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Discovery of Regulatory T Cells and Their Prospective Therapeutic Applications*

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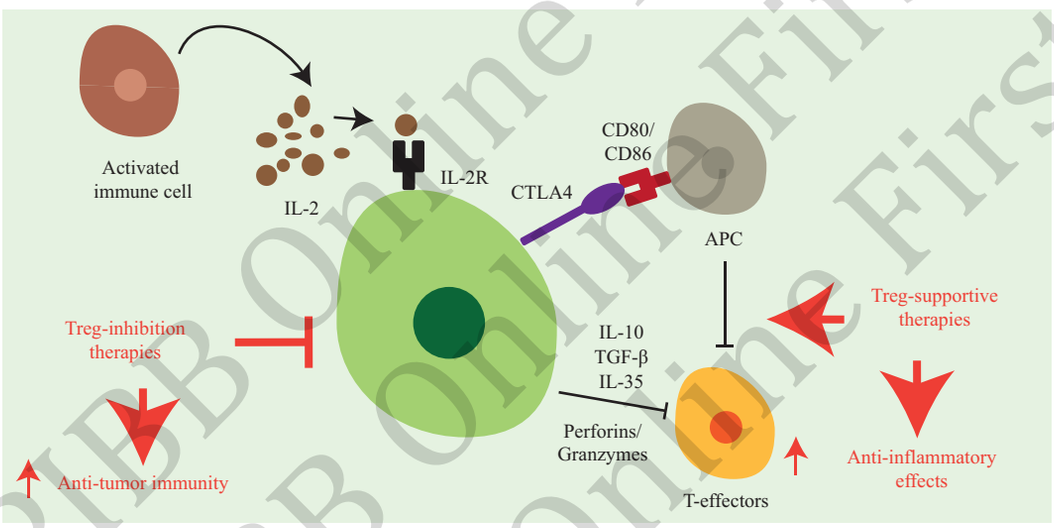
Graphical abstract



Abstract Regulatory T cells (Tregs) are a specialized subset of $CD4^+$ T cells defined by expression of the lineage-specifying transcription factor FOXP3 and a potent capacity to maintain peripheral immune tolerance. The modern concept of Tregs was catalyzed by Shimon Sakaguchi's identification of $CD4^+CD25^+$ suppressive T cells and subsequent work establishing FOXP3 as a central determinant of Treg development and function; together with landmark FOXP3 genetic discoveries by Mary E. Brunkow and Fred Ramsdell, these advances transformed understanding of immune homeostasis and were recognized by the 2025 Nobel Prize in Physiology or Medicine. Under normal physiological conditions, $FOXP3^+$ Tregs restrain autoreactive lymphocytes, prevent excessive inflammation, and shape antigen-presenting cell activity through contact-dependent pathways and suppressive cytokines, thereby protecting tissues from immune-mediated damage. Disruption of Treg abundance, stability, or suppressive capacity can therefore lead to immune dysregulation and disease. Over the past two decades, Tregs have become a major focus of immunology because their roles are highly context dependent. In autoimmune and chronic inflammatory diseases, impaired Treg function or insufficient Treg

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activity contributes to loss of tolerance and persistent tissue injury, supporting therapeutic approaches designed to enhance Treg number, stability, and suppressive potency. In contrast, many cancers exploit Tregs by promoting their expansion, activation, and recruitment into the tumor microenvironment (TME), where they blunt antitumor immunity by suppressing cytotoxic T-cell priming and effector function, limiting dendritic cell activation, and fostering immune escape. In both settings, immune checkpoint pathways critically influence Treg biology. Beyond PD-1/PD-L1 and CTLA-4, emerging checkpoints and costimulatory receptors, including TIGIT, TIM-3, LAG-3, and OX40, modulate Treg generation, stability, and suppressive programs, thereby shaping the balance between tolerance and immunity. Meanwhile, immunometabolic adaptations further tune Treg fitness and function in inflamed tissues and tumors; lipid utilization and mitochondrial programs, among other metabolic axes, enable Tregs to persist in nutrient- and oxygen-restricted microenvironments, while microenvironmental stress can drive functional remodeling or fragility in a subset-dependent manner. In this review, we summarize the discovery and defining biological features of Tregs, highlight core suppressive mechanisms and regulatory circuits, and synthesize evidence for the dual roles of Tregs in preventing autoimmunity yet enabling tumor immune evasion. We further outline current and emerging therapeutic strategies aimed at augmenting Treg activity to restore tolerance in autoimmune disease, or selectively depleting, functionally inhibiting, and reprogramming tumor-resident Tregs to enhance cancer immunotherapy, including immune checkpoint blockade and combination approaches. Finally, we discuss how deeper insight into Treg heterogeneity, checkpoint control, and immunometabolic regulation may enable more precise Treg-directed interventions and inform next-generation immunotherapeutic combinations across immune-mediated and malignant diseases.

Key words regulatory T cells, immune tolerance, tumor microenvironment, autoimmune diseases, cancer immunotherapy
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The immune system plays a vital role in protecting the host from germs and infections. However, the immune system must also be able to distinguish between "self" and "non-self" to maintain the body's health and protect it from disease[1]. Immune tolerance comprises mechanisms that limit the immune system from attacking the body's own tissues [2].

The theoretical foundations of immunological tolerance originated in the early 20th century. In 1938, Traub[3] discovered that embryonic mice infected with the lymphocytic choriomeningitis virus (LCMV) exhibited an initial indication of immunological unresponsiveness, as they did not generate antibody responses in later life. In 1945, Owen[4] observed that dizygotic twin heifers sharing the same placental circulation did not reject one another's erythrocytes, illustrating a chimeric natural tolerance. Building on these findings, Billingham *et al*. [5] (1952) laid the groundwork for modern transplantation immunology by experimentally proving that exposing the developing immune system to foreign antigens may result in lifelong tolerance. According to Burnet's clonal selection theory, first proposed in 1959[6], immunological tolerance occurs when lymphocytes with receptors specific to self-antigens are eliminated or rendered inactive during embryonic development. Lederberg (1959) and Mitchison (1964) expanded upon these concepts, demonstrating that antigen exposure during immune maturation influences cell activation or tolerance[7-8]. In the following years, we learned more about how cells and molecules tolerate each other. Nossal and Pike (1980) proposed the concept of clonal anergy, suggesting that lymphocytes exposed to antigen in the absence of co-stimulation become inactive[9]. These findings illustrated that modern tolerance exists in central and peripheral groups. Central tolerance facilitates the elimination of self-reactive lymphocytes through negative selection in the bone marrow and thymus. At the same time, peripheral tolerance keeps autoreactive cells in check by immune modulation, anergy, and clonal deletion. However, the unanswered question was how self-reactive cells evade central deletion and prevent tissue damage within the body.

