Review

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Regulatory T Cells and the Evolution of Immune Tolerance: From Thymic Selection to CAR-Treg Therapies

Mark Rhoge[1], Nour Younis[1,2], Jamil Azzi[1,*]

[1]Renal Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
[2]Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX 75390, USA
*Correspondence: jazzi@bwh.harvard.edu (Jamil Azzi)
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The immune system, composed of innate and adaptive immunity, orchestrates a complex network of responses to maintain immune equilibrium. Central to this balance are regulatory T cells (Tregs), particularly $CD4^+$ regs, which preserve self-tolerance and prevent autoimmunity. Advances in immunoregulation have elucidated key pathways governing Tregs function, including forkhead box P3 (FOXP3) regulation, metabolic dependencies, and interactions with signaling molecules like interleukin (IL)-2 and Notch-1. In addition to $CD4^+$ Tregs, emerging research highlights the critical role of Qa-1-restricted $CD8^+$ Tregs in promoting transplant tolerance and modulating autoimmune responses. Therapeutic strategies leveraging Tregs, from IL-2-based therapies to genetically engineered chimeric antigen receptor (CAR)-Tregs, have shown promise in modulating allo- and autoimmune responses. This review explores (1) the historical development of immunoregulation, (2) the role of innate and adaptive immune cells in immunoregulation, and (3) the most recent innovations in Treg-based therapies, emphasizing their potential for clinical application in transplantation, autoimmune disorders, and cancer immunotherapy.

Keywords: regulatory T cells; immune tolerance; CAR-Tregs; transplantation; autoimmunity; immunotherapy

Introduction

The immune system must continually balance robust pathogen defense with the prevention of self-harm, a delicate equilibrium known as immune tolerance. Central to this process are regulatory T cells (Tregs), which actively suppress unwanted immune activation to prevent autoimmunity, allograft rejection, and excessive inflammation while preserving responses to foreign antigens [1,2]. Discovered through seminal studies on thymic function in the 1960s, Tregs have evolved from a conceptual mechanism of self-nonreactivity to a cornerstone of modern immunotherapy [3]. Advances in molecular immunology have revealed their developmental origins, functional heterogeneity, and therapeutic manipulability, from natural $FOXP3^+$ $CD4^+$ Tregs to engineered CAR-Tregs that bypass major histocompatibility complex (MHC) restrictions [4]. This review traces the historical foundations of immunoregulation, examines the contributions of innate and adaptive immune cells to tolerance, and evaluates cutting-edge Treg-based therapies, with a focus on their translational potential in transplantation, autoimmunity, and cancer.

History of Immunoregulation

To understand the immunological response, it was integral to determine the organs involved in generating and maintaining our immune defense. In the early 1960s, Jacques Miller and colleagues conducted thymectomy procedures on mice to elucidate the role of the thymus [2]. Neonatal removal of the thymus showed decreased lymphocytes in the peripheral blood, spleen, lymph nodes, and Peyer's patches, causing immune deficiencies and reduced delayed-type hypersensitivity reactions, highlighting the thymus's contribution to these processes. However, thymectomy performed on 3-week-old mice caused no significant immune abnormalities or deficiencies, suggesting that the thymus's immunological function is particularly established during the neonatal period. Later, the thymus's role in T cell maturation and differentiation was highlighted, particularly in the generation of Tregs, which are critical for immune regulation and preventing autoimmunity [2,5].

Further research revealed the role of dendritic cells (DCs) in thymic T cell maturation and selection. DC antigen presentation facilitates the elimination of auto-reactive cells and the selection of Tregs, thereby ensuring immune tolerance [6]. In the thymus, Treg development is shaped by positive and negative selection based on T cell receptor (TCR) affinity for self-peptide–MHC complexes. During thymic positive selection, developing T cells that can moderately recognize self-peptide–MHC complexes are rescued from apoptosis and allowed to mature, ensuring MHC restriction [7]. Positive selection is followed by negative

selection, a process where T cells with high affinity for self-MHC are eliminated, while others with intermediate affinity are converted into FOXP3-expressing Tregs. These Tregs play a crucial role in immune regulation, modulating autoimmunity, inflammatory syndromes, and antitumor immunity [8,9].

These findings contributed to the understanding of adaptive immunity, where antigen-specific responses evolve to combat pathogens, contrasting the innate immune system's nonspecific defense mechanisms. Importantly, while the thymus is critical for generating T cells, its role extends beyond simple T cell production to the establishment of immune tolerance via Tregs, underscoring its function in immune regulation. The innate and adaptive immune systems work in tandem, with the innate response preceding the adaptive response as antigen-specific B and T cells undergo clonal expansion [10,11].

