Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.53.008433

Targeting Tumor-Infitrating Treg Cells

Jianlei Xing*

China Medical University, China

***Corresponding author:** Jianlei Xing, China Medical University, Address: No.77 Puhe Road, Shenyang North New Area Shenyang 100001, China

ARTICLE INFO

Received: October 27, 2023

Published: November 07, 2023

Citation: Jianlei Xing. Targeting Tumor-Infitrating Treg Cells. Biomed J Sci & Tech Res 53(4)-2023. BJSTR. MS.ID.008433.

ABSTRACT

Regulatory T cells (Tregs) play an important role in maintaining peripheral immune tolerance and preventing autoimmune diseases. However, they are also a major obstacle to effective anti-tumor immunity and immunotherapy, and Treg cells infiltrate in large numbers around tumor tissue, called tumor-infiltrating regulatory T cells (TI-Tregs). TI-Tregs have distinct biological features from conventional T cells and Treg cells in other tissues, and these unique features provide an opportunity for immunotherapy targeting TI-Tregs. TI-Tregs play an immunosuppressive role in the tumor microenvironment through different mechanisms, which are mainly characterized by the secretion of immunosuppressive cytokines and the high expression of various molecules on the cell surface, such as immune checkpoint molecules, chemokine receptors, CD39, CD73 and other nucleotidases, which are often associated with poor prognosis of tumor patients. The removal of Treg cells may enhance the anti-tumor immune response but may also cause an autoimmune response. Therefore, selectively, or preferentially targeting Treg cells in tumors without affecting their ability to maintain peripheral immune homeostasis has become an important research direction for tumor immunotherapies with greater efficacy and reduced potential to induce systemic toxicity. Therefore, we reviewed the occurrence, development, and mechanism of TI-Tregs in cancer and the therapeutic application targeting TI-Tregs, emphasizing the important role of tumor immunotherapy in cancer therapy.

Keywords: Tumor-Infiltrating Regulatory T Cells; Tumor Microenvironment; Immune Escape; Targeted Therapy

Abbreviations: TME: The Tumor Microenvironment; PDAC: Pancreatic Ductal Adenocarcinoma; CTLA-4: Cytotoxic T Lymphocyt-Associated Antigen 4; PD-1: Programmed Death Receptor 1; LAG-3: Lymphocyte Activation Gene-3; RORgt: Retinoid Associated Orphan Receptor gt

Introduction

The tumor microenvironment (TME) is a dynamic system composed of multiple cell types, Includes several populations of immune cells (i.e., macrophages, neutrophils, mast cells, myeloid suppressor cells, dendritic cells, NK cells, T and B lymphocytes), cytokines, blood vessels, cancer cells, and their surrounding mesenchyma (including fibroblasts, endothelial cells, pericytes, and mesenchymal cells), which work together to promote tumor progression [1]. TME is an immunosuppressive environment characterized by the presence of mediators capable of neutralizing immune surveillance, damaging the infiltration of T cells and facilitating the accumulation and activation of regulatory T cells, thus promoting the spread of cancer [2]. Tumor invasion Treg is a major group of immune cells,in various solid tumors including gastric [3], lung [4], ovarian [5], pancreatic ductal adenocarcinoma (PDAC) [6], melanomas [7], breast [8] and hepatocellular cancer [4], TI-Treg can account for more than 50% of all CD4+ T cells.Because the infiltration of large amounts of Treg into the tumor in the immunosuppressive tumor microenvironment will hinder the development of effective anti-tumor immunity and is often associated with poor prognosis [9-11].

Origin and Enrichment of Tumor-Infiltrating TREGs

Sources of Tumor-Infiltrating TREGs: Treg cells, a subgroup of CD4+T lymphocytes, were first reported to be involved in maintaining self-tolerance in the 1970s but lacked specific molecular markers [12]. It was not until 1995 found that IL-2 receptor alpha chain (CD25) was constitutionally expressed on Tregs, and the concept of Treg cells

was formally proposed [13]. Later, the fork head box P3 transcription factor (Foxp3) was found to be related to the differentiation of Treg [14,15]. As a characteristic transcription factor of Treg, Foxp3 plays an important role in regulating the development and function of Treg [16,17]. Treg cells play a crucial role in immunosuppression and maintenance of peripheral immune tolerance. Since the accumulation of Treg cells in the most tumor microenvironment is closely related to the reduction of patient survival time [18], it is an important target for human tumor immunotherapy. Two main subgroups of tumor infiltrating regulatory T cells have been found, one is from the thymus, known as natural regulatory T cells (nTreg, CD4+CD25hiCD127Low), and the other is differentiated from CD4+CD25+T cells, mediated by TGF-β1 and interleukin-2. They are called inductive or regulatory T cells (iTreg), also known as type 1 regulatory T cells (Tr1) [18,19]. Both recruited and induced TREGs can be activated in the tumor or in the draining lymph nodes in response to tumor-associated antigens. They then inhibit the immune anti-tumor response mediated by NK cells or effector T cells, thereby allowing tumor progression [9].

Enrichment of Treg in Tumor Infiltration: In the most solid TME, the changes associated with tumor growth, such as altered nutrient composition and oxygenavailability, cytokines and chemokines released by tumor cells, stroma and immune cells also favor Treg infiltration [20]. Tregs display a limited TCR repertoire within the TME, suggestive of a clonal enrichment for Tregs that recognize tumor associated antigens and tumor specific antigens. It is possible that TME imposes a bottleneck for the incoming tumor-specific CD4 + T cells due to hostile metabolic environment where the ones that differentiate into pTregs survive and others face their demise. This may gradually build a tumor-specific Treg repertoire [20]. Tumor cells recruit Treg cells by releasing chemokines, which then cause Treg cells to aggregate in the tumor microenvironment. Treg cells migrated to TME through chemokine receptors such as CCR4, CCR8, CCR10 and CXCR3. CCR4 was bound by CCL17 and CCL22, CCR8 was bound by CCL1, CCR10 was bound by CCL28, and CXCR3 was activated by CXCL9/10/11. Thymus derived Treg cells preferentially recognize autoantigens by high-affinity TCR and are asexually amplified in TME. Treg cells are recruited and recognize the abundant homologous antigens in TME, which leads to Treg cell activation and proliferation, promoting the development of an immunosuppressive tumor microenvironment. Meanwhile, study has shown that patients with breast cancer and mouse with melanoma models, TI-Tregs were selectively activated in the bone marrow and egressed into the peripheral blood. Mechanistically, Tregs in bone marrow express CCR2 (peripheral homing receptor), due to the expression of CCL2 (CCR2 ligand) in breast cancer tissues, the activation and output of tumor antigen specific Tregs in BM leads to the accumulation of Tregs in breast tumor tissues [21].