While working on this challenging issue, Shimon Sakaguchi made one of the most important discoveries in immunology. Since this discovery, Fred Ramsdell, Mary Brunkow, and Shimon Sakaguchi won the 2025 Nobel Prize in Physiology or Medicine for discovering how regulatory T cells (Tregs) maintain the immune system's balance by preventing it from attacking the body's own tissues. This was a major discovery in the field of immune tolerance (Figure 1).

Fig. 1 Tregs act as immune “peacekeepers” to preserve self-tolerance

Tregs maintain immune homeostasis by suppressing autoreactive immune cells that could otherwise damage self-tissues.

1 Sakaguchi’s discovery and the birth of regulatory T cells

Shimon Sakaguchi, a distinguished professor at Osaka, provides the biological basis of immune tolerance and the concept of "$CD4^+$ $CD25^+$ Tregs". Prior to his research, the dominant theory of self-tolerance was based on the idea that autoreactive T cells were merely destroyed throughout development, or the thymic deletion mode. However, a contradictory finding in research involving neonatal thymectomy caught Sakaguchi's interest. Due to conflicting findings and a lack of a molecular definition, the immunology community was highly skeptical of "suppressor T cells". In this context, Shimon Sakaguchi and his coworkers initiated a series of investigations that would subtly pave the way for one of the most significant breakthroughs in contemporary immunology. Sakaguchi found that transferring spleen cells from healthy adult mice could prevent the emergence of severe autoimmune disease in day-three thymectomized (d3Tx) animals, which normally develop the disease on their own. Notably, this protection could not be provided by spleen cells from newborn or juvenile mice, indicating that suppressive T cells arise later in life. While the elimination of Lyt-2, 3^+ cells had no effect, the protection was abolished when these protective spleen cells were treated with complement and an anti-Lyt-1 antibody. These findings suggested that Lyt-1^+ ($CD4^+$) T cells, rather than the cytotoxic Lyt-2^+ ($CD8^+$) subset, were the protective population[10]. In 1985, Sakaguchi *et al.*[11] demonstrated that the ablation of this Lyt-1^+ population triggered organ-specific autoimmune disorders. This finding demonstrated that self-tolerance requires active regulation by suppressive T cells, not just the passive absence of autoreactive lymphocytes. This paradigm reconceptualized the immune system as a meticulously calibrated equilibrium regulated by active mechanisms, contesting the entrenched notion that self-tolerance is exclusively derived from clonal deletion.

Sakaguchi *et al.*[12] released the seminal 1995 "Genesis of Treg Biology" study ten years later, following an era of advancements in monoclonal antibody technologies. In this paper, he provided the first conclusive phenotypic and functional characterization of what he termed $CD4^+CD25^+$ Tregs. In normal mice, CD25, the α-chain of the interleukin (IL)-2 receptor, was expressed by about 10% – 15% of peripheral $CD4^+$ T cells. Following the selective depletion of $CD4^+CD25^+$ cells, the residual $CD4^+CD25^-$ cells were transferred into immunodeficient nude mice, which caused a variety of autoimmune diseases, including thyroiditis, gastritis, insulitis, polyarthritis, and glomerulonephritis. In a dose-dependent manner, disease was prevented by reconstitution with $CD4^+CD25^+$ cells. It demonstrated that these same cells controlled both self-reactivity and overall immunological activation because they inhibited immune responses to foreign antigens and grafts[12]. The 1995 study[12] provided the first concrete evidence that, even in a normally functioning immunological milieu, autoreactive effector T cells could be released by eliminating a small, specialised population of $CD4^+CD25^+$ cells. The ramifications were far-

reaching: self-tolerance was a dominant, T cell-mediated process that consistently inhibited potentially harmful reactions rather than a passive result of thymic deletion. The mechanism of central and peripheral immune tolerance is described in Figure 2. Subsequently, Read *et al.*[13] (2000) offered a crucial molecular insight into Treg biology. They demonstrated that CTLA-4, an inhibitory immunological checkpoint molecule, restrains excessive T cell activation by limiting costimulatory signaling, thereby providing insight into how cell contact-dependent Tregs can inhibit immunological responses.

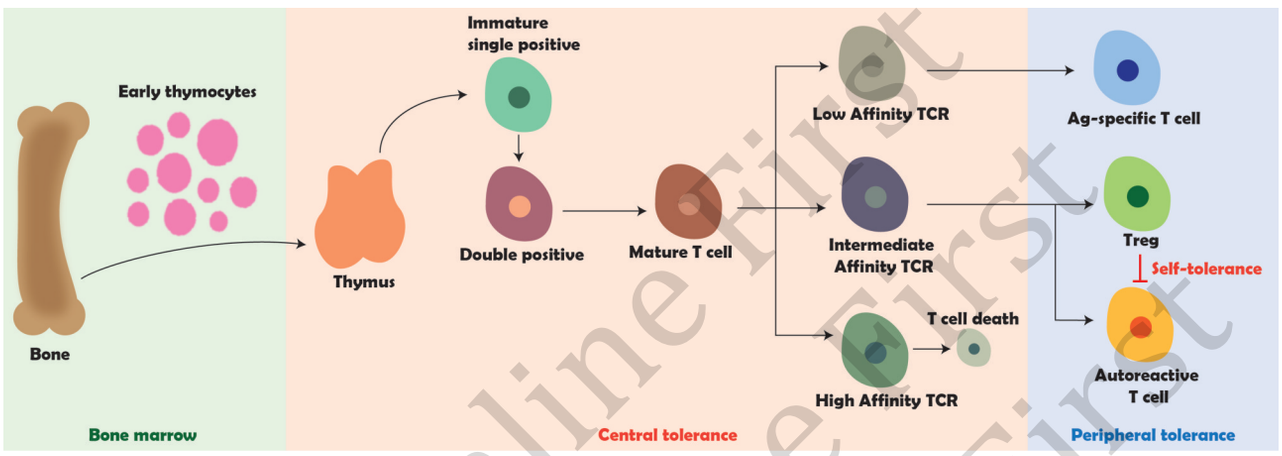

Fig. 2　Central and peripheral tolerance mechanisms governing T-cell fate

Hematopoietic precursors from the bone marrow migrate to the thymus and progress through DN （DN1 – DN4） and DP stages before maturing into $CD4^+$ or $CD8^+$ T cells. High-affinity self-reactive TCRs are deleted during central tolerance， whereas low- or intermediate-affinity T cells exit to the periphery. Peripheral tolerance further eliminates autoreactive T cells or converts them into $FOXP3^+$ regulatory T cells， collectively ensuring maintenance of self-tolerance.