Innate Immunity and Immunoregulation

The innate immune system represents the body's first line of defense against internal and external threats. It provides a rapid, non-specific response through various immune cells and molecular mechanisms, including phagocytic cells, natural killer (NK) cells, antigen-presenting cells (APCs), complement proteins, and pattern recognition receptors (PRRs).

Phagocytic cells, such as neutrophils, monocytes, and macrophages, play crucial roles in inflammation and pathogen clearance. Neutrophils act as the first responders, rapidly migrating to sites of infection and engulfing pathogens. Monocytes circulate in the peripheral blood and differentiate into macrophages at inflamed tissues, where they release pro-inflammatory cytokines and aid in antigen presentation. Dendritic cells (DCs), residing in the skin and mucosal surfaces, play a pivotal role in capturing antigens through phagocytosis, endocytosis, and macropinocytosis before transporting them to lymph nodes for immune activation [12].

Beyond its defensive role, the innate immune system is tightly regulated to prevent excessive inflammation and autoimmune reactions. Myeloid regulatory cells (Mregs), including regulatory macrophages and myeloid-derived suppressor cells (MDSCs), help maintain immune balance by suppressing T cell activation, modulating antigen presentation, and secreting anti-inflammatory cytokines like IL-10 and transforming growth factor (TGF)-β. Similarly, NK cells—typically known for their cytotoxic function—also contribute to immune regulation by producing immunosuppressive cytokines in response to infection. Complement proteins further refine immune responses by modulating inflammation, clearing apoptotic debris, and interacting with regulatory B cells (Bregs) to promote immune tolerance [13].

PRRs serve as key mediators in innate immunity, detecting molecular patterns associated with pathogens and cellular damage. They are categorized into four major groups: Toll-like receptors (TLRs), NOD-like receptors (NLRs), retinoic acid-inducible gene (RIG)-like receptors (RLRs), and C-type lectin receptors (CLRs). These receptors not only recognize microbial features but also influence immune regulation through cytokine signaling and feedback mechanisms that prevent excessive immune activation [14].

Adaptive Immunity and Immunoregulation

The adaptive immune system provides antigen-specific defense against pathogens and malignancies while preserving immunological memory. However, its activation must be precisely regulated to prevent autoimmunity and allograft rejection. Immunoregulation, particularly through specialized T cell subsets, ensures the maintenance of self-tolerance and immune homeostasis. Tregs, including both $CD4^+$ and $CD8^+$ populations, have emerged as key mediators of immune suppression, modulating effector responses across various contexts such as transplantation, infection, and cancer. Recent insights into $CD8^+$ Tregs highlight their distinct but complementary role alongside $CD4^+$ Tregs in promoting long-term graft survival and preventing immune-mediated tissue injury [15–17]. Beyond Tregs, other regulatory cells like Bregs and NKregs interact with Tregs to enhance adaptive tolerance [18].

CD8 Regulatory T Cells

$CD8^+$ T cells, although traditionally recognized as pro-inflammatory cytotoxic cells, also include a regulatory subset, $CD8^+$ Tregs, with immunosuppressive functions similar to $CD4^+$ Tregs. CD8 Tregs function primarily through the recognition of self-peptides. These $CD8^+$ Tregs have been characterized by the expression of surface receptors such as CD44, CD122, and Ly49/KIR, which contribute to their ability to regulate immune responses by targeting self-reactive $CD4^+$ T cells [19].

Among the different subsets of $CD8^+$ Tregs, those restricted by the non-classical MHC class Ib molecule HLA-E (Qa-1 in mice) have been extensively studied for their role in maintaining self-tolerance and immune homeostasis. These $CD8^+$ Tregs recognize self-peptides, such as FL9, presented by Qa-1/HLA-E on activated $CD4^+$ T cells, enabling them to selectively detect and suppress autoreactive T cells in peripheral tissues. Studies investigating Qa-1 expression and FL9 peptide presentation on $CD4^+$ cells have demonstrated that Qa-1 serves as a key ligand recognized by $CD8^+$ Tregs, facilitating the maintenance of peripheral tolerance without being expressed by the $CD8^+$ Tregs themselves. A review [20] outlines how Qa-1–FL9–specific $CD8^+$ Tregs contribute to the immunosuppression of $CD4^+$ cells during immune responses, with significant implications for long-term graft survival and autoimmune disease management.