Secondly, immunosuppressive cytokines released by tumor cells and immune cells, such as TGF-β and IL-10, can also promote the increase of Treg in the tumor microenvironment [22]. Within the glioma, macrophages and microglia produce CCL2 and are able to recruit CCR4+ Treg from the periphery into the TME [23]. In addition, by expressing T cell co-stimulatory molecules (ICOS) and binding to ICOS ligand (ICOSL) of plasmacytoid dendritic cells, tumor-infiltrating Treg cells can promote the proliferation and activation of tumor-infiltrating Treg cells in gastric cancer [24], thereby achieving the enrichment of Treg cells in the tumor microenvironment and promoting tumor immune escape.

Characteristics and Functions of Tumor Infiltrating TREGs

Characteristics of Tumor Infiltrating TREGs: Foxp3 transcription factor (Foxp3) plays a crucial role in the development and programming of Treg cells, and activation of STAT3 after co-stimulation by T cell receptor /CD28 plays a crucial role in FOXP3 expression [25]. In addition, the upregulation of Foxp3 in Treg cells may involve the binding of STAT3 and STAT5 proteins to the STAT binding site located in Foxp3's first intron [26]. Foxp3 endows Treg with various essential characteristics, including high expression of CD25 and cell surface molecules, such as cytotoxic T lymphocyt-associated antigen 4 (CTLA-4), and inhibition of pro-inflammatory cytokines such as IL-4 and IL-17 [27]. At the same time, Foxp3 can interact with about 700 target genes and multiple micrornas to jointly regulate the development and function of Tregs. Tumor-infiltrating Treg cells exhibit a fairly active inhibitory phenotype with high expression of immune checkpoint molecules, including CTLA-4, programmed death receptor 1 (PD-1), T-cell immunoglobulin, and mucin domain 3 (TIM-3). Lymphocyte activation Gene-3 (LAG-3) and T cell immune receptor (TIGIT) with immunoglobulin and ITIM domains [28]. In addition, in human head and neck squamous cell carcinomas, IL1R1+TI-Treg cells had responded to antigen recently and demonstrate that they are clonally expanded with superior suppressive function compared with IL1R1−TI-Treg cells [29]. It may be used as a specific target for TI-Treg in human head and neck squamous cell carcinomas.

Studies have shown that tumor infiltrating Treg cells have stronger immunosuppressive function, and CD39 and CD73 are highly expressed [30,31], and CD39 and CD73 are functional in them [32], and the main function of CD39 and CD73 is to dephosphorylate extracellular adenosine triphosphate into adenosine. Adenosine binds to adenosine receptors (A1R,A2aR,A2bR,A3R) to mediate the immunosuppressive function of Treg cells [33]. Study has shown that in ovarian cancer CD39, CD103, and PD-1 triple-positive Tregs exhibited higher TCRdiversity and a tumor-resident phenotype [7]. CD36 was selectively up-regulated in TI-Tregs of breast cancer patients and melanoma mouse model as a central metabolic modulator. CD36 fine-tuned mitochondrial fitness via PPAR-β signaling, programming T reg cells to adapt to a lactic acid-enriched TME [34]. TI-Tregs tend to have a high glycolytic phenotype, in colorectal cancer patients TI-Tregs featured low activity of MondoA-TXNIP axis and increased glucose uptake. Mechanistically, suppression of MondoA-TXNIP axis

induced hyper-glycolytic Th17-like Tregs, which facilitated Th17 inflammation, promoted IL-17A-induced of CD8 +T cell exhaustion and drove colorectal carcinogenesis [35]. In a mouse model of liver cancer, lactate degradation reduces Treg cell induction, increases antitumor immunity, and decreases tumor growth in mice.

Mechanistically, lactate modulates Treg cell generation through lactylation of Lys72 in MOESIN, which improves MOESIN interaction withTGF-β receptor and downstream SMAD3 signaling. It can be seen that the metabolism in TME affects the occurrence, development and functional changes of TI-Treg. The intrinsic stability and maintenance of Treg lineages depend on the continued high expression of Foxp3 [26]. The stability of Treg lineages is also regulated by epigenetics. The Foxp3 locus contains several conserved atypical enhancer sequences targeted by epigenetic modifications and several transcription factors [36]. Phosphorylation of signal transducers 3 and nuclear factors activating T can promote FOXP3 expression after activating TGF-β signaling, which plays a key role in inducing extra-thymus treg cells [37]. The stability of Treg cells is not always constant. It has strong adaptability in the inflammatory environment, and dendritic cell-derived interleukin-6 can induce the transformation of Treg cells into helper T cell 17 (Th17) cells under local inflammatory stimulation [38]. Th17 cells, as representatives of the pro-inflammatory subgroup of CD4+T cells, mainly secrete the pro-inflammatory cytokine interleukin-17. The retinoid associated orphan receptor gt (RORgt) is a unique lineage-specific transcription factor for TH17. Both Th17 and Treg cells share a common key regulatory factor TGF-β, which is involved in the activation of Rorgt and Foxp3. When stimulated by pro-inflammatory cytokines such as interleukin-6 or interleukin-21, low concentrations of TGF-B induce the development of Th17 cells, and correspondingly high concentrations of TGF-β promote the differentiation of naive CD4+T cells into TreGs and maintain immune tolerance.

IL-6 and IL-21 also upregulate RORgt expression by inhibiting FOXP3 activity in a signal sensor and activator of transcription (STAT3) -dependent manner. In addition, tumor necrosis factor-α can reduce FoxP3 expression by binding to the tumor necrosis factor receptor RII and interfering with the inhibitory function of Treg cells. At the same time, it promotes the recruitment of protein kinase C-Q and inhibits Treg function by activating downstream Akt signaling [39]. In various tumor including lung, colorectal, ovarian, bladder, stomach, melanoma or kidney cancer of human and mouse models of colon, breast, and kidney cancer, CCR8 + Tregs constituted 30 to 80% of tumor Tregs and less than 10% of Tregs in other tissues [40]. In mouse colon cancer, melanoma and human NSCLC, breast carcinomas and melanoma, the CCR8 protein was only prominent on the highly activated and strongly T-cell suppressive TI-Treg subpopulation, compared with the corresponding normal tissue and peripheral blood [41-43]. Epigenetic mechanisms play vital roles not only in cancer initiation and progression, but also in the activation, differentiation and effector function(s) of TI-Tregs. DNA methylation, a prominent epigenetic regulation mechanism,studies have shown that the DNA methylation of the CpG island in the enhancer region controls expression of Foxp3 in T cells [44-46] . Foxp3 can be regulated by a number of cis-acting elements,which are located on the promoter and the enhancer regions(CNS0, CNS1, CNS2, and CNS3) of the Foxp3 locus [36,47]. These regions contain binding sequences for transcription factors that are induced by extracellular signaling, including TCR, CD28, TGF-bR, and IL-2R signaling.

