigen processing, and reactivate exhausted T cells, restoring their proliferation and function. TIM-3 is usually co-expressed with other immune checkpoint receptors, and preclinical studies indicate that co-blockade of TIM-3 and another immune checkpoint receptor may further reinvigorate exhausted T cells [22].

Killer Cell Immunoglobulin-like Receptors (KIRs) cell pathway

Killer cell Immunoglobulin-like Receptors (KIRs) are expressed on the surface of NK cells. They are inhibitory immune checkpoint receptors that stop NK cells from killing normal cells. Nearly every normal cell expresses the ligand for inhibitory KIRs. Tumor cells upregulate the ligand for inhibitory KIRs, to appear as normal cells and escape detection by NK cells. In preclinical studies, blockade of inhibitory KIRs, however, has been shown to help restore NK cell-mediated immune activity [23].

Immune Pathways: Stimulation of the Activating Pathways

CD137: Potentiator of innate and adaptive immunity

CD137, or 4-1BB, is an activating receptor appears on both natural killer (NK) cells and T cells, thus play an important role in both innate and adaptive immunity, it also plays a critical role in the development of memory T cells. It is suggested that activation of CD137 signaling can stimulate both cytotoxic T-cell and NK-cell activity and generate a lasting memory response [24].

Glucocorticoid-Induced TNFR-Related Protein (GITR)

Upon activation of T-cells, an activating receptor known as Glucocorticoid-induced TNFR-related protein (GITR) is expressed. GITR acts as a costimulatory receptor that enhances cell reproduction and the generation of cancer-killing activity [25]. It is expected that activation of GITR signaling can help enhance immunity through the activation of cytotoxic T cells and inhibition of Treg activity [26].

Inducible T-cell co-Stimulator (ICOS)

Inducible T-cell co-stimulator (ICOS) is a receptor expressed on the surface of activated cytotoxic T cells, other types of T-cells, and NK cells. They are similar in structure to CTLA4. However, it has an opposing function. This receptor when interacts with its ligand, B7RP-1which is expressed on APCs and DCs and macrophage, leads to activation of cytotoxic T-cells, as well as the survival of memory T-cells; additionally, it may enhance the function of NK cells [27]. Experiments have shown that stimulation of ICOS during CTLA-4 blockade was shown to enhance T-cell activity. Also, mouse models demonstrate that ICOS expression may enhance the antitumor response of NK cells [28].

CD40-CD40L: Activates and amplifies T-cell stimulation

CD40 is an activating receptor expressed on the surface of activated cytotoxic T cells and regulatory T cells (Tregs). It plays a dual role in the immune response, both activating and amplifying T-cell responses.

A. Activation: On cytotoxic T cells, CD40 binds to its ligand (CD40L), resulting in stimulatory signals that promote T-cell reproduction, function, and survival.

B. Amplification: On Tregs, CD40-CD40L signaling blocks the ability of Tregs to suppress T cells and reduces Treg generation, thus amplifies the T-cell activation [29].

Signaling Lymphocytic Activation Molecule Family member 7 (SLAMF7)

Signaling Lymphocytic Activation Molecule Family member 7 (SLAMF7) is an activating receptor expressed on the surface of virtually all NK cells meanwhile, SLAMF7 is not expressed on solid tissues or hematopoietic stem cells [30]. Engagement of SLAMF7 activates NK yet normal spare cells. NK cells kill tumor cells, released tumor antigens are then uptake by APC, which further stimulate T cytotoxic cells and memory cells. Ongoing research aims to understand how NK cell activation through SLAMF7 impacts long-term immunity [31].

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