However, it is important to note that HLA-E (Qa-1)-restricted CD8$^+$ Tregs are not the only described subset of CD8$^+$ Tregs. Other populations, including those expressing LAG-3, CTLA-4, or CD39, have also been reported to mediate immune suppression through various mechanisms, including cytokine production and direct cytotoxicity. These alternative CD8$^+$ Treg subsets contribute to immune regulation in different contexts, including autoimmunity, infection, and transplantation tolerance [19].

While Qa-1-restricted CD8$^+$ Tregs share overarching goals with CD4$^+$ FOXP3$^+$ Tregs in promoting immune tolerance, their functions are largely complementary rather than redundant [21,22]. CD4$^+$ Tregs primarily exert early, broad suppression during the priming phase of immune responses through cytokine-mediated mechanisms (e.g., IL-10, TGF-β) and cell contact, preventing initial inflammation and effector T cell proliferation. In contrast, Qa-1-restricted CD8$^+$ Tregs act later, post-antigen restimulation, by perforin dependent cytolysis to eliminate activated, self-reactive CD4$^+$ T cells, such as follicular helper T (Tfh) cells, thereby controlling spontaneous germinal center reactions and autoantibody production, roles not fully covered by CD4$^+$ Tregs alone [23,24]. This non-redundancy is evident in models where deficiency in Qa-1-restricted CD8$^+$ Tregs leads to exaggerated autoimmunity (e.g., SLE-like disease) despite intact CD4$^+$ Tregs [20,21,25]. However, synergies exist, as both can cooperate for durable tolerance in transplantation and autoimmunity, with CD8$^+$ Tregs potentially suppressing memory responses resistant to CD4$^+$ regulation [26]. Comparatively, limitations of Qa-1-restricted CD8$^+$ Tregs include their delayed onset (requiring prior immune activation and Qa-1 upregulation on targets), dependence on IL-15 for homeostasis (unlike IL-2 for CD4$^+$ Tregs), and MHC class I restriction, which broadens target access but introduces heterogeneity and challenges in expansion or therapeutic translation [22]. Strengths lie in their potent, cytotoxic elimination of autoreactive clones, offering more definitive suppression than the often-reversible mechanisms of CD4$^+$ Tregs, though this may inadvertently hinder anti-tumor immunity [20].

Focusing on Qa-1-restricted CD8+ Tregs, several experiments have explored the role of the FL9 peptide in modulating alloimmunity. Results showed that presentation of the FL9 peptide by Qa-1 molecules is specifically used to activate Qa-1–restricted CD8$^+$ Tregs, leading to the suppression of Qa-1$^+$ CD4$^+$ T cell populations. In murine heart transplant models, flow cytometric analysis revealed that effector memory CD4$^+$ T cells (Tem: CD44$^+$ CD62L$^-$ CD4$^+$) and follicular helper T cells (Tfh: PD-1$^+$ CXCR5$^+$ CD4$^+$) exhibited high Qa-1 expression, suggesting that CD8$^+$ Tregs may specifically target these subsets, thereby promoting graft tolerance. Additional experiments demonstrated that upregulation of Qa-1 led to a significant increase in Tem and Tfh cells compared to wild-type controls, implying that CD8$^+$ Treg-mediated suppression extends to germinal center (GC) B cells, thereby reducing antibody responses to the allograft [25].

Continued transplant experiments in mice further supported the role of Qa-1-restricted CD8$^+$ Tregs in both cellular and antibody-mediated immune responses. Treatment with variations of FL9-based vaccines demonstrated that CD8$^+$ Tregs effectively recognize and suppress pathogenic CD4$^+$ Tfh cells, highlighting a potential therapeutic approach to reducing antibody-mediated injury in murine models of heart and kidney allograft rejection. While HLA-E (Qa-1)-restricted CD8$^+$ Tregs play a crucial role in this context, further research is needed to fully characterize the contributions of other CD8$^+$ Treg subsets to transplant tolerance and immune regulation [20].