Function of Tumor-Infiltrating TREGs: nTregs mediate inhibition through cell-contact-dependent mechanisms, such as granzyme B, perforin, or the Fas/Fas ligand pathway, and constitute a major regulatory T cell subpopulation for the maintenance of peripheral tolerance. Tr1 mediates the inhibition of the non-contact mechanism by producing immunosuppressive factors such as TGF-β and IL-10 [18,48]. Tr1 cells are activated in the tumor microenvironment, co-expressing CD39 and CD73, and producing adenosine by hydrolyzing exogenous adenosine triphosphate or adenosine diphosphate. The expression of cyclooxygenase-2 was up-regulated to produce prostaglandin E2. Two factors, adenosine, and prostaglandin E2, are abundant in the tumor microenvironment and work together to exert a powerful immunosuppressive effect. Studies have shown that the synergistic inhibition mediated by adenosine and prostaglandin E2 is one of the mechanisms of TR1-induced immunosuppression. It not only acts on immune effector cells, but also acts on Tr1 itself in an autocrine way. Prostaglandin E2 induces the expansion of Tr1 cells and regulates their activity, thus contributing to the creation and maintenance of an immune tolerance environment. The proliferation of Tr1 in tumor cells and the production of interleukin-10 and TGF-β responsible for its inhibitory function depend on the expression of cyclooxygenase-2 [49].

The collaboration between adenosine and prostaglandin E2 is mediated at the level of adenylate cyclase-7, which together with cellular phosphodiesterase is responsible for regulating the level of 3 '5' -cyclic adenosine phosphate in cells, thereby exerting immunosuppressive effects. The inhibitory function of Tr1 is blocked in the presence of extracellular nucleotidyase antagonists and indomethacin, confirming that both adenosine and prostaglandin E2 are involved in TR1-mediated immunosuppression [50]. In addition, Treg acts on its own A2aR in an autocrine manner by co-expressing CD39 and CD73, further promoting its proliferation and immunosuppressive function. A2aR stimulation not only promoted the proliferation of natural Treg cells, but also promoted Foxp3-T cells to induce new Treg cells. Stimulation of T cells in the presence of A2aR agonists can induce the expression of FoxP3 and LAG3 messenger RNA in T cells, further promoting the formation of TGF-β-induced Tregs [51]. In addition to enhancing the immunosuppressive function of Treg by acting on itself through adenosine /A2aR, Treg cells have also been found to actively produce extracellular adenosine through CD39 and CD73 [50] and block the activation of effector T cells. The study showed that when Tregs suppressed the immune response, an increase in cyclic adenosine phosphate was observed in the target cells. Tregs express

cyclooxygenase-2 and produce prostaglandin E2, thus stimulating the production of adenosine cyclic phosphate in target cells [50]. Adenosine produced by Tregs performs immunosuppression by triggering A2AR-dependent effector cell activation inhibition. Along with adenosine, prostaglandin E2 from Tregs has been found to play a role in the immunomodulatory activity of tregs.

In summary, Treg cells exert their immunosuppressive function through multiple mechanisms, as shown in the figure. The first immunosuppressive mechanism involving cytokines includes Treg cells with high expression of CD25 which binds to interleukin-2 to competitively inhibit effector T cells. Inhibition by the production of inhibitory cytokines, such as TGF-β, interleukin-10 and interleukin-35, directly killing effector T cells or antigen-presenting cells by secreting perforin, granase B or Fas/Fas ligand interactions. The second immunosuppressive mechanism involves immune molecular checkpoints that inhibit effector T cells through the LAG-3/ major histocompatibility complex 2 pathway and induce further activation of TREGs by inducing the ICOS/ICOSL and PD-1/PD-1 ligand pathways. A third immunosuppressive mechanism includes metabolic regulation of indoleamino-2, 3-dioxygenase expression in dendritic cells, which depletes T cells because key amino acids for survival are depleted. In addition, CD39 and CD73 expressed in activated Treg cells metabolize adenosine triphosphate to produce adenosine, causing Treg cells to send negative signals to effector T cells and antigen-presenting cells, resulting in T cell inhibition. The fourth immunosuppressive mechanism includes Treg expression of CTLA4, and dendritic cells down-regulate CD80/86 expression by binding to CTLA4, which leads to the maturation of antigen-presenting cells and attenuated T cell activation [22] (Figure 1).

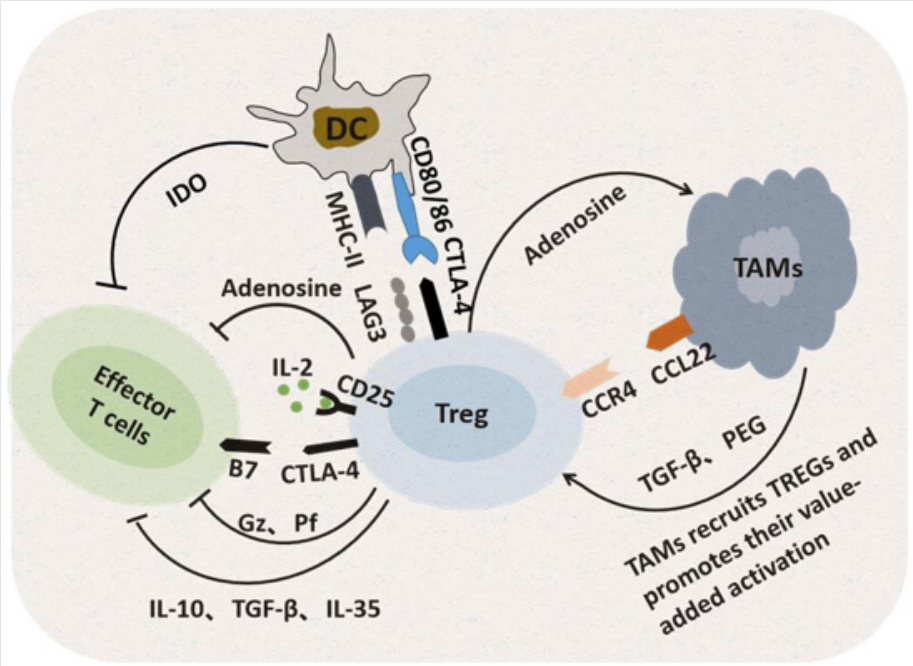

Figure 1: Immunosuppressive mechanism of tumor infiltrating Treg.

