



THE ROLE OF TREG CELLS IN IMMUNE EVASION IN TUMOR MICROENVIRONMENT

Tamalika Paul*

Department of Environmental Studies (Science), City College, 102/1, Raja Rammohan Sarani, Kolkata -700009, India.



*Corresponding Author: Tamalika Paul

Department of Environmental Studies (Science), City College, 102/1, Raja Rammohan Sarani, Kolkata -700009, India. Email id: tamalikapaul3@gmail.com, DOI: <https://doi.org/10.5281/zenodo.19704056>

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ABSTRACT

The tumour microenvironment (TME) plays an important role in immune suppression, cancer progression, metastasis and therapy resistance. Among the different cellular components of the tumor microenvironment, Tregs comprise diverse, heterogeneous subsets. Tumour-infiltrating Treg cells consist of a phenotypically and functionally distinct subset and contribute to cancer prognosis and clinical outcomes. Treg cells are important immunosuppressors cells. Treg cells are key contributors to immune evasion because they suppress pro-inflammatory responses, induce metabolic disruption and promote metastasis within the tumour microenvironment. They inhibit the effector T cells' function. In this way, Treg cells establish immunosuppressive tumor microenvironment, thus enabling tumor immune evasion. So, understanding the Treg biology in tumour microenvironment is very crucial for designing potent cancer therapy. In this review, the role of Tregs in cancer progression and tumour microenvironment is discussed. It is also discussed that the therapeutic opportunities for targeting Tregs cells to promote anti-tumor immune responses and also clinical benefits.

KEYWORDS: Regulatory T cells (Tregs), Tumor micro environment, Immune evasion, Immune tolerance, Immunomodulation.

INTRODUCTION

Our immune cells are able to recognize and destruct cancer cells. This process is known as immunosurveillance. But cancer cells have ability to evade host's immune response through immunosubversion^[1] and through immunoediting.^[2] Some of immune systems in our body inhibit tumor growth but other some immune systems promote tumor growth by promoting chronic inflammation.^[3] Some immunosuppressor cells and suppressor T cells have involved in inducing tumor growth. Regulatory T cell (Treg cells) is one of most important immunosuppressor T cells. In cancer, Tregs infiltrate tumor microenvironment then they destruct anti-tumor immune responses that cause poorer prognoses.^[4] So, Treg cells play an important role in immune evasion in cancer.

Treg cells are seen throughout the tumor microenvironment. Treg cells create 'Physical', 'trafficking' barriers to immune effector cells so that these immune effector T cells can not able to enter into

tumor microenvironment and performs their function.^[5] Other side, Treg cells have different types of inhibitory receptors such as TIM-3, PD1, and LAG-3 and also release inhibitory cytokines such as TGF β , IL-10, and IL-35 that suppress the anti-tumor T cell response in Tumor microenvironment.^[6] Treg cells also produce different TGF β that induces the development of cancer-associated fibroblast (CAF) that induces deposition of extracellular matrix within stroma. For this effector T cells can not migrate into tumor microenvironment.^[7] Treg cells also produce inhibitory IL-10 and VEGF that promote deregulated angiogenesis.^[8]

In this review, it will be discussed about Treg cells biology and its function. In this review, it will be also discussed about how Treg cells induce pro-tumorigenic effect by suppressing anti-tumor immune response in tumor microenvironment.

Treg recruitment and expansion in Tumors

Treg is responsible for development of immune suppressive tumor microenvironment by suppressing antitumor immunoresponse, so that it promotes immune evasion.^[9] The higher accumulation of Treg cells particular FoxP3+ Treg cells are found in tumor microenvironment that cause poor prognosis in many types of cancers including lung cancer^[10], ovarian cancer^[11,12], non-Hodgkin's lymphoma^[13], pancreatic ductal adenocarcinoma^[14,15], melanoma, other malignancy.^[16,17]

The mechanisms by which Treg cells are accumulated within Tumor microenvironment are discussed below.^[18] In step 1, malignant cells and other immune cells secrete chemokines in tumor microenvironment. This chemokines attract and bind to chemokine receptors of Treg cells that attracts Treg cells toward tumor. Then these Treg cells enter to the tumor. These chemokines-chemokines receptors combinations are CCL5-CCR5, CCL28-CCR10, CCL9/10/11-CXCR3, CCL 22-CCR4. In step 2, malignant cells secrete TGF beta and IL10 highly. These TGF Beta, IL10 are involved in proliferation of these Treg within Tumor microenvironment.