CD4 Regulatory T Cells

CD4 T cells expressing the high-affinity IL-2 α chain receptor (CD25) are defined as regulatory CD4$^+$ T cells (Tregs) essential for maintaining self-tolerance, and immune homeostasis. The transcription factor, FOXP3, is the master regulator of Tregs [1]. Mutations in FOXP3 have been linked to the development of an inflammatory X-linked disease in mice, known as Scurfy, characterized by the absence of Tregs. This underscores the indispensable role of FOXP3 in Treg function. In humans, this disorder termed immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, is also marked by Treg dysfunction [27–29]. Besides focusing on FOXP3 mutations, it is equally important to explore proteins interacting with FOXP3, as mutations in genes responsible for FOXP3 regulators might explain the cause for IPEX-like phenotype observed in patients without FOXP3 mutations. For instance, DNA methylation and histone acetylation have an immense impact on FOXP3 and therefore affect Tregs function. Treg-specific demethylated region (TSDR), a conserved locus within FOXP3, is positively influenced by DNA demethylation. It regulates gene transcription and maintains FOXP3 expression, as demonstrated in experiments comparing DNA-methylated and demethylated TSDR regions through TGF-β-dependent processes and TCR signaling [30]. Further investigation into FOXP3 transcription reveals that multiple histone deacetylases (HDACs) and histone acetyltransferases (HATs) are involved in controlling FOXP3 stability and complex assembly, thereby influencing Treg activity [31]. The functional diversity of Tregs is further shaped by their differentiation into distinct subpopulations, which is regulated by FOXP3 expression and epigenetic modifications. Tregs exhibit distinct differentiation states, including naive Tregs (nTregs), central memory Tregs (cmTregs), effector memory Tregs (emTregs), and effector Tregs (eTregs), which are critical for their functional diversity, as illustrated in Fig. 1 [32].