Therapy Targeting Tumor Infiltrating TREGs

Treg cells play an important role in maintaining peripheral tolerance and preventing autoimmunity. However, they are also a major obstacle to effective anti-tumor immunity and immunotherapy, so that Treg cells in tumors can be selectively or preferentially targeted without affecting their ability to maintain peripheral immune homeostasis. In fact, preliminary observations from human ovarian cancer patients have shown that elevated Treg cell frequency at tumor sites is associated with poorer clinical outcomes. However, later data collected from a wider range of cancer types led to different correlations between the number of Treg cells within tumors and disease outcomes. There are three possible reasons for this difference. First, Treg cells cannot be clearly distinguished from activated T cells, which can express Foxp3. Second, Treg cells can promote tumor development by limiting anti-tumor immunity, or by limiting the stromal environment required for its growth and metastasis. Third, Treg cells found in tumors may be heterogeneous in terms of functional status and/or stability, which in turn may influence their positive or negative impact on tumor progression [52]. While the above issues warrant further investigation, it is generally accepted that Treg cells influence the tumor microenvironment and targeting them could be beneficial.

Drugs targeting Treg: Since 1959, alkylating agents, such as the lead compound cyclophosphamide (CTX), have been recognized as potent cytotoxic and lymphatic ablative agents integral to immunotherapy regiments for tumors. CTX significantly affects Treg cell homeostasis, promotes the secretion of type I interferon, and promotes the induction of anti-tumor cytotoxic T lymphocytes and the proliferation of adoptive metastatic T cells [53]. The polarization of CD4+T cells towards Th1 and/or Th17 lymphocytes ultimately affects the Treg/ effector T cell ratio, which is conducive to tumor regression. Studies have shown that of all chemotherapy drugs used to treat tumors, CTX is the most effective in ablating TREgs in rodents. A single injection of low-dose CTX (30mg/kg) resulted in strong depletion of CD4+CD25+Treg cells on day 7 after treatment. Although this Treg loss is transient, it allows cancer-specific immunotherapy to promote effective T cell and dependent antitumor effects [54]. Later studies found that CTX not only reduced TreGs in the blood and lymphatic organs of tumor-bearing animals, but also reduced the number of Tregs infiltrating the tumor bed [53]. Studies have shown that the CTX prodrug equifosfamide can indeed selectively induce FOXP3-expressing T cell death in vivo and in vitro. In fact, Tregs are involved in their immunosuppressive effects by expressing the transcription factor Foxp3 [55], which is associated with increased expression of pro-apoptotic molecules [56], which may contribute to their higher sensitivity to low doses of CTX [57].

Tumor necrosis factor-type II tumor necrosis factor receptor interaction plays a decisive role in the activation, expansion, and phenotypic stability of inhibitory CD4+Foxp3+ regulatory T cells (TREGs). So far, three signaling pathways of tumor necrosis factor II receptor in T lymphocytes have been reported, such as IKK/NFκB, MAPK (Erk1/2, p38, JNK) and PI3K/Akt pathway [58]. CTX is often used as cytotoxic chemotherapy in cancer treatment [59], and a single dose of CTX can deplete the maximum inhibitory Treg in colon cancer mice, thus activating the anti-tumor immune response [54]. In addition, VanderMost et al reported that CTX treatment reduced TREGs with high expression of tumor necrosis factor receptor type II in a mouse mesioma model [60]. This effect of CTX is based on its ability to induce co-expression of type II tumor necrosis factor receptor and Ki-67 replicating Treg death [60,61]. In addition, CTX combined with Etanercept, a therapeutic TNF antagonist, can significantly inhibit the growth of colon cancer tumor models established in mice by blocking the interaction of tumor necrosis factor-type II tumor necrosis factor receptor and eliminating Treg activity expressing type II tumor necrosis factor receptor [62]. The study suggests that in multiple myeloma, progression after high-dose mefaran combined with autologous stem cell transplantation may be due in part to immune dysfunction. Treg cells reconstituted rapidly after autologous stem cell transplantation and inhibited the immune response of myeloma cells. Elimination of Treg with anti-CD25 in vivo and in vitro can significantly reduce and delay Treg recovery after autologous stem cell transplantation and can be used as a platform for post-transplantation immunotherapy to improve prognosis after autologous stem cell transplantation [63].

However, CTX and anti-CD25 elimination of TreGs have defects, such as the depletion of tumor-infiltrating Treg cells and the reduction of TreGs in the autoimmune immune system, and the depletion of effector T cells in the anti-tumor immune system due to off-target effects [64]. Therefore, effective new cancer immunotherapies are needed to specifically target large and specific TreGs in tumor tissue. Imatinib, a tyrosine kinase inhibitor that blocks STAT3 and STAT5 signaling, has been shown to reduce the abundance of Treg cells and weaken their inhibitory function. However, the poor solubility and cytotoxic effects of this hydrophobic drug on normal cells limit its use [65]. In addition, chemokine receptor 8 (CCR8) is a chemokine receptor that is primarily expressed on TreGs and is thought to be key to CCR8+ Treg-mediated immunosuppression. Studies have shown that CCR8 is upregulated in human tumor resident Tregs in patients with breast, colon, and lung cancer compared to normal tissue TreGs [42,43]. The study showed that CCR8 blocking in a mouse colon cancer model altered the suppressor cell profile of TME by reducing tumor invasion of CCR8+Foxp3+Tregs, while increasing the frequency of tumor specific effector cell invasion. The combined treatment of CCR8 monoclonal antibody and listeria-based tumor vaccine can increase the invasion of vaccine-induced effector T cells to the tumor and increase its function, thereby improving the anti-tumor immunity, tumor regression, and prolonging the survival period of tumor-bearing mice [66].

Immune Checkpoint Blockers and Adenosine/Adenosine Receptor Pathway Blocking: Immune checkpoint blocking has been recognized as a promising approach to restoring immune cells' ability to attack tumor cells. Immune checkpoint blockers such as antibodies against PD-1, PD-1 ligand, or CTLA4 have been commercialized. However, immune checkpoint blocking is often combined with other traditional therapies [67]. Adenosine is an important immunosuppressive metabolite in TME. Adenosine, derived primarily from extracellular adenosine triphosphate, regulates the function of every tissue and organ through receptor-dependent and non-receptor-dependent mechanisms, the former mediated by four G-protein-coupled receptors (A1R, A2aR, A2bR, A3R). The A1R and A3R subtypes inhibited the activity of adenylyl cyclase, while the A2aR and A2bR stimulated the activity of adenylyl cyclase, thereby regulating the level of cyclic adenosine phosphate. Adenosine can be produced by hydrolyzing adenosine diphosphate or S-adenosine homocysteine with intracellular CD73 or S-adenosine homocysteine hydrolase. Tumor-infiltrating Treg cells produce adenosine through the expression of CD39 and CD73, thus exerting their immunosuppressive function, while expressing A2aR to regulate their own proliferation, activation and function [68]. Therefore, targeting adenosine/adenosine receptor pathway is expected to be a new target to inhibit tumor invasion of Treg cells.