Sphingosine 1-phosphate (SIP), a lipid bioactive molecule has role in angiogenesis. SIP-R (Sphingosine 1-phosphate receptor) is also important immune cells trafficking.^[19] In several research study, SIPR1 signaling involved in Treg cells accumulation within Tumor Microenvironment.^[20] In this review, it was focused basically on the mechanisms by which Treg cells evade or suppress immune response in Tumor microenvironment.

Mechanisms of Treg-mediated Immune evasion in tumor microenvironment

Treg cells has suppressive role in immune evasion and also Treg cells have distinct phenotypic and functional markers that are responsible for immune suppression in tumor microenvironment. These includes T cell immunoglobulin and mucin -domain containing 3 (TIM3), Programmed Death 1 (PD1), Lymphocyte Activating gene -3(LAG3), inducible T cell stimulator, CD25, CD69.^{[21],[22],[23],[24],[25]} Treg cells suppress the activity of CD4+ T cells by secreting TGF beta and IL10 in colorectal cancer reducing Th1-mediated anti-tumor responses.^[26] In tumour microenvironment, Fox3⁻CD69⁺CTLA4⁺ Treg cells are mostly found in HCC.^[27] These Treg cells suppress the activity of effector T cells by membrane bound TGF beta.^[28] Elevated expression of tumour infiltrating (TI) FoxP3⁺ Treg cells in gastric cancer patients has suppressive activity on effector T cells proliferation and promote to gastric cancer progression in a COX-2 and prostaglandin E2 (PGE-2) dependent manner.^[29] The different types of markers expressed on TI treg cells, has suppressive activity on effector T cells. TI Treg cells expressing CTLA4, PD1, LAG3, TIM3 have immunosuppressive activity on

effector T cells.^[30,31] CTLA4 is highly expressed on TI Treg cells. CTLA-4 is highly expressed on TI-Tregs. CTLA-4 binds to CD80/CD86 on antigen-presenting cells (APCs), blocking CD28 costimulatory signaling required for effector T cell activation.^[32,33] This results in impaired proliferation and cytokine production of CD8⁺ and CD4⁺ effector T cells.^[34] The programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis represents one of the most crucial pathways exploited by tumors to suppress anti-tumor immunity. PD-1 is an inhibitory receptor expressed on regulatory T cells (Tregs).^{[35],[36]} Within the tumor microenvironment (TME), PD-L1 is abundantly expressed on tumor cells, tumor-associated macrophages and stromal fibroblasts, which together create an immunosuppressive niche. When PD-1 on Tregs interacts with PD-L1 on tumor or stromal cells, this interaction suppresses the cytotoxic activity of effector CD8⁺ T cells and enhances the stability, proliferation, suppressive function of Tregs themselves.^{[37],[38]}

So, all research studies indicate that Tumour infiltrating Treg cells have suppressive activity on effector T cells proliferation in TME.

Treg mediated modulation of other immune cells in tumour microenvironment

The TME plays a key role in how cancer avoids the immune system and affects the success of immunotherapy.^[39] Tumor cells and various immune and stromal cells work together to create tumour microenvironment that is rich in pro-angiogenic growth factors, hypoxic, and highly immunosuppressive.^[40] Within tumour microenvironment, Treg cells can interact with stromal cells, cancer cells, other immune cells that enhance Treg cells' immune suppressive activity.^[41] Circulating Tregs can suppress NK cells using membrane-bound TGF-β. This reduces the expression of the activating NK cell receptor (NKG2D) in gastrointestinal stromal tumor patients.^{[42],[43]} MDSC is immunosuppressive cells. It suppresses the activity of other immune cells along with Treg cells within TME.^[44] Other side, the stroma cells play a crucial role in cancer initiation, progression, and metastasis. In vitro studies suggest stromal cells recruit and generate Tregs at tumor site. Cell to cell contact, soluble mediators-including prostaglandin E(2), transforming growth factor β play a vital role for interaction between Treg cells and stromal cells.^[45] Other study, ECs (Epithelium Cells) and LECs (lymphatic endothelial cells) play crucial roles in immune response and cell trafficking, enhancing Treg migration and triggering Treg generation under inflammatory conditions. Treg cells interacts with EC cells and impairs the EC selectin expression, prevents adhesion to Treg and restrain Treg migration.^{[46],[47],[48]} TEX (Tumor-derived exosomes) improve Treg function by delivering tumor factors that boost suppressive activity and resistance to apoptosis.^{[49],[50]}