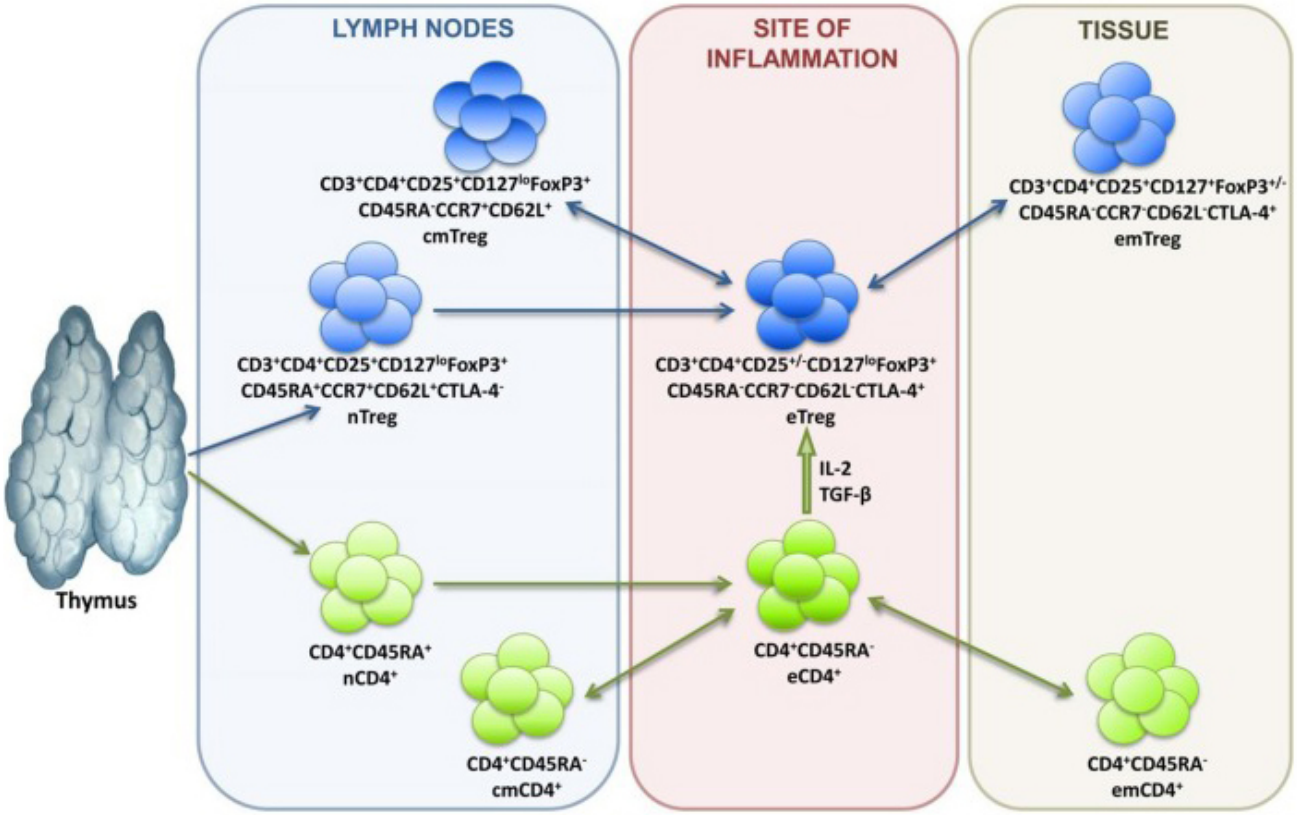

Fig. 1. Treg lymphocyte differentiation dynamics. Reproduced from Shevyrev and Tereshchenko (2020) [32], licensed under CC BY. Treg, regulatory T cell; cmTreg, central memory Treg; nTreg, naive Treg; FOXP3, forkhead box P3; TGF, transforming growth factor; IL, interleukin.

Moreover, certain molecules, like mTOR, play a crucial role in modulating Treg function by exerting opposing effects. On one hand, mTOR signaling promotes the differentiation of conventional T cells, while on the other hand, inhibiting this pathway enhances Treg function [26]. The metabolism of Treg and T effector cells also differ in interesting ways and is an area of continued interest. Naive T cells mainly use oxidative phosphorylation at rest, but upon activation, these cells switch to glycolysis. Conversely, Tregs depend on energy from fatty acid oxidation to power immunosuppression [33].

An emerging area of research highlights tissue-resident Tregs, which adapt to specific microenivornments in organs like the skin, lung, and gut. In the skin, Tregs express GATA3 and amphiregulin (AREG) to suppress fibrosis and promote keratinocyte proliferation for wound healing. Lung-resident Tregs, enriched in IL-4R and Notch4, produce IL-10 and TGF-β to maintain tolerance against inhaled antigens while aiding repair after injury. In the gut, RORγt+ Tregs support epithelial barrier integrity via AREG and IL-10 during inflammation, such as in colitis. These adaptations enable localized suppression and tissue repair, distinct from lymphoid Treg, with implications for organ-specific therapies in autoimmunity and transplantation [34,35].

Tregs have emerged as crucial players in solid organ transplantation, harnessing their suppressive function to thwart autoimmune responses and prevent effector cell-mediated allo-immunity. Tregs' functions, such as inhibiting IL-2 mRNA in target T cells and engaging with molecules like CTLA-4 and CD80/86 on APCs hinder T cell activation, have been suggested as prime targets for therapeutic interventions [36]. Promoting Treg function often involves manipulation of IL-2, a pivotal cytokine necessary for the generation, expansion, and maintenance of FOXP3$^+$ Tregs [37]. Tregs do not produce IL-2 but rather rely on IL-2 produced by other immune cells. Low-dose IL-2 therapy preferentially promotes Treg proliferation due to their high-affinity IL-2 receptor (CD25), suppressing effector T cell and natural killer (NK) cell functions. To enhance precision, engineered IL-2 muteins with increased affinity for CD25 (e.g., no-α muteins avoiding IL-2Rα binding or reduced IL-2Rβ affinity to limit NK cell activation) have been developed, showing promise in preclinical and early clinical trials for transplantation and autoimmunity [38,39]. In contrast, IL-2/anti-IL-2 antibody complexes extend IL-2 half-life and selectively boost Treg expansion by stabilizing IL-2-CD25 interactions, but they risk off-target effects on IL-2Rβ/γ-expressing cells and require careful dosing to avoid toxicity. Both approaches aim to enhance

Treg function, but muteins offer superior specificity by design, while complexes provide simpler administration but less control over effector cell activation [40–42] These IL-2 based strategies hold significant potential to revolutionize solid organ transplantation and autoimmune disease management [43].

Beyond IL-2 modulation, other therapies target Treg pathways: CTLA-4-Ig (abatacept) blocks CD28 co-stimulation on effector T cells while sparing CTLA-4 on Tregs, promoting tolerance in rheumatoid arthritis and transplantation trials; TGF-β delivery enhances Treg differentiation and stability in preclinical autoimmunity models; and small molecules like PI3K inhibitors boost Treg metabolism and survival for improved graft protection. These approaches complement IL-2 strategies, offering multi-faceted Treg enhancement with reduced off-target risks [44,45].