2　Identification and mechanistic insights of FOXP3

The second major breakthrough in the field of immune tolerance was achieved by Mary Brunkow and Fred Ramsdell, whose pioneering genetic research fundamentally advanced the understanding of Treg biology. Mary Brunkow and Fred Ramsdell of Celltech Chiroscience discovered in 2001 that mutations in the Foxp3 gene caused the deadly autoimmune condition seen in scurfy mice. They also discovered that immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, a debilitating congenital autoimmune illness in boys, is caused by a mutation in the human ortholog, FOXP3[14]. Hori, Nomura, and Sakaguchi[15] (2003) demonstrated that FOXP3 expression characterises and produces T Tregs. They also demonstrated that naïve $CD4^+$ T cells induced to express FOXP3 became suppressive cells identical to natural Tregs. These findings revealed the developmental blueprint and molecular signature of Tregs, proving that FOXP3 is the master transcription factor controlling their suppressive activity and differentiation.

By turning a functional phenomenon into a genetically defined lineage, the discovery of Foxp3 by Ramsdell and Brunkow ushered in the molecular era of regulatory T cell biology. Later functional investigations showed that FOXP3 uses several structural domains to exert its activity. For instance, the C-terminal forkhead domain is essential for DNA binding and transcriptional suppression. Studies utilizing FOXP3-Gal4 fusion hybrids indicate that the amino-terminal segment of FOXP3 is crucial for transcriptional repression[16]. This suggests that the C-terminal forkhead domain forms the repressive complex. Building on this, biochemical analyses identified a chromatin-remodelling complex composed of HDAC7, HDAC9, and the acetyltransferase KAT5 (TIP60) that associates with FOXP3 at amino acid residues 107 – 190, mediating

its epigenetic regulatory functions[17-18].

In subsequent years, our findings made a significant breakthrough by discovering the interaction of FOXP3 with Eos, a zinc-finger transcription factor belonging to the Ikaros family. We established that Eos binds to the same N-terminal region of FOXP3 required for repression and that this contact is essential for FOXP3's ability to quiet its target genes. By enlisting more chromatin-remodelling enzymes, Eos connects FOXP3 to a broader co-repressor complex, which, in turn, stops the transcription of inflammatory genes. Through the combination of sequence-specific DNA recognition and Eos-mediated epigenetic repression, this study offered the first comprehensive mechanistic explanation of how FOXP3 stabilizes the Treg phenotype[19]. Following this, our findings demonstrated that microRNA-17 (miR-17) directly targets Eos and other FOXP3 co-regulators through 3' UTR binding, thereby attenuating Treg suppressive activity and acting as a critical inflammatory regulator of Treg stability. They also demonstrated that IL-6 triggers the expression of miR-17 through HIF-1α signaling. MiR-17 reduction enhances Treg-mediated immune suppression, and overexpression of miR-17 converts Tregs into an effector-like phenotype, thereby exacerbating inflammation in murine colitis[20].

Other FOXP3 domains also provide unique regulatory roles, as Eos was discovered to be a crucial co-repressor of FOXP3. Both experimental mutagenesis and patients with IPEX syndrome exhibit mutations in the leucine-zipper region, which interfere with transcriptional regulation and disrupt FOXP3 homodimerization[16-17]. The structural flexibility that underlies FOXP3's regulatory ability is demonstrated by these mutations, which result in a domain-swapped dimer conformation that connects two DNA molecules[21]. Subsequent investigation revealed that the amino-terminal region of FOXP3 serves as a flexible hub for protein-protein interactions that regulate Treg lineage commitment. For example, in the area between the leucine zipper and the forkhead domain, runt-related transcription factor 1 (RUNX1) binds to FOXP3 to form a complex that mediates transcriptional suppression at specific target genes[22].

To perform its dual function of suppressing and activating gene transcription, FOXP3 also directly interacts with the nuclear factor of activated T cells (NFAT) at the IL-2 promoter[23-24]. The body of data suggests that FOXP3 is a multifunctional scaffold that orchestrates a vast network of cofactors to either activate or repress transcription, based on the environment, rather than acting solely as an on/off switch for immune genes. In fact, more than 360 proteins have been identified to interact directly or indirectly with FOXP3 through proteomic mapping of the FOXP3 interactome, generating vast multiprotein complexes whose exact roles remain unknown[25].

The nuclear receptors retinoic acid receptor – related orphan receptor gamma t (RORγt) and retinoic acid receptor – related orphan receptor alpha (RORα), transcription factors that promote the development of naïve $CD4^+$ T cells toward the pro-inflammatory TH17 lineage, were found to interact with regions in exon 2 of FOXP3. FOXP3 redirects cell fate toward the Treg lineage and enhances immunological tolerance by directly binding to RORγt and RORα, thereby inhibiting their transcriptional activity[26-27]. Immunologists have been studying the cytokine-mediated regulation of $CD4^+$ T cell differentiation for about 20 years. This process involves the relative amounts of transforming growth factor beta (TGF-β) and IL-6, which influence whether naïve T cells develop a pro-inflammatory Th17 phenotype or a tolerogenic Treg phenotype. This approach, however, was unable to adequately describe how immune cells adjust to the environmental and metabolic limitations seen at mucosal or inflammatory sites[28].

After the molecular network of FOXP3 was characterized, the focus shifted to the ways in which environmental signals affect T cell fate determinations. Our team made a significant breakthrough when we discovered that hypoxia acts as a metabolic switch, regulating the Treg-Th17 equilibrium through the transcription factor hypoxia-inducible factor-1α (HIF-1α). We demonstrated that HIF-1α is both necessary and sufficient for Th17 development, and that it is induced downstream of IL-6 and STAT3 signaling. By binding to the RORγt promoter, HIF-1α works with RORγt and p300 to mainly increase the transcription of the hallmark Th17 cytokine IL-17A. At the same time, HIF-1α targets FOXP3 for ubiquitin-mediated degradation and directly binds to it, acting as a negative regulator of Treg differentiation[29]. This establishes that HIF-1α plays a dual role by actively suppressing the Treg lineage while simultaneously promoting the Th17

program. Collectively, these studies highlight that PTMs of Foxp3 can limit the Treg function by regulating the immunosuppressive mechanism[30].