Tumor-infiltrating T-regulatory cells take metabolic advantages to survive in tumour microenvironment and evade immune response

Cancer cells use glycolysis to survive and grow, creating a tough environment for surrounding cells, including immune cells in tumor microenvironment. Then tumour microenvironment, which has low sugar, low oxygen, and low pH, is harmful for effector T cells that depend on glycolysis, limiting their ability to fight tumors.^{[51],[52]} In contrast, regulatory T (Treg) cells can thrive in these tumour microenvironments. Treg cells can use harmful metabolites, such as lactic acid, for their survival, while the lack of amino acids affect on effector T cell activation but helps Treg proliferation.^{[53],[54]} Additionally, factors like hypoxia enhance Treg cell activity and migration.^[55] Now, it will be discussed how Treg cell takes metabolic advantages to survive in tumour microenvironment.

Oxidative phosphorylation is main energy source for naive T cells. Once activated by TCR stimulation and co-stimulation, T cells change their energy source from oxidative phosphorylation to glycolysis for growth and maintenance. In contrast, regulatory T cells can activate, proliferate and exert immune suppression in tumour microenvironment where glycolysis is restricted.^{[56],[57]} So, in tumour microenvironment, abundance of T regulatory cells is more than T effector cells. Treg can survive under restricted glucose metabolism in tumour microenvironment through CTLA-4 overexpression, which blocks CD28 signaling towards glucose utilization that ensure Treg cells' stability and function.^[58]

Cancer cells use anaerobic glycolysis, or "Warburg metabolism," where glycolysis happens even when oxygen is present to support their energy and growth needs. Rapidly dividing cancer cells consume a lot of glucose, which reduces its levels in the tumor environment.^[59] The level of lactic acid becomes high in the Tumour microenvironment.^[60] Low glucose and high lactic acid hinder the function of T effector cells, weakening immune response.^{[61],[62]} Lactic acid disrupts T cell growth through its NAD(H) redox state. Treg cells utilize lactic acid as a fuel and modify their metabolism, activating them within the tumor microenvironment.^[63] Lactic acid enters into Treg cells through MCT1 which is lactic acid transporter and promote nuclear translocation of NFAT1, thereby enhancing PD-1 expression.^[64]

Expression of fatty acid synthase is high in some types of cancer cells because fatty acid synthase is required for synthesis of phospholipid, cell membrane component that is required for cancer cell growth.^[65] So high amount of fatty acid is accumulated in tumour microenvironment (TME).^[66] In TME, CD36, a coreceptor of fatty acid uptake is highly upregulated in intratumoral Treg cells. Treg activated AMP-activated protein kinase and dependent on Fatty acid oxidation.^{[67],[68],[69]} Activated AMP-activated protein kinase is sufficient to decrease

Glut1 and increase Treg generation in TME.^[70] Foxp3 upregulates the electron transport chain in Treg cells, enhancing their ability to utilize fatty acid, as fuel for oxidative phosphorylation.^[71] Treg cells have ability to absorb Fatty acid. So, enhanced Fatty acid availability in tumour microenvironment promotes Treg cells to survival, proliferation and exert immune-suppressive functions.^[72] Enhanced fatty acid availability in tumor microenvironment cause cytotoxic T cell dysfunction. When fatty acid enters into Tc cells, fatty acid cause mitochondrial dysfunction.^[73] Otherside, rate of catabolism of fatty acid is low in Tc cells that causes lipotoxicity in Tc cells in pancreatic cancer.^[74] Cholesterol induces ER stress in CD8+ T cell (Tc cells) in the tumor microenvironment that cause CD8+ T cells dysfunction.^[75]