Arruga, et al. showed that targeting A2aR had no effect on tumor size and weight in a mouse model of chronic lymphocytic leukemia, but it could save immune cell dysfunction by reducing the accumulation of Treg, restoring T cell CD107a expression, and increasing

the secretion of interleukin-2 and interferon-γ [69]. It showed that anti-A2AR affected the function of Treg cells and T cells but not tumor cells. Willingham et al. showed that anti-A2AR, combined with anti-PD-1 ligand or anti-CTLA-4 treatment, eliminated tumors in up to 90% of treated mice, including restoring immune responses in models with incomplete responses to PD-1 ligand or anti-CTLA-4 monoclonal antibodies. Recent studies have shown that the immunomodulatory mechanism of CD73 blockers is different from that of PD-1 blockers in a mouse model of colorectal cancer. The expression of Nt5e (CD73 gene) and Entpd1(CD39 gene) affects T cell receptor diversity and T cell transcription profile, suggesting that they play an important role in tumor T cell failure, while PD-1 blocking significantly increases the receptor diversity of ENTPD1-T cells and Pdcd1 (PD-1 gene) +T cells. Anti-cd73 increased the anticancer function of immunosuppressive Tregs and depleted T cells, while PD-1 blockers quantitatively decreased the number of TREgs and M2 macrophages with high Malat1 expression. PD-1 blocking induced Treg loss, and anti-CD73 treatment led to increased activation of CD8+T cells, and the combination of the two had a synergistic effect. Targeting A2aR and CD73 can synergistically enhance anti-tumor immunity [70].

Nano-Targeted Treg and Combination Therapy: Cancer immunotherapy not only treats cancer by inducing a strong anti-tumor immune response, but also controls metastasis and prevents its recurrence. Therefore, cancer immunotherapy has significant advantages over traditional cancer treatments. However, existing cancer immunotherapies also have some limitations, such as inducing destructive autoimmunity

[71] and a lack of effective delivery of cancer antigens to immune cells [72]. In addition, the immunosuppressant TME itself can impair the efficacy of cancer immunotherapy [73]. Nanotechnology offers an opportunity to overcome these shortcomings of traditional cancer immunotherapies, thereby improving their efficacy. Nanoparticles have several unique properties compared to bulk structures, such as small particle size, tunable shape, strong cell penetration, and enhanced/improved magnetic, electrical, mechanical, and optical properties [74]. Nanomaterials passively accumulate in TME by enhancing permeability and retention effects, reflecting the disordered tumor vascular thinning. Nanomaterial-based approaches can modulate the immunological characteristics of TME and can be used to deplete or reprogram Treg cells [67]. The results show that the nano-platform has many advantages, including:

1. Delivering antigens and adjuvants to the same antigen-presenting cells or intracellular compartments.
2. Prolonging the half-life of biologically active cargo molecules by avoiding enzymatic degradation in the blood circulation.
3. Increased accumulation in tumor tissues through size-dependent enhanced permeability and retention effects.
4. Surface modifications for specific tissues or cells.
5. Safe stimulus-sensitive behavior.
6. Drug tolerance is higher due to less accumulation in off-target organs and tissues.
7. Surface coupling of antigens and co-stimulatory molecules to design artificial antigen precursors to effectively activate T cells.
8. Diversified routes of administration, such as nasal administration or subcutaneous administration of the microneedle patch.
9. Innate immunomodulatory function of genetically engineered nanoparticles [74].

In a 4T1 mouse model of breast tumors, sequential application of iron oxide nanoparticle mediated photothermal therapy helps to preferentially depletes tumor-recruited Tregs, thereby enhancing anti-CTLA-4 based cancer immunotherapy against unresponsive tumors such as breast tumors [75]. In addition, in a mouse melanoma model, an imatinib-loaded hybrid nanoparticle modified peptide targeting Treg cells was used to target the Nrp1 receptor on Treg cells and bind to a well-known anti-CTLA-4 immuno checkpoint inhibitor. The peptide modified hybrid nanoparticles showed good stability and effective targeting to Treg cells and enhanced the down-regulation effect of imatinib on Treg cells by inhibiting the phosphorylation of STAT3 and STAT5. CD8+T cells can be activated by down-regulating immunosuppressed Treg cells, thereby activating a powerful anti-tumor immune response. Compared with injection of free imatinib, hybrid nanoparticle modified peptides loaded with imatinib can promote tumor accumulation and regression in vivo, as free imatinib exhibits lower tumor accumulation and has side effects on other organs [65]. The abnormality of TGF-β signaling pathway in TME is closely related to the obstruction of T cell differentiation, the generation of Treg subsets, and the inhibition of tumor-killing effect of cytotoxic lymphocytes, thus leading to the formation of tumor immune environment [76,77]. Therefore, inhibition of TGF-β signaling pathway can enhance the infiltration of T cells while reducing the production of immunosuppressive Treg cells, further enhancing the immune response [78]. Huang et al. reported a dual approach to alleviating immunosuppression by using selective aggregation and deep penetration of nanomaterials and reducing Treg cells by inhibiting the transforming growth factor-β pathway. The combination of increased cytotoxic T lymphocytes (optimized killing weapon) and PD-1/PD-1 ligand immune checkpoint blocking (“ protective “neutralization of tumor cells) is an effective strategy for treating primary breast tumors and metastases in 4T1 mice [79].

Prospect

Tumor infiltrating Treg cells play an immunosuppressive role through different mechanisms. The removal of Treg cells can enhance the anti-tumor immune response but may also cause autoimmunity. Therefore, a key question in designing cancer immunotherapies targeting TreGs is how to specifically eliminate Treg cells that infiltrate tumor tissue without affecting tumor reactive effector T cells.

This can be achieved by differentially controlling Tregs and effector T cells in different ways. Treg-specific loss of signaling molecules such as PI3K [80] can impair Treg function and thus enhance tumor immunity, suggesting that some T-cell signaling inhibitors can be used for selective loss or dysfunction of Treg cells in the tumor immune environment. Tumor Treg cells and effector conventional T cells may also have different metabolic patterns and can be targeted by small molecules [81]. Further refining strategies for Treg cell failure or dysfunction through biologics or chemical agents while enhancing the tumor-killing activity of effector conventional T cells is expected to make cancer immunotherapy more effective with fewer side effects in the near future. More importantly, the tumor microenvironment is a complex and variable environment that ultimately promotes tumor growth through multiple cell interactions. Therefore, we should not be limited to simply targeting tumor infiltrating Treg cells but should be combined with immune checkpoint blockers to inhibit tumor progression from multiple mechanisms.