3 Immunosuppressive mechanisms of Tregs

Tregs use a variety of highly varied and context-dependent strategies to dampen immune responses in autoimmune, cancer, inflammatory, and metabolic diseases[31-36]. These processes can be grouped into two categories: those that require direct cell-to-cell contact and those that are facilitated by soluble substances, such as local competition for growth factors and the production of inhibitory cytokines[37].

One important component of Treg function is based on cell-to-cell interaction. Tregs can transmit regulatory signals by directly binding to effector T cells, B cells, and other immune cells via receptor-ligand pairs on their surface[38]. Through direct cell-to-cell interaction, Tregs can mediate immunosuppression, mainly by using TGF-β[39]. By reducing the activation and proliferation of several immune cell types, such as T-cells, macrophages, and DCs, this TGF-β cytokine plays a crucial part in preserving immunological homeostasis[40]. Accordingly, membrane-bound TGF-β on Treg cells is presented to adjacent target cells in a contact-dependent manner, directly engaging TGF-β receptors and initiating immunosuppressive signaling pathways[41]. Additionally, it has been noted that both mouse and human Tregs exhibit significant expression of galectin-1, a member of the β-galactoside-binding protein family known to induce T cell death[42]. Through cytolytic processes, Tregs can directly destroy autoreactive or hyperactive immune cells. They utilize the proteases granzyme A and granzyme B, which induce target cells to undergo apoptosis. Perforin, a protein that creates pores in the target cell membrane to allow granzyme access, may or may not be involved in this process[43-45]. According to another study, activated Tregs also cause effector T cells to undergo apoptosis through a tumor-necrosis-factor-related apoptosis-inducing ligand-death receptor 5 (TRAIL-DR5) pathway[46]. To further inhibit the immune system, Tregs can also alter the maturation and activity of antigen-presenting cells (APCs), including DCs. Tregs can stimulate the production of indoleamine 2, 3-dioxygenase (IDO), an enzyme that catalyzes the degradation of tryptophan, thereby limiting an amino acid required for T-cell proliferation and function[47-48], through interactions involving CTLA-4 and CD80/CD86 on APCs[49-50]. By catabolizing tryptophan, IDO also produces immunosuppressive metabolites (kynurenines) that reduce T cell activation and enhance regulatory cell function[51-52]. Additionally, research indicates that Treg cells suppress DCs and effector T cells through MHC class II LAG-3 engagement, thereby reducing DCs' capacity to trigger immunological responses[53-55].

The release of anti-inflammatory cytokines, such as IL-10, TGF- β, and IL-35 (Ebi3-IL-12α heterodimer), is another way of Treg-mediated suppression[56-59]. Since Tregs can inhibit the growth and activation of effector T cells and other immune cells, these cytokines are crucial for reducing immunological activity. A strong suppressor of inflammatory reactions, IL-10 inhibits the activation and cytokine production of a variety of immune cells, including T cells, DCs, and macrophages[60]. Tregs release a cytokine called IL-35, which has been demonstrated to directly inhibit effector T cell growth and induce a regulatory phenotype in other T cell populations[61-62]. Although TGF-β has a complicated and sometimes contentious role, it may act as an immune suppression mediator when membrane-bound[63].

Tregs can inhibit immune responses by disrupting metabolism in addition to producing cytokines. Tregs, for instance, have high levels of the ectonucleotidases CD39 (ectonucleoside triphosphate diphospho-hydrolase-1) and CD73 (ecto-5' -nucleotidase), which convert adenosine triphosphate (ATP) into adenosine (ADO) [64-66]. This inhibits effector T cell function by activating the ADO receptor 2 A, which raises intracellular cyclic adenosine monophosphate (cAMP) levels and depletes pro-inflammatory ATP, preventing the proliferation and cytokine production of effector T cells[67-69]. Additionally, ADO stimulates myeloid-derived suppressor cells (MDSCs) to differentiate, proliferate, and exhibit suppressor function[70-71]. These two ectoenzymes hydrolyze ATP to produce ADO. CD39 first converts ATP to ADP and AMP, followed by CD73, which further converts AMP to ADO. Tregs can also induce effector T cells to undergo apoptosis by depriving them of the cytokines necessary for their development and survival, such as

IL-2. The IL-2 receptor alpha chain, CD25, which Tregs produce in significant quantities, sequesters IL-2 and inhibits other cells from acquiring it[72-73]. Furthermore, Tregs raise intracellular cAMP levels in target cells, which further prevents them from proliferating and producing cytokines[74-75].

Tumor-infiltrating lymphocytes are a hallmark of cancer because of their well-established roles in immune evasion and cancer development[76]. Tumor-associated macrophages (TAMs), myeloid-derived suppressor cells, and Tregs all contribute to the development of an immunosuppressive TME[77]. In addition to tumour cells, the TME is a dynamic and complex environment that also contains a range of stromal and immunological cells that work together to affect tumour development, progression, and response to treatment[78]. Tregs are frequently detected in large quantities among the immune cells in the TME, especially in tumors that are thought to be "immunologically cold", meaning they are less penetrated by effector immune cells and more resistant to immune-mediated elimination[76]. Many human tumours have been found to have a high density of tumor-infiltrating Treg cells, including those in the head and neck[79], lung[80], breast[81], oesophagus[82], stomach[83], colorectal[84], liver[85], pancreas[86], and ovary[87]. The high concentration of $FOXP3^+$ T cells in tumors is positively correlated with the progression of cancer and leads to tumor immunosuppression[88]. Reduced tumor-infiltrating $CD8^+$ T cell to $FOXP3^+$ Treg cell ratios have been associated with a poor prognosis[89].