Glutamine, a non-essential amino acid, is utilized by cancer cells to support the TCA cycle. Glutamine is uptaken by glutamine transporters, such as ASCT2 (SLC1A5), SNAT1 (SLC38A1), SNAT2 (SLC38A2), and SNAT5 (SLC38A5). These transporters are highly expressed by cancer cells.^{[76],[77]} Under hypoxic and dysfunctional mitochondrial conditions, cancer cells decrease glutamine metabolism for lipid biosynthesis.^[78] In glucose-limited environments, glutamine derivatives such as fumaric and malic acids increase, suggesting glutamine drives a glucose-independent TCA cycle.^[79] Glutamine metabolism inhibits glucose uptake in the TME. Glutamine deficiency in the TME prevents naive CD4+ T cells from differentiation into TH1 cells and promotes Treg cell differentiation via α -ketoglutarate (α -KG), a metabolite of glutamine.^{[80],[81]} High glutamate levels change cytokine production by dendritic cells and boost Treg cells in autoimmune models.^[82] Increased glutamate promotes Treg cells and enhances their proliferative that causes immune suppressive function.^[83] Tryptophan is very important amino acid that is required for protein synthesis, serotonin production, and immune cell function.^[84] When tryptophan is low, GCN2 (general control nondepressible-2) sense tryptophan depletion.^[85] This incident downregulate mTOR pathway reduces the growth and activation of effector T cells while inducing a Treg cell phenotype in naive CD4+ T cells.^[86] Tryptophan is metabolized into kynurenine by three rate-limiting enzymes, indoleamine 2,3-dioxygenase 1 (IDO1), IDO2, and tryptophan 2,3-dioxygenase (TDO). Kynurenine inhibit immune function by inhibiting antigen presenting cell differentiation.^[87] and promoting Treg differentiation^{[88],[89]}, and blocking IL-2 signaling.^[90] High levels of IDO1, which is linked to inflammation and found in many cancers, are associated with worse outcomes.^{[91],[92]}

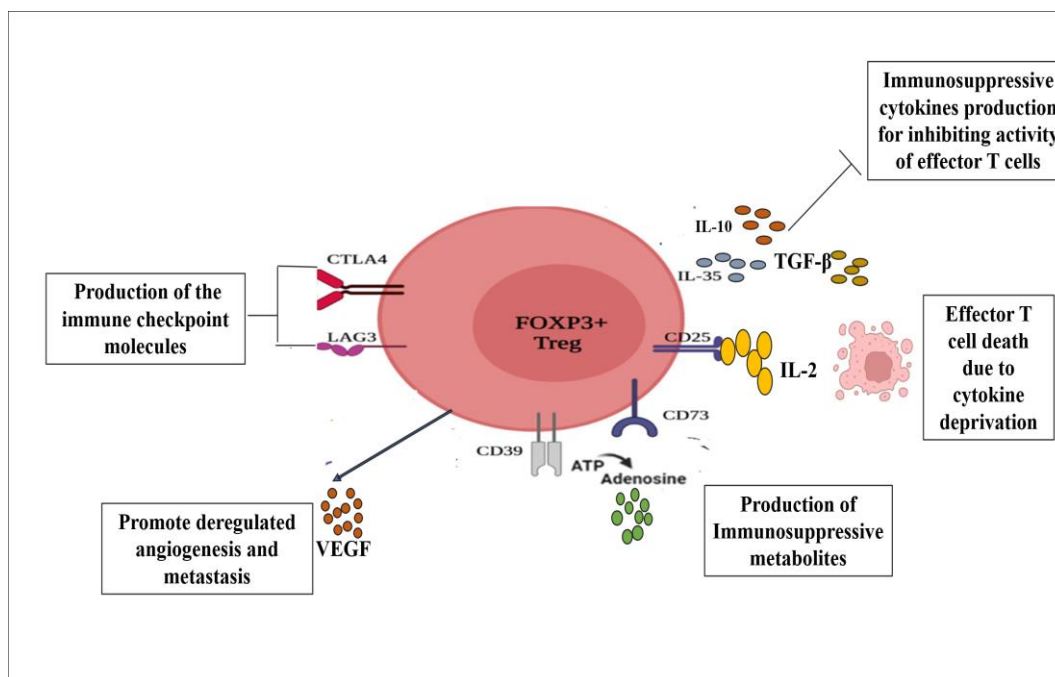


Figure 1: Schematic illustration of the immunosuppressive functions of tumor-infiltrating Tregs in tumour microenvironment: Tumor-infiltrating Tregs deploy multiple immunosuppressive functions through different complementary mechanisms. Treg cells promote the secretion of immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor- β (TGF- β), which inhibit effector T-cell activation and proliferation. Tregs consume most of the IL2 present in the TME which causes IL2 deprivation. So, IL2 is less available to other effector T cells leading to their apoptosis. Metabolic perturbation occurs by generation of adenosine by ectoenzymes CD39 and CD73. Tregs promote tumor progression by producing VEGF, thereby contributing to deregulated angiogenesis and metastasis. TI Treg cells promote expression of immune checkpoint molecules like CTLA4, LAG3, contributing to uncontrolled tumor progression.