References

1. Antonioli L, M Fornai, C Pellegrini, VD Antongiovanni, R Turiello, et al. (2021) Adenosine Signaling in the Tumor Microenvironment. Adv Exp Med Biol 1270: 145-167.
2. Tuccitto A, E Shahaj, E Vergani, S Ferro, V Huber, et al. (2019) Immunosuppressive Circuits in Tumor Microenvironment and Their Influence on Cancer Treatment Efficacy. Virchows Arch 474(4): 407-420.
3. Johnston FM, M Beckman (2019) Updates on Management of Gastric Cancer. Curr Oncol Rep 21(8): 67.
4. Zheng C, L Zheng, JK Yoo, H Guo, Y Zhang, et al. (2017) Landscape of Infiltrating T Cells in Liver Cancer Revealed by Single-Cell Sequencing. Cell 169(7): 1342-1356.e16.
5. You Y, Y Li, M Li, M Lei, M Wu, et al. (2018) Ovarian Cancer Stem Cells Promote Tumour Immune Privilege and Invasion Via Ccl5 and Regulatory T Cells. Clin ExpImmunol 191(1): 60-73.
6. Tang Y, X Xu, S Guo, C Zhang, Y Tang, et al. (2014) An Increased Abundance of Tumor-Infiltrating Regulatory T Cells Is Correlated with the Progression and Prognosis of Pancreatic Ductal Adenocarcinoma. PLoS One 9(3): e91551.
7. Vence L, AK Palucka, JW Fay, T Ito, YJ Liu, et al. (2007) Circulating Tumor Antigen-Specific Regulatory T Cells in Patients with Metastatic Melanoma. Proc Natl Acad Sci USA 104(52): 20884-20889.
8. Loyher PL, J Rochefort, C Baudesson de Chanville, P Hamon, et al. (2016) Ccr2 Influences T Regulatory Cell Migration to Tumors and Serves as a Biomarker of Cyclophosphamide Sensitivity. Cancer Res 76(22): 6483-6494.
9. Nishikawa H, S Sakaguchi (2014) Regulatory T Cells in Cancer Immunotherapy. Curr OpinImmunol 27: 1-7.
10. Tanaka A, S Sakaguchi (2017) Regulatory T Cells in Cancer Immunotherapy. Cell Res 27(1): 109-118.
11. Takeuchi Y, H Nishikawa (2016) Roles of Regulatory T Cells in Cancer Immunity. Int Immunol 28(8): 401-409.
12. Gershon RK, K Kondo (1970) Cell Interactions in the Induction of Tolerance: The Role of Thymic Lymphocytes. Immunology 18(5): 723-737.
13. Sakaguchi S, N Sakaguchi, M Asano, M Itoh, M Toda (1995) Immunologic Self-Tolerance Maintained by Activated T Cells Expressing Il-2 Receptor Alpha-Chains (Cd25). Breakdown of a Single Mechanism of Self-Tolerance Causes Various Autoimmune Diseases. J Immunol 155(3): 1151-1164.
14. Brunkow ME, EW Jeffery, KA Hjerrild, B Paeper, LB Clark, et al. (2001) Disruption of a New Forkhead/Winged-Helix Protein, Scurfin, Results in the Fatal Lymphoproliferative Disorder of the Scurfy Mouse. Nat Genet 27(1): 68-73.
15. Fontenot JD, JP Rasmussen, LM Williams, JL Dooley, AG Farr, et al. (2005) Regulatory T Cell Lineage Specification by the Forkhead Transcription Factor Foxp3. Immunity 22(3): 329-341.
16. Josefowicz SZ, LF Lu, AY Rudensky (2012) Regulatory T Cells: Mechanisms of Differentiation and Function. Annu Rev Immunol 30 : 531-564.
17. Loddenkemper C, J Maul, E Berg, H Stein, M Zeitz, et al. (2006) Analysis of Foxp3 Protein Expression in Human Cd4(+)Cd25(+) Regulatory T Cells at the Single-Cell Level. Eur J Immunol 36(1): 245; author reply 46.
18. Whiteside TL (2012) What Are Regulatory T Cells (Treg) Regulating in Cancer and Why? Semin Cancer Biol 22(4): 327-334.
19. Jonuleit H, E Schmitt, M Stassen, A Tuettenberg, J Knop, et al. (2001) Identification and Functional Characterization of Human Cd4(+)Cd25(+) T Cells with Regulatory Properties Isolated from Peripheral Blood. J Exp Med 193(11): 1285-1294.
20. McRitchie BR, B Akkaya (2022) Exhaust the Exhausters: Targeting Regulatory T Cells in the Tumor Microenvironment. Front Immunol 13: 940052.
21. Ge Y, HH Bohm, A Rathinasamy, M Xydia, X Hu, et al. (2019) Tumor-Specific Regulatory T Cells from the Bone Marrow Orchestrate Antitumor Immunity in Breast Cancer. Cancer Immunol Res 7(12): 1998-2012.
22. Ohue Y, H Nishikawa (2019) Regulatory T (Treg) Cells in Cancer: Can Treg Cells Be a New Therapeutic Target? Cancer Sci 110(7): 2080-2089.
23. Chang AL, J Miska, DA Wainwright, M Dey, CV Rivetta, et al. (2016) Ccl2 Produced by the Glioma Microenvironment Is Essential for the Recruitment of Regulatory T Cells and Myeloid-Derived Suppressor Cells. Cancer Res 76(19): 5671-5682.
24. Nagase H, T Takeoka, S Urakawa, A Morimoto Okazawa, A Kawashima, et al. (2017) $Icos^+$ $Foxp3^+$ Tils in Gastric Cancer Are Prognostic Markers and Effector Regulatory T Cells Associated with Helicobacter Pylori. Int J Cancer140(3): 686-695.
25. Pallandre JR, E Brillard, G Crehange, A Radlovic, JP Remy Martin, et al. (2007) Role of Stat3 in $Cd4^+Cd25^+Foxp3^+$ Regulatory Lymphocyte Generation: Implications in Graft-Versus-Host Disease and Antitumor Immunity. J Immunol 179(11) : 7593-7604.
26. Zorn E, EA Nelson, M Mohseni, F Porcheray, H Kim, et al. (2006) Il-2 Regulates Foxp3 Expression in Human $Cd4^+Cd25^+$ Regulatory T Cells through a Stat-Dependent Mechanism and Induces the Expansion of These Cells in Vivo. Blood 108(5): 1571-1579.
27. Gavin MA, JP Rasmussen, JD Fontenot, V Vasta, VC Manganiello, et al. (2007) Foxp3-Dependent Programme of Regulatory T-Cell Differentiation. Nature 445(7129): 771-775.
28. Sasidharan Nair V, E Elkord (2018) Immune Checkpoint Inhibitors in Cancer Therapy: A Focus on T-Regulatory Cells. Immunol Cell Biol 96(1): 21-33.
29. Mair F, JR Erickson, M Frutoso, AJ Konecny, E Greene, et al. (2022) Extricating Human Tumour Immune Alterations from Tissue Inflammation. Nature 605(7911): 728-735.
30. Li XY, AK Moesta, C Xiao, K Nakamura, M Casey, et al. (2019) Targeting Cd39 in Cancer Reveals an Extracellular Atp- and Inflammasome-Driven Tumor Immunity. Cancer Discov 9(12): 1754-1773.