Several variables, including the production of chemokines that attract Tregs, contribute to the accumulation of Tregs inside the TME. For instance, DCs, tumour cells, and TAMs release C－C motif chemokine ligand 22 (CCL22), which binds to C－C chemokine receptor 4 (CCR4) on Tregs, facilitating their migration to the tumour site [90, 91]. Treg migration is significantly influenced by the elevated expression of CCR4 on these cells[91-92]. On the other hand, in some models of inflammatory diseases,

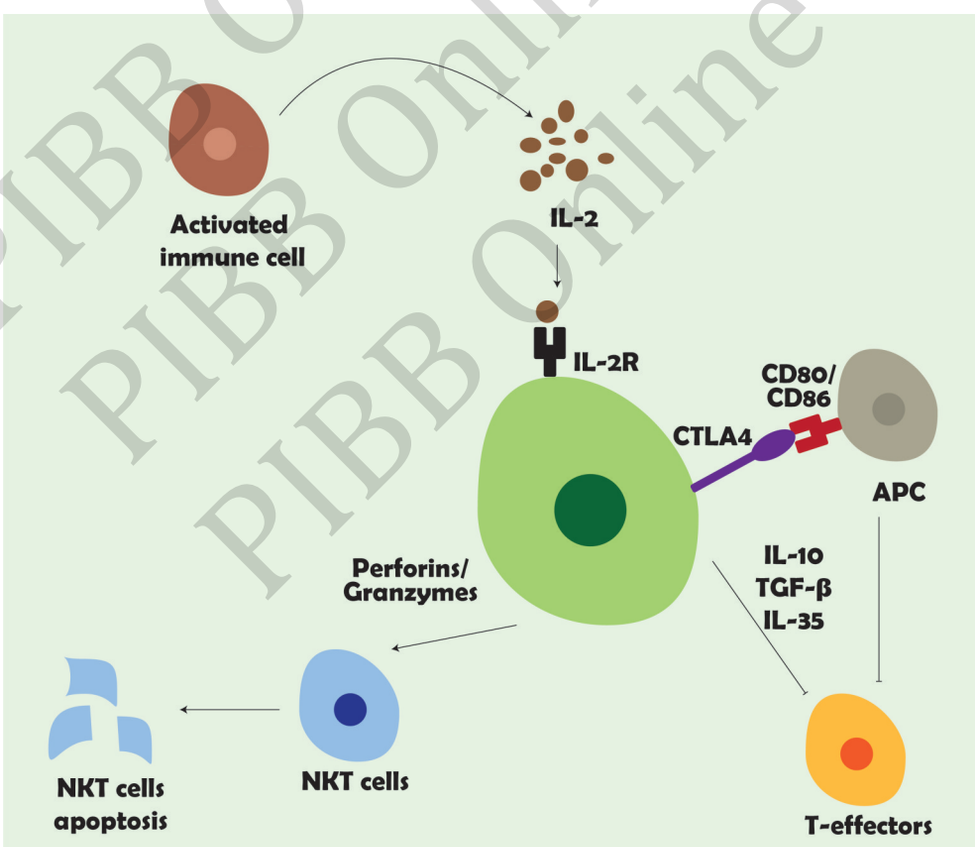

Fig. 3 Immunosuppressive mechanism of Tregs

Tregs suppress immune responses by consuming IL-2 *via* high-affinity IL-2 receptors and by inhibiting antigen-presenting cell （APC） co-stimulation through CTLA-4－mediated blockade of CD80/CD86. Tregs further dampen effector and NKT cell activity by secreting immunosuppressive cytokines （IL-10， TGF-β， IL-35） and inducing cytotoxic effects through perforin/granzyme pathways.

mouse Tregs deficient in CCR4 are unable to migrate into inflammatory tissues and are therefore ineffective in modulating immune responses[93]. Other chemokine receptors, including CCR5, CCR6, and CCR10, are also expressed by activated Treg cells, facilitating their trafficking to specific tissue regions[94-96]. According to a study, tumour cells and macrophages in the microenvironment release the chemokine CCL22, which is crucial for attracting Treg cells to the TME[97-98]. Furthermore, TGF-β, IL-10, and IDO, an enzyme that depletes tryptophan and generates a local environment that supports Treg formation and function, are all often produced by the TME and aid in the growth and survival of Tregs[99-100]. Figure 3 illustrates the immunosuppressive mechanism of Tregs.

4 Treg−based therapies

Since these discoveries, Tregs have emerged as an innovative therapeutic target. Strategies to increase or improve Tregs in autoimmunity and transplantation aimed to restore tolerance without causing widespread immunosuppression. Treg depletion or reprogramming strategies in cancer were intended to boost antitumor responses. Basic immunology was translated into precision medicine by the 2010s, when Treg-based clinical trials, ranging from adoptive Treg transfer to low-dose IL-2 therapy, had started worldwide. Therapeutics based on Tregs have advanced from theoretical immunologic constructs to a translational reality during the last 5 years, representing one of the most advanced frontiers in immune modulation.

For autoimmune diseases, several strategies have been employed and adopted thus far. For instance, Methotrexate (MTX), the mainstay treatment for rheumatoid arthritis (RA), improves Treg stability and suppressive functions through multiple mechanisms[101]. MTX strengthens the stable Treg lineage commitment by increasing the expression of FOXP3 and encouraging demethylation of the FOXP3 conserved non-coding sequence-2 (CNS2) regulatory region[101-102]. By upregulating CD39 on Tregs, MTX increases the synthesis of extracellular adenosine, which inhibits the proliferation of effector T cells through adenosine A2A receptor (A2A) signaling[101, 103-104]. Similarly, cytokine blockade also indirectly increases the Treg population in autoimmune diseases, thereby reducing disease severity. TNF antagonists, such as infliximab and adalimumab, restore Treg function by reversing TNF-induced FOXP3 dephosphorylation and inhibiting protein kinase Cθ (PKCθ) recruitment to the Treg immunological synapse[105-108]. Given IL-6's critical role in inhibiting FOXP3 induction while promoting RORγt expression, IL-6 inhibition strongly favors Treg differentiation [109]. Therefore, it has been investigated that IL-6 blockade with tocilizumab rebalances the Th17/Treg axis[110], increasing $CD39^+$ Treg frequencies[111]. IL-1β blockade using anakinra reduces IL-1β -driven RORγt expression, thereby preventing Treg conversion into IL-17 – producing ex-Tregs, a key mechanism in highly inflammatory conditions, such as systemic JIA[112]. Meanwhile, our lab has identified several other factors, such as PPARα[113-114], Aryl hydrocarbon receptor (AhR) [32], Nrf2[33], and HIF1α[115-116], which influence the function of Tregs.