Biology of Treg cells: Treg cells have immunosuppressive activity. Treg cells can be classified into several subtypes based on their origin, function and expression of specific biomarkers. So, Firstly, Treg cells are classified into different categories. Naturally occurring Treg cells (nTreg cell) are originated in thymus and has central role in central immune tolerance.^[93] These nTreg cells has biomarker CD4+CD25+FoxP3+ maintaining immunotolerance and preventing autoimmune diseases. Otherside peripherally induced Treg cells are generated from naïve T cells in periphery. Adaptive induced Treg cells can be induced in response to specific antigen.^[94] Otherside, Type 1 Regulatory T cells (Tr1) produce high level of IL10 and have role in immunosuppression.^[95] Th3 cells produce high level of TGF beta and have role in immune evasion. Peripheral Treg cells is unstable than thymus nTreg cells.^[96]

In tumour microenvironment, Treg cells can be classified based on origin, function and impact on tumor progression. Tumour infiltrating Treg cells can infiltrate into tumour tissue and contribute immune suppression and promote tumour growth.^[97] Otheside, tumour induced regulatory T cells are activated and differentiated from conventional T cells in Tumour microenvironment.^[98] These Treg cells suppress the

activation of effector T cells by secreting cytokines like IL10, TGF beta.

Activated tumour infiltrating Treg cells in Tumour microenvironment (TME) has enhanced immune suppressive capacity as compare to Treg cells isolated from peripheral blood of healthy person.^[99] Because Treg cells' activation is increased in TME. Tumour tissue express tumour associated antigen (TAA) and neoepitope which Treg cells detect and bind with high affinity as compare to effector T cells that promotes specifically Treg cells' activation in TME.^[100] There are three different types of Treg cells in TME.^[101] They are 1. CD45RA⁺FoxP3^{hi} activated "effector" Tregs 2. CD45RA⁺FoxP3^{lo} resting Tregs 3. cytokine-secreting CD45RA⁺FoxP3^{lo} non-suppressive T cells, or "non-Tregs". Effector Treg cells are terminally differentiated and have high capacity of immune capacity as compare to resting Treg cells in TME that cause poor prognosis in different types of cancer patients.^{[102],[103],[104]} Effector Treg cells migrates efficiently toward TME as compare to other Treg cells^[105] It may be due to effector Treg cells express different types of chemokines receptors such as CXCR3/4, CCR2 and attract efficiently in response to cancer cells derived chemokines that cause migration of effector Treg cells toward tumour.^[106]

Exosomes and Treg Interactions within Tumor microenvironment

Tumor-derived exosomes (TEX) represent a crucial mode for cells-to-cells communication within the tumor microenvironment (TME). The large quantities of exosomes are produced by tumor. These exosomes can carry immunosuppressive and immunostimulatory ligands and receptors. Tumor derived exosome mirrors many molecular characteristics of their parental tumor cells.^[107] These exosomes transmit signal from tumor to other cells various immune and stromal cell populations, including regulatory T cells (Treg) within tumor microenvironment. The molecular content of Tumor-derived exosomes is typically enriched with immunosuppressive proteins and inhibitory ligands that collectively inhibits antitumor immune responses. Several research indicate that TEX suppress proliferation and cytotoxic function of CD8⁺ effector T cells (Teff) but promoting the expansion and activation of Treg cells. So, it is concluded that Tumor-derived exosomes enhance both the number and suppressive capacity of Treg within the TME.^[108] In vitro co-incubation experiments using TEX with Treg cells bearing CD39 and CD73 ectonucleotidases significantly promote the production of adenosine by Treg. Adenosine is a key immunosuppressive metabolite. So, Tumor-derived exosomes (TEX) induce unique transcriptional reprogramming in Treg, not seen in Teff cells.^[109] These transcriptional alterations induced in Treg after co-incubation with TEX lead to upregulation of genes associated with immunosuppressive protein production. It strengthens the immunosuppressive potential of Treg in the tumor microenvironment.^[108] T cells do not internalize tumor derived exosomes. Exosomes likely act via surface receptor- ligand interactions to trigger downstream transcriptional changes in Treg cells. Otherside, re-programming of Treg by TEX is also occurred by horizontal transfer of miRNA. Treg cells show unique responsiveness to TEX compared to CD4⁺ or CD8⁺ T cells indicating that they might utilize distinct signaling mechanisms for activation than other lymphoid cells.^{[110][111]}