31. Kim HR, HJ Park, J Son, JG Lee, KY Chung, et al. (2019) Tumor Microenvironment Dictates Regulatory T Cell Phenotype: Upregulated Immune Checkpoints Reinforce Suppressive Function. J Immunother Cancer 7(1): 339.

32. Maj T, W Wang, J Crespo, H Zhang, W Wang, et al. (2017) Oxidative Stress Controls Regulatory T Cell Apoptosis and Suppressor Activity and Pd-L1-Blockade Resistance in Tumor. Nat Immunol 18(12): 1332-1341.

33. Beavis PA, MA Henderson, L Giuffrida, JK Mills, K Sek, et al. (2017) Targeting the Adenosine 2a Receptor Enhances Chimeric Antigen Receptor T Cell Efficacy. J Clin Invest 127(3): 929-941.

34. Wang H, F Franco, YC Tsui, X Xie, MP Trefny, et al. (2020) Cd36-Mediated Metabolic Adaptation Supports Regulatory T Cell Survival and Function in Tumors. Nat Immunol 21(3): 298-308.

35. Lu Y, Y Li, Q Liu, N Tian, P Du, et al. (2021) Mondoa-Thioredoxin-Interacting Protein Axis Maintains Regulatory T-Cell Identity and Function in Colorectal Cancer Microenvironment. Gastroenterology 161(2): 575-591. e16.

36. Zheng Y, S Josefowicz, A Chaudhry, XP Peng, K Forbush, et al. (2010) Role of Conserved Non-Coding DNA Elements in the Foxp3 Gene in Regulatory T-Cell Fate. Nature 463(7282): 808-812.

37. Tone Y, K Furuuchi, Y Kojima, ML Tykocinski, MI Greene, et al. (2008) Smad3 and Nfat Cooperate to Induce Foxp3 Expression through Its Enhancer. Nat Immunol 9(2): 194-202.

38. Xu L, A Kitani, I Fuss, W Strober (2007) Cutting Edge: Regulatory T Cells Induce $Cd4^{+}Cd25$-Foxp3- T Cells or Are Self-Induced to Become Th17 Cells in the Absence of Exogenous Tgf-Beta. J Immunol 178(11): 6725-6729.

39. Zhang Y, J Guo, R Jia (2021) Treg: A Promising Immunotherapeutic Target in Oral Diseases. Front Immunol 12: 667862.

40. Kidani Y, W Nogami, Y Yasumizu, A Kawashima, A Tanaka, et al. (2022) Ccr8-Targeted Specific Depletion of Clonally Expanded Treg Cells in Tumor Tissues Evokes Potent Tumor Immunity with Long-Lasting Memory. Proc Natl Acad Sci USA 119(7): e2114282119.

41. Van Damme H, B Dombrecht, M Kiss, H Roose, E Allen, et al. (2021) Therapeutic Depletion of Ccr8(+) Tumor-Infiltrating Regulatory T Cells Elicits Antitumor Immunity and Synergizes with Anti-Pd-1 Therapy. J Immunother Cancer 9(2): e001749.

42. Plitas G, C Konopacki, K Wu, PD Bos, M Morrow, et al. (2016) Regulatory T Cells Exhibit Distinct Features in Human Breast Cancer. Immunity 45(5): 1122-1134.

43. De Simone M, A Arrigoni, G Rossetti, P Gruarin, V Ranzani, et al. (2016) Transcriptional Landscape of Human Tissue Lymphocytes Unveils Uniqueness of Tumor-Infiltrating T Regulatory Cells. Immunity 45(5): 1135-1147.

44. Floess S, J Freyer, C Siewert, U Baron, S Olek, et al. (2007) Epigenetic Control of the Foxp3 Locus in Regulatory T Cells. PLoS Bio l5(2): e38.

45. Lal G, N Zhang, W van der Touw, Y Ding, W Ju, et al. (2009) Epigenetic Regulation of Foxp3 Expression in Regulatory T Cells by DNA Methylation. J Immunol 182(1): 259-273.

46. Lal G, JS Bromberg (2009) Epigenetic Mechanisms of Regulation of Foxp3 Expression. Blood 114(18): 3727-3735.

47. Placek K, G Hu, K Cui, D Zhang, Y Ding, et al. (2017) Mll4 Prepares the Enhancer Landscape for Foxp3 Induction Via Chromatin Looping. Nat Immunol 18(9): 1035-1045.

48. Decking UK, G Schlieper, K Kroll, J Schrader (1997) Hypoxia-Induced Inhibition of Adenosine Kinase Potentiates Cardiac Adenosine Release. Circ Res 81(2): 154-164.

49. Bergmann C, L Strauss, R Zeidler, S Lang, TL Whiteside (2007) Expansion of Human T Regulatory Type 1 Cells in the Microenvironment of Cyclooxygenase 2 Overexpressing Head and Neck Squamous Cell Carcinoma. Cancer Res 67(18): 8865-8873.

50. Whiteside TL, EK Jackson (2013) Adenosine and Prostaglandin E2 Production by Human Inducible Regulatory T Cells in Health and Disease. Front Immunol 4: 212.

51. Ohta A, M Sitkovsky (2014) Extracellular Adenosine-Mediated Modulation of Regulatory T Cells. Front Immunol 5: 304.

52. Liu C, CJ Workman, DA Vignali (2016) Targeting Regulatory T Cells in Tumors. FEBSJ 283(14): 2731-2748.

53. Sistigu A, S Viaud, N Chaput, L Bracci, E Proietti, L Zitvogel (2011) Immunomodulatory Effects of Cyclophosphamide and Implementations for Vaccine Design. Semin Immunopathol 33(4): 369-383.

54. Ghiringhelli F, N Larmonier, E Schmitt, A Parcellier, D Cathelin, et al. (2004) $Cd4^{+}Cd25^{+}$ Regulatory T Cells Suppress Tumor Immunity but Are Sensitive to Cyclophosphamide Which Allows Immunotherapy of Established Tumors to Be Curative. Eur J Immunol 34(2): 336-344.

55. Hori S, T Nomura, S Sakaguchi (2003) Control of Regulatory T Cell Development by the Transcription Factor Foxp3. Science 299(5609): 1057-1061.

56. Kasprowicz DJ, N Droin, DM Soper, F Ramsdell, DR Greenet al. (2005) Dynamic Regulation of Foxp3 Expression Controls the Balance between $Cd4^{+}$ T Cell Activation and Cell Death. Eur J Immunol 35(12): 3424-3432.