The use of CTLA4-Ig (Abatacept) and JAK inhibitors has also been employed to treat autoimmune diseases and mitigate inflammation. It has been studied that Abatacept binds to CD80/86 on APCs, thereby reducing CD28-mediated co-stimulation[117]. Although CD28 is necessary for Treg thymic development and maintenance, abatacept induces tolerogenic dendritic cells that support the expansion of peripheral Tregs *in vivo*[118]. JAK inhibitors such as tofacitinib inhibit IL-6/JAK1-3 signaling in effector T cells more strongly than IL-2RA-dependent JAK3 – STAT5 signaling in Tregs, thereby reducing effector-driven inflammation while largely preserving Treg suppressive capacity[119-120].

In addition to indirect Treg expansion, various strategies to directly enhance endogenous Tregs have also been identified. It has been well understood that Tregs uniquely express the high-affinity IL-2 receptor ($CD25^+CD122^+CD132^+$), enabling preferential expansion with low-dose IL-2[121]. Clinical trials in RA, systemic lupus erythematosus (SLE), and psoriatic arthritis (PsA) show increased Treg frequencies and reduced disease activity[36, 110, 122-123]. Engineered IL-2 variants dramatically enhance Treg selectivity[124-125]. For instance, IL-2-anti-IL-2 complex (JES6-1) increases IL-2 half-life and biases signaling toward CD25-rich Tregs[126]. IL-2 muteins (*e.g.*, NKTR-358) are designed to reduce CD122 interaction, minimizing effector T-cell

activation[127-128]. Likewise, IL-2-Fc fusion proteins prolong circulation and sustain Treg expansion[126, 129].

Another attractive strategy to expand Tregs in autoimmune diseases is the use of mTOR inhibitors. Rapamycin, an mTOR inhibitor, represents a central strategy to favor Treg responses in autoimmune disease selectively. Rapamycin targets mTORC1 to preferentially suppress glycolysis-dependent effector T cells while promoting oxidative phosphorylation-driven differentiation and maintenance of Tregs[130-131]. This enhances FOXP3 stability and reinforces lineage commitment, thereby restoring the disturbed Th17/Treg balance. When combined with low-dose IL-2, rapamycin acts synergistically, resulting in more efficient Treg induction and a more tolerogenic immune milieu[34, 132].

Likewise, adoptive Treg cell therapy constitutes a complementary and increasingly sophisticated approach to restoring immune tolerance. Polyclonal autologous Tregs can be isolated from peripheral blood based on their $CD4^+CD25^+CD127$ Low phenotype, expanded *ex vivo* using IL-2 in the presence of rapamycin to preserve their regulatory program, and subsequently reinfused into patients[133-134]. Antigen-specific Tregs offer even greater precision and potency, as they home to and act within antigen-rich tissues[135]. In preclinical models, collagen II-specific Tregs have been shown to prevent arthritis in murine collagen-induced arthritis[136-137]. In contrast, proinsulin- or GAD65-specific Tregs demonstrate promising disease-modifying potential in type 1 diabetes by selectively suppressing islet-directed immune responses[138-140]. In parallel, chimeric antigen receptor (CAR) -Tregs engineered with chimeric antigen receptors recognizing defined tissue or alloantigens, such as HLA-A2 in transplantation, can be directed to specific anatomical sites where they deliver highly focused immunoregulation[141-142].

In cancer, Treg-based strategies primarily aim to reduce intratumoral Tregs or inhibit their suppressive activity ("Treg-DOWN") to enhance effector T-cell function. One major approach is the depletion of Tregs using drugs and antibodies. Tyrosine kinase inhibitors (TKIs), such as sunitinib, can reduce the frequencies of Treg and MDSCs[143-144]. In contrast, imatinib has been reported to deplete highly suppressive effector Tregs preferentially[145]. Another widely used depletion strategy is metronomic low-dose cyclophosphamide (LD-CPA), which can selectively reduce the number of cycling Tregs, improve the Teff/Treg ratio, and enhance responses to vaccines and checkpoint blockade[146-147]. Antibody-based depletion has focused on CD25, although early agents (*e. g.*, daclizumab, denileukin diftitox) were limited by co-depletion of activated effector T cells[148-149]. Newer Fc-engineered anti-CD25 antibodies are designed to deplete intratumoral Tregs better while sparing systemic immunity and preserving IL-2 signaling[150]. Additional targets include chemokine receptors enriched on tumor Tregs, such as CCR4 (*e. g.*, mogamulizumab in CTCL) [151] and CCR8 (*e. g.*, afucosylated anti-CCR8 antibodies such as BAY 3375968) [152], as well as OX40, where agonistic antibodies can drive Fc-dependent depletion of $OX40^{hi}$ intratumoral Tregs[153-155].

A second strategy is blocking Treg recruitment to the tumor. Antagonists of chemokine receptors, such as CCR4 or CCR8, can reduce Treg trafficking driven by tumor chemokines (*e. g.*, CCL17/CCL22). For example, the CCR4 antagonist FLX475 has been tested as a means to limit Treg entry and enhance responses to anti-PD-1 therapy[156-157]. Treg migration can also be curtailed by sphingosine-1-phosphate (S1P) receptor modulators (*e. g.*, fingolimod, ozanimod, siponimod), which sequester T cells in lymphoid organs, or by targeting adhesion mechanisms such as LFA-1/ICAM-1 and E-/P-selectins, which support rolling and extravasation into tumor tissue[158-159].

Rather than removing Tregs, some approaches aim to destabilize them, causing them to lose their suppressive function within the TME. Disruption of neuropilin-1 (Nrp1) signaling in Tregs can impair FOXP3 stability and promote a fragile phenotype that is less suppressive and more permissive to $CD8^+$ T-cell activity[35, 160]. Pharmacologic strategies include MALT1 inhibition (*e. g.*, (S) -mepazine) [161-162] and TGF-β pathway blockade (*e. g.*, galunisertib) [163-164], both of which can weaken intratumoral Treg programs and support antitumor immunity.

Another major category is functional inhibition, where therapies aim to reduce Treg-mediated suppression while primarily restoring effector T-cell activity. CTLA-4 blockade (*e. g.*, ipilimumab) can inhibit Treg function and, in some contexts, promote Fc-dependent depletion of intratumoral Tregs, although this comes with a higher risk of immune-

related adverse events[165]. PD-1/PD-L1 blockade primarily reinvigorates exhausted effector T cells; however, its impact on Tregs is context-dependent: in some tumors, it is associated with reduced Treg activity, whereas in others, it can expand PD-1$^+$ Tregs[166-167]. Other suppressive pathways relevant to Tregs include adenosine signaling (*via* CD39/CD73)[168], checkpoints such as TIGIT and LAG-3, and IDO-mediated tryptophan depletion[169-171], which can be targeted to further alleviate suppression.