Therapeutic implication to target Treg cells

Targeting Treg cells in tumor microenvironment is very important for treatment in cancer patients. Reducing the function of Treg cells can promote antitumor immune response.^[112] Combining Treg cells targeting chemotherapy with immunotherapy (e.g checkpoint inhibitors) may enhance treatment efficiency. CTLA-4 monoclonal antibodies (mAbs) block the interaction between CTLA-4 on T cells and B7 ligands (CD80/CD86) on antigen-presenting cells, thereby enhancing CD28-mediated co-stimulatory signaling and promoting effector T-cell activation.^[113] CTLA-4 blockade can increase Treg proliferation in the periphery while intra-tumoral Tregs may be depleted via Fc receptor-mediated cytotoxicity. Ipilimumab and tremelimumab are two well-known IgG1 and IgG2 anti-CTLA-4 mAbs, respectively. Ipilimumab treatment

significantly increases Ag-specific humoral and CTL responses in metastatic prostate cancer and advanced melanoma patients. Intra-tumoral Tregs can be selectively depleted through Fc receptor-dependent mechanisms while peripheral FoxP3⁺ Treg frequencies often remain stable or slightly increase.^{[114],[115]} Tremelimumab induces broad expansion and activation of CD4⁺ and CD8⁺ T cell subsets including suppressive Tregs.^[116] It suggests that CTLA-4 blockade expands and activates Tregs similarly to CTLs and Teff without affecting Treg cells' suppressive activity. Anti-CTLA-4 mAbs, when activated by Teff and CTLs, can exert anti-tumor activity through antibody-dependent cell-mediated cytotoxicity (ADCC)-mediated depletion of intra-tumoral Tregs. It was recently reported in preclinical murine model.^{[117][118]} In a clinical study of melanoma patients, ipilimumab was required for Fc gamma receptor III -expressing non-classical monocytes to mediate ADCC of Tregs.^[119] In Head and Neck Cancer Patients, Ipilimumab depletes tumour infiltration CTLA-4+ Tregs and induces NK cell-mediated ADCC.^[120] CD25 is highly expressed on TI Treg cells. CD25 which is IL-2 receptor α -chain is highly expressed on Tregs. Tregs do not synthesize IL-2, but they consume IL-2 efficiently via CD25, which leads to IL-2 deprivation in the microenvironment. CD25 was good target for cancer immunotherapy. But expression of CD25+ is moderate on CD4⁺ T cells and CD⁺ T cells. Conventional anti-CD25 antibodies is unable to deplete Treg within tumors because expression of the inhibitory Fc γ receptor Fc γ RIIb is high in the tumor microenvironment, which inhibits antibody-dependent cell cytotoxicity. Fc-optimized anti-CD25 antibody has enhanced affinity for activating Fc γ receptors, which successfully depleted Treg in tumors. So, Treg cells are seen in low amount within tumor microenvironment but Teff is increased and show anti-tumor activity within tumor microenvironment.^[121] Optimized anti-CD25 antibodies deplete Tregs while IL-2-STAT5 signaling is preserved on effector T cells that enhance effector activation and antitumor immunity.^[122] BAY 3375968, a novel Fc-optimized anti-CCR8 antibody is administrated for blocking chemokine receptors such as CCR8 which guide Treg migration into tumors, has shown promise in limiting Treg infiltration.^[123] CD39 and CD73 ectonucleotidases is highly expressed on Treg cells. CD39 and CD73 promote the production of adenosine by Treg. Adenosine is a key immunosuppressive metabolite. The blocking CD39 or CD73 activity or targeting adenosine signaling pathway give promising therapeutic strategy to inhibit Treg-mediated immune suppression.^[124] For instance, the anti-CD73 antibody MEDI9447 (Oleclumab) gives encouraging results in clinical trials and limit Treg function and enhance antitumor immunity.^[125]