57. Brode S, T Raine, P Zaccone, A Cooke (2006) Cyclophosphamide-Induced Type-1 Diabetes in the Nod Mouse Is Associated with a Reduction of $Cd4^{+}Cd25^{+}Foxp3^{+}$ Regulatory T Cells. J Immunol 177(10): 6603-6612.

58. Zou H, R Li, H Hu, Y Hu, X Chen (2018) Modulation of Regulatory T Cell Activity by Tnf Receptor Type Ii-Targeting Pharmacological Agents. Front Immunol 9: 594.

59. Lutsiak ME, RT Semnani, R De Pascalis, SV Kashmiri, J Schlom, et al. (2005) Inhibition of $Cd4(+)25^{+}$ T Regulatory Cell Function Implicated in Enhanced Immune Response by Low-Dose Cyclophosphamide. Blood 105(7): 2862-2868.

60. van der Most RG, AJ Currie, S Mahendran, A Prosser, A Darabi, et al. (2009) Tumor Eradication after Cyclophosphamide Depends on Concurrent Depletion of Regulatory T Cells: A Role for Cycling Tnfr2-Expressing Effector-Suppressor T Cells in Limiting Effective Chemotherapy. Cancer Immunol Immunother 58(8): 1219-1228.

61. Chen X, JJ Subleski, H Kopf, OM Howard, DN Mannel, et al. (2008) Cutting Edge: Expression of Tnfr2 Defines a Maximally Suppressive Subset of Mouse Cd4+Cd25+Foxp3+ T Regulatory Cells: Applicability to Tumor-Infiltrating T Regulatory Cells. J Immunol 180(10): 6467-6471.

62. Chang LY, YC Lin, JM Chiang, J Mahalingam, SH Su, et al. (2015) Blockade of Tnf-Alpha Signaling Benefits Cancer Therapy by Suppressing Effector Regulatory T Cell Expansion. Oncoimmunology 4(10): e1040215.

63. Derman BA, Y Zha, TM Zimmerman, R Malloy, A Jakubowiak, et al. (2020) Regulatory T-Cell Depletion in the Setting of Autologous Stem Cell Transplantation for Multiple Myeloma: Pilot Study. J Immunother Cancer 8(1): e000286.

64. Barsheshet Y, G Wildbaum, E Levy, A Vitenshtein, C Akinseye, et al. (2017) $Ccr8^{+}Foxp3^{+}$ T_{reg} Cells as Master Drivers of Immune Regulation. Proc Natl Acad Sci USA 114(23): 6086-6091.

65. Ou W, RK Thapa, L Jiang, ZC Soe, M Gautam, et al. (2018) Regulatory T Cell-Targeted Hybrid Nanoparticles Combined with Immuno-Checkpoint Blockage for Cancer Immunotherapy. JControl Release 281: 84-96.

66. Villarreal DO, A L Huillier, S Armington, C Mottershead, EV Filippova, et al. (2018) Targeting Ccr8 Induces Protective Antitumor Immunity and Enhances Vaccine-Induced Responses in Colon Cancer. Cancer Res 78(18): 5340-5348.

67. Le QV, J Suh, YK Oh (2019) Nanomaterial-Based Modulation of Tumor Microenvironments for Enhancing Chemo/Immunotherapy. AAPSJ 21(4): 64.

68. Allard B, D Allard, L Buisseret, J Stagg (2020) The Adenosine Pathway in Immuno-Oncology. Nat Rev Clin Oncol 17(10): 611-629.

69. Arruga F, S Serra, N Vitale, G Guerra, A Papait, et al. (2021) Targeting of the A2a Adenosine Receptor Counteracts Immunosuppression in Vivo in a Mouse Model of Chronic Lymphocytic Leukemia. Haematologica 106(5): 1343-53.

70. Arabella Young, Shin Foong Ngiow, Deborah S Barkauskas, Erin Sult, Carl Hay, et al. (2016) Co-Inhibition of Cd73 and A2ar Adenosine Signaling Improves Anti-Tumor Immune Responses. CancerCell 30(3): 391-403.

71. Giao Q Phan, James C Yang, Richard M Sherry, Patrick Hwu, Suzanne L Topalian, et al. (2003) Cancer Regression and Autoimmunity Induced by Cytotoxic T Lymphocyte-Associated Antigen 4 Blockade in Patients with Metastatic Melanoma. Proc Natl Acad Sci USA 100(14): 8372-8377.

72. Buabeid MA, EA Arafa, G Murtaza (2020) Emerging Prospects for Nanoparticle-Enabled Cancer Immunotherapy. JImmunolRes 2020: 9624532.

73. Munn DH, V Bronte (2016) Immune Suppressive Mechanisms in the Tumor Microenvironment. CurrOpinImmunol 39: 1-6.

74. Thakur N, S Thakur, S Chatterjee, J Das, PC Sil (2020) Nanoparticles as Smart Carriers for Enhanced Cancer Immunotherapy. FrontChem 8: 597806.

75. Hongwei Chen, Xin Luan, Hayley J Paholak, Joseph P Burnett, Nicholas O Stevers (2020) Depleting Tumor-Associated Tregs Via Nanoparticle-Mediated Hyperthermia to Enhance Anti-Ctla-4 Immunotherapy. Nanomedicine(Lond) 15(1): 77-92.

76. Ungefroren H (2019) Blockade of Tgf-Beta Signaling: A Potential Target for Cancer Immunotherapy? ExpertOpinTherTargets 23(8): 679-93.

77. Polanczyk MJ, E Walker, D Haley, BS Guerrouahen, ET Akporiaye (2019) Blockade of Tgf-Beta Signaling to Enhance the Antitumor Response Is Accompanied by Dysregulation of the Functional Activity of Cd4(+)Cd25(+) Foxp3(+) and Cd4(+)Cd25(-)Foxp3(+) T Cells. JTranslMed 17(1): 219.

78. Ganesh K, J Massague (2018) Tgf-Beta Inhibition and Immunotherapy: Checkmate. Immunity 48(4): 626-628.

79. Ju Huang, Liang Zhang, Weichen Zhou, Jingxue Wang, Ruo Zhang (2021) Dual Mitigation of Immunosuppression Combined with Photothermal Inhibition for Highly Effective Primary Tumor and Metastases Therapy. Biomaterials 274: 120856.

80. Khaled Ali, Dalya R Soond, Roberto Pineiro, Thorsten Hagemann, Wayne Pearce, et al. (2014) Inactivation of Pi(3)K P110delta Breaks Regulatory T-Cell-Mediated Immune Tolerance to Cancer. Nature 510(7505): 407-411.

81. Gabriel SS, A Kallies (2016) Sugars and Fat - a Healthy Way to Generate Functional Regulatory T Cells. EurJImmunol 46(12): 2705-2709.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.53.008433

Jianlei Xing. Biomed J Sci & Tech Res