More recently, metabolic reprogramming has emerged as a way to selectively weaken tumor Tregs. Tumor Tregs often rely on fatty acid oxidation (FAO) and lipid synthesis; inhibitors of carnitine palmitoyltransferase 1 (CPT1) or lipid-regulatory programs such as SREBP/SCAP can reduce Treg fitness and improve responses to checkpoint blockade[172]. Mitochondrial targeting approaches (*e.g.*, disrupting oxidative phosphorylation with agents such as oligomycin or interfering with lipid-handling proteins like FABP5) can also reduce Treg suppressive capacity[173-177]. In glucose-poor, lactate-rich tumors, Tregs can depend on lactate uptake and metabolic flexibility[178-179]; therefore, targeting MCT1, glycolysis regulators (*e.g.*, HK2, GLUT1), or pathways that constrain glycolytic programs can impair intratumoral Tregs[172, 180]. Modulating the AMP-activated protein kinase (AMPK)-mTOR axis, including Treg-specific inhibition of AMPKα1, has also been linked to reduced Treg metabolic support and enhanced antitumor immunity[181].

Alongside these therapies, combination therapies are frequently pursued to treat tumors. Pairing LD-CPA or Treg-depleting antibodies with anti-PD-1/PD-L1 can improve effector: Treg ratios and overcome resistance to checkpoint blockade[182-183]. Treg modulation can also enhance cancer vaccines (*e.g.*, dendritic cell or neoantigen vaccines) and oncolytic virus strategies by allowing stronger priming and expansion of tumor-specific effector T cells[184-185]. In adoptive cell therapy settings, including CAR-T approaches, Treg depletion can improve antitumor activity, and engineered T cells designed to resist suppressive signals (*e. g.*, TGF- β) provide an additional route to counteract Treg-dominated TME[186-187]. Likewise, our recent study found that deletion of HIF1α in T cells, along with Treg inhibition, exerts strong anti-tumor immunity[115-116]. Treg-based therapies therefore follow opposite goals as they aim to restore and expand functional Tregs to reestablish immune tolerance in autoimmune diseases, while in cancer, they seek to deplete, exclude, or disable intratumoral Tregs to relieve immunosuppression and enhance antitumor immunity (Figure 4).

The development of Treg-based therapies progresses from target identification and lead discovery through preclinical *in vitro* and *in vivo* testing, phased clinical trials for safety and efficacy assessment, and ultimately regulatory review, approval, and post-marketing surveillance (Figure 5). The creation of engineered, antigen-specific Tregs, such as TCR-Tregs and CAR-Tregs, has enabled the field to mature rapidly in the US and Europe[188-189]. These next-generation modalities, which offer a targeted approach to immunological tolerance and could eventually replace conventional immunosuppressive regimens, are being evaluated in autoimmune disorders and solid-organ transplantation. First-in-human feasibility and clinical safety standards for antigen-directed Tregs have been set by innovative initiatives, including Sangamo's TX200 in kidney transplantation[190] and Quell Therapeutics' QEL-001 in liver transplantation[191]. With its early efficacy in RA and antigen-specific Treg functioning, Sonoma Biotherapeutics' SBT-77-7101 represents a paradigm change in autoimmune illnesses from symptomatic immunosuppression to proper immunological reprogramming[192]. These advances reveal that the Western Treg pipeline is trial-rich, precision-engineered, and company-driven.

On the other hand, the Treg therapeutic strategies in China are still in their early stages of translational maturation, despite the country's strong passion and extensive infrastructure for cell and gene therapy (CGT). Currently, investigator-initiated trials (IITs) rather than official investigational new drug (IND) frameworks govern the majority of Chinese activities[193-194]. Rapid exploratory research is facilitated by IITs, which are primarily overseen by the National Health Commission (NHC). However, they frequently lack the standardized regulatory comparability, quality control (QC) validation, and good manufacturing practice (GMP) oversight required for international registration[195]. China's efforts have therefore focused on small-scale preclinical or polyclonal Treg expansion projects, as well as low-dose IL-2 clinical studies, which have

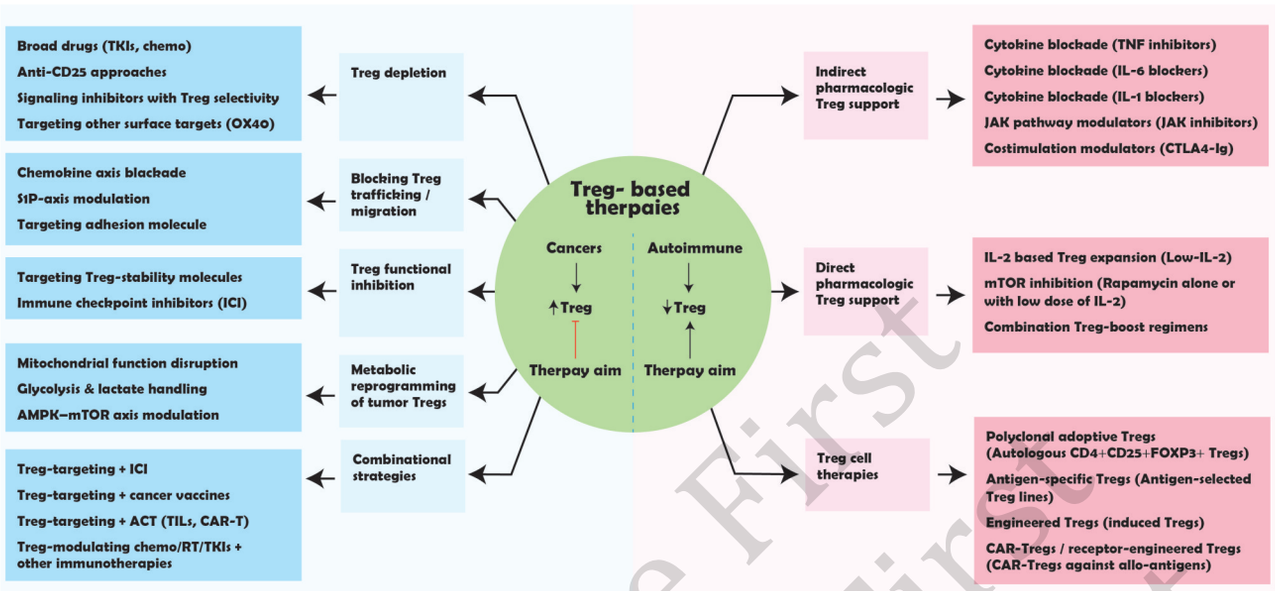

Fig. 4 Overview of Treg–based therapeutic strategies in cancer and autoimmune diseases