Tumor-infiltrating regulatory T (Treg) cells exhibit distinct metabolic adaptations that able them to survive and maintain immunosuppressive functions within the hypoxic tumor microenvironment (TME). These unique

metabolic traits have opened new treatment option to specially target on metabolism of Treg cells, while leaving effector T cell activity. For instance, Indoleamine 2,3-dioxygenase (IDO) is overexpressed in various human cancers, and its high expression are correlated with tumor progression, advanced stages, and metastasis. IDO inhibits activation of Teff by depletion of an essential amino acid, tryptophan. while simultaneously promoting the differentiation and activation of regulatory T cells (Treg) and myeloid-derived suppressor cells

(MDSCs) through production of kynurenine. Inhibitors of IDO such as epacadostat when combined with PD-1 checkpoint blockade show promising results in recent clinical trials.^{[126],[127],[128]}

So, targeting of metabolism and immune checkpoints represents a promising therapeutic strategy to overcome Treg-mediated immune evasion and give promising therapeutic outcomes of current immunotherapies.

Therapeutic Implications for Targeting Treg Cells

Sl no.	Therapeutic strategy	Target	Mechanism	Representative Agents	Reference
1	Immune Checkpoint Blockade	CTLA-4, PD-1, PD-L1	Blocks inhibitory receptors on Treg and can reduce their suppressive function of intra-tumoral Treg activity in the tumor microenvironment (TME) thereby enhancing anti-tumor immunity and also depleting some intratumoral Treg via Fc-mediated ADCC with certain antibodies.	Tremelimumab, Ipilimumab (anti-CTLA-4), Pembrolizumab, Nivolumab (anti-PD-1)	J DiDomenico et al, 2018 ^[129] N Sobhani et al, 2021 ^[130]
2	Targeting Treg Metabolism	IDO1, CD73	1. Inhibit IDO1-mediated tryptophan to kynurenine conversion so, promotes Treg differentiation and suppresses Teff cells. 2. prevent ATP to adenosine conversion, lowering adenosine-driven immuno suppression	Epacadostat (IDO1 inhibitor), Oclumab (Anti-CD73 antibody)	CM Kelly et al, 2023 ^[131] J Bendell et al, 2023 ^[132]
3	Chemokine Receptor Blockade	CCR4, CCR5	Prevent chemokine-driven Treg recruitment (e.g., CCR4, CCR5 axes) to reduce Treg infiltration in tumor microenvironment	CCR4 inhibitors (mogamulizumab), BAY 3375968 (afucosylated anti-CCR8)	H.G Roider et al, 2024 ^[133] Ueda R., 2015 ^[134]
4	Modulating IL-2 signaling	IL-2/STAT5 pathway	Engineer IL-2 variants or IL-2 that preferentially expand effector T cells while minimizing Treg expansion.	IL-2 muteins, pegylated IL-2 variants	B Tong et al, 2024 ^[135] S Belli et al, 2024 ^[136]
5	Treg Depletion via Surface Markers	CD25	Target CD25 expressed highly on intratumoral Treg; it improves ADCC to deplete Treg while effector T cell responses is activated	RG6292 / (afucosylated anti-CD25)	L Pousse et al, 2023 ^[137]

CONCLUSION

Treg cells have immunosuppressive activity and act as key regulator of immune evasion. Treg cells promote tumour growth in tumor bearing host. Treg cells effectively suppress the function of effector T cells by secreting inhibitory cytokines (TGF- β , IL-10, and IL-35), as well as through metabolic adaptation and the expression of immune checkpoint receptors (PD-1, CTLA-4, LAG-3, and TIM-3). High Treg cell infiltration in the tumour microenvironment is associated with a poor prognosis in patients with various types of cancer. Control Treg cell function and depletion of Treg cells have been tested in the clinic, but these therapies mostly fail to selectively inhibit and deplete Treg cells. Because selective targeting of Treg cells in tumor microenvironment while preserving systemic immune

balance is a major opportunity and challenge in cancer immunotherapy.

So, in future research, it should be focused on identifying tumor-specific Treg cells subsets and also designing therapies that selectively inhibit function of Treg cells without compromising immune tolerance in healthy tissues.

Conflict of Interest: The author declares no conflict of interest.

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