This schematic summarizes the opposing therapeutic principles of Treg targeting in cancer and autoimmune diseases. In cancer, Treg-based therapies aim to reduce intratumoral Tregs to relieve immunosuppression and enhance antitumor immunity. Major strategies include Treg depletion, blockade of Treg trafficking and migration, functional inhibition of Tregs, metabolic reprogramming of tumor Tregs, and combinatorial strategies that integrate Treg targeting with immune checkpoint blockade, cancer vaccines, adoptive cell therapy, or conventional chemotherapy and radiotherapy. In contrast, in autoimmune diseases, therapeutic approaches seek to expand or reinforce Tregs to restore immune tolerance. These include indirect pharmacological Treg support, direct pharmacological Treg enhancement, and Treg cell therapies, such as the adoptive transfer of polyclonal Tregs, antigen-specific Tregs, and engineered Tregs, including induced Tregs and CAR-Tregs. Together, the figure highlights the context-dependent, bidirectional manipulation of Tregs as a central strategy in immunotherapy.

produced positive results in RA and SLE. However, notable advancements are being made: businesses like Sailxin Bio, Bennu Biotherapeutics, and BodyHecon have started creating autologous or engineered Treg products, and Huaqi Biotech has published China's first enterprise-level Treg quality standard (Q/430111HQ 002-2024), which codifies functional and phenotypic parameters ($CD4^+CD25^+FOXP3^+$). These recent efforts are bridging the gap between academic research and commercial scalability.

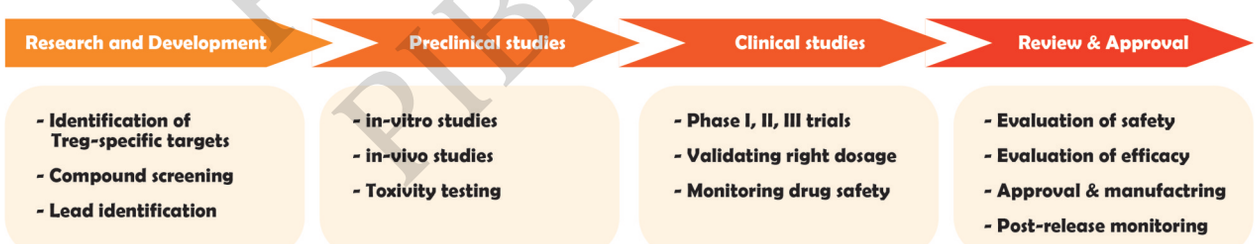

Fig. 5 Translational roadmap of Treg–based therapy development

A schematic overview of the stepwise development of Treg-based therapies. These therapies progress through research and preclinical studies to clinical trials and regulatory approval.

5 Future perspectives of Treg−based therapies

Despite encouraging progress, several challenges continue to limit the global translation of Treg-based therapies. In China, most Treg studies remain at the investigator-initiated trial stage, largely due to regulatory pathways that differ from FDA-style IND development, limited GMP-standardized manufacturing platforms, and insufficient experience with antigen-specific or genetically engineered Treg products. In contrast, Western programs have advanced into later-phase trials but face their own obstacles, including maintaining Treg lineage stability after *ex vivo* expansion, defining optimal dosing and durability, controlling manufacturing costs, and minimizing the risk of nonspecific immunosuppression. These challenges highlight the need for improved standardization, robust potency assays, and a shift toward antigen-specific or CAR-engineered Tregs, which offer greater precision, tissue targeting, and therapeutic efficacy in autoimmune diseases and transplantation. In the future, well-planned, multicenter clinical trials are necessary to assess the long-term safety, persistence, and efficacy among various patient types. Meanwhile, standardized immunological biomarkers must be utilized to determine Treg dynamics and their association with Tregs. Furthermore, next-generation technologies such as CAR- or TCR-engineered Tregs, nanomedicine-based *in vivo* targeting, and mRNA- and miRNA-mediated therapies should be investigated to achieve effective, precise, antigen-specific, and long-lasting tolerance. Additionally, standardizing manufacturing quality, potency testing, and regulatory criteria is necessary worldwide to ensure the widespread clinical translation of these products. Lastly, to improve therapeutic design and deepen our understanding of Treg plasticity, we should implement lessons learned from checkpoint blocking and cancer immunotherapy. These initiatives will certify Treg-based immune modulation as a pillar of precision medicine, turning the idea of tolerance induction into a therapeutic practice.

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调节性T细胞的发现及其潜在的临床应用

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摘要　日本免疫学家Shimon Sakaguchi首次鉴定出$CD4^+CD25^+$抑制性T细胞亚群，又明确了FOXP3是其发育分化的核心转录因子，将其命名为调节性T细胞（Treg）。与发现*Foxp3*基因的美国科学家Mary E. Brunkow与Fred Ramsdell一起获得了2025年的诺贝尔生理学或医学奖。在正常生理条件下，$FOXP3^+$Treg细胞在维持机体免疫稳态中发挥至关重要的作用。在过去的二十年里，Treg因其介导的免疫耐受而受到了极大关注。一方面，Treg能够有效抑制效应T细胞的活化，阻止过度免疫应答，从而防止过度免疫反应和自身免疫病的发生。另一方面，肿瘤微环境中Treg的过度扩增、活化和富集严重抑制了机体抗肿瘤免疫应答，进而导致肿瘤免疫逃逸及肿瘤发生。在本综述中，我们系统回顾了Treg细胞的发现、生物学特征、抑制作用机制以及Treg在维持机体免疫稳态中的调节作用；同时我们也概述了Treg细胞潜在的临床应用前景。深入剖析Treg细胞的异质性、免疫检查点调节和免疫代谢控制等的分子机制，为靶向Treg精准干预自身免疫病与肿瘤治疗奠定理论基础，并为开发下一代新免疫联合疗法提供新策略。

关键词　调节性T细胞，免疫耐受，肿瘤微环境，自身免疫性疾病，肿瘤免疫治疗

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