Other studies highlighted the role of Notch-1 in Tregs function. Notch-1 is involved in T-cell survival and their differentiation into the different helper subsets. Notch-1 inhibition prolongs allograft organ transplant survival in murine models by favoring Tregs. Humanized anti-Notch-1 antibody (aNotch-1) induced decreased allograft-infiltrating immune cells and prolonged survival [46]. As solid organ transplantation survival is a continued area of interest within the medical field, the effect of Notch-1, among other molecules, on Tregs continues to be explored.

Although Tregs confer protection against autoimmunity and graft rejection, they facilitate cancer progression by suppressing anti-tumor immune responses in the tumor microenvironment (TME). Tregs infiltrate tumors via chemokine receptors like CCR4 and CCR8 which guide their migration and accumulation, dampening effector T cell and NK cell activity through IL-10, TGF-β, and direct cell contact (e.g., CTLA-4 binding to CD80/86 on APCs) [47]. Strategies to counter this include anti-CD25 monoclonal antibodies (e.g., daclizumab), which deplete Tregs by targeting their high-affinity IL-2 receptor, and IL-2 toxin conjugates that selectively eliminate Tregs. Blocking CCR4 and CCR8 with small-molecule inhibitors or antibodies reduces Treg recruitment, enhancing anti-tumor immunity in preclinical models. Immune checkpoint inhibitors targeting CTLA-4 (e.g., ipilimumab) and PD-1 (e.g., pembrolizumab) disrupt Treg suppression, boosting cytotoxic T cell responses [48]. Clinical trials (2020–2024) show CTLA-4/PD-1 inhibitors improve survival in melanoma and lung cancer (e.g., 20–30% response rates in advanced cases), though Treg depletion can risk autoimmune side effects. Combination therapies, like CCR4 inhibitors with PD-1 blockade, are showing promise in trials for solid tumors, with ongoing studies exploring Treg-specific targets to balance efficacy and safety [35,36]. In colorectal cancer, Tregs promote tumor progression, but targeting them with checkpoint inhibitors shows promise for enhancing immunotherapy [49]. These findings underscore the potential of precision Treg-targeting strategies to improve cancer immunotherapy outcomes while mitigating risks of immune-related adverse events.

Genetic Engineering Modifications

Increasing attention has been directed toward chimeric antigen receptor (CAR) T cells and their potential applications in immunology. Compared to Tregs engineered with conventional T cell receptors (TCRs), CAR-Tregs offer the advantage of non–MHC-restricted recognition and reduced dependency on IL-2 signaling for survival and function [4]. In the context of organ transplantation, donor and recipient tissues are typically matched at the level of HLAs; however, due to the extensive polymorphism of HLA alleles, mismatches frequently occur, leading to T cell-mediated allograft rejection. To address this, CAR-Tregs have been engineered to recognize mismatched HLAs expressed by the graft, often utilizing CAR constructs based on HLA-A2–specific monoclonal antibodies, given the high prevalence of HLA-A2 in the population. The structure and suppressive mechanisms of CAR-Tregs, including their ability to secrete immunosuppressive cytokines and induce effector T cell apoptosis are illustrated in Fig. 2 [50]. Researchers have experimented with the function of CAR-Tregs and their viability on murine models to deduce the most effective therapies. Building on the foundational role of IL-2 in Treg proliferation and maintenance (as discussed earlier), additional cytokines such as IL-33 have shown importance for Tregs in tissues, while IL-7 is key for circulation of Tregs throughout secondary lymphoid organs such as the spleen, lymph nodes, and Peyer's patches [51–53]. Future investigations must address several important considerations, including the persistence and stability of CAR-Tregs over time, their functional efficacy in sensitized recipients, and their performance in combination with conventional immunosuppressive therapies such as rapamycin [54].

Discussion

Tregs offer transformative potential for transplantation, autoimmunity, and cancer immunotherapy, but limitations hinder their clinical translation. A key challenge is the instability of the Treg phenotype, particularly for $CD4^+$ $FOXP3^+$ Tregs, which can lose suppressive function or convert to effector T cells under inflammatory conditions, risking exacerbated autoimmunity or graft rejection [35]. $CD8^+$ Qa-1-restricted Tregs, while potent, face delayed activation due to Qa-1 upregulation requirements and IL-15 dependence, complicating scalable therapies. CAR-Treg therapies, despite bypassing MHC restrictions, struggle with persistence *in vivo* and potential off-target suppression, especially in sensitized recipients with pre-existing immunity. Current IL-2 based strategies (muteins, complexes) show promise but risk toxicity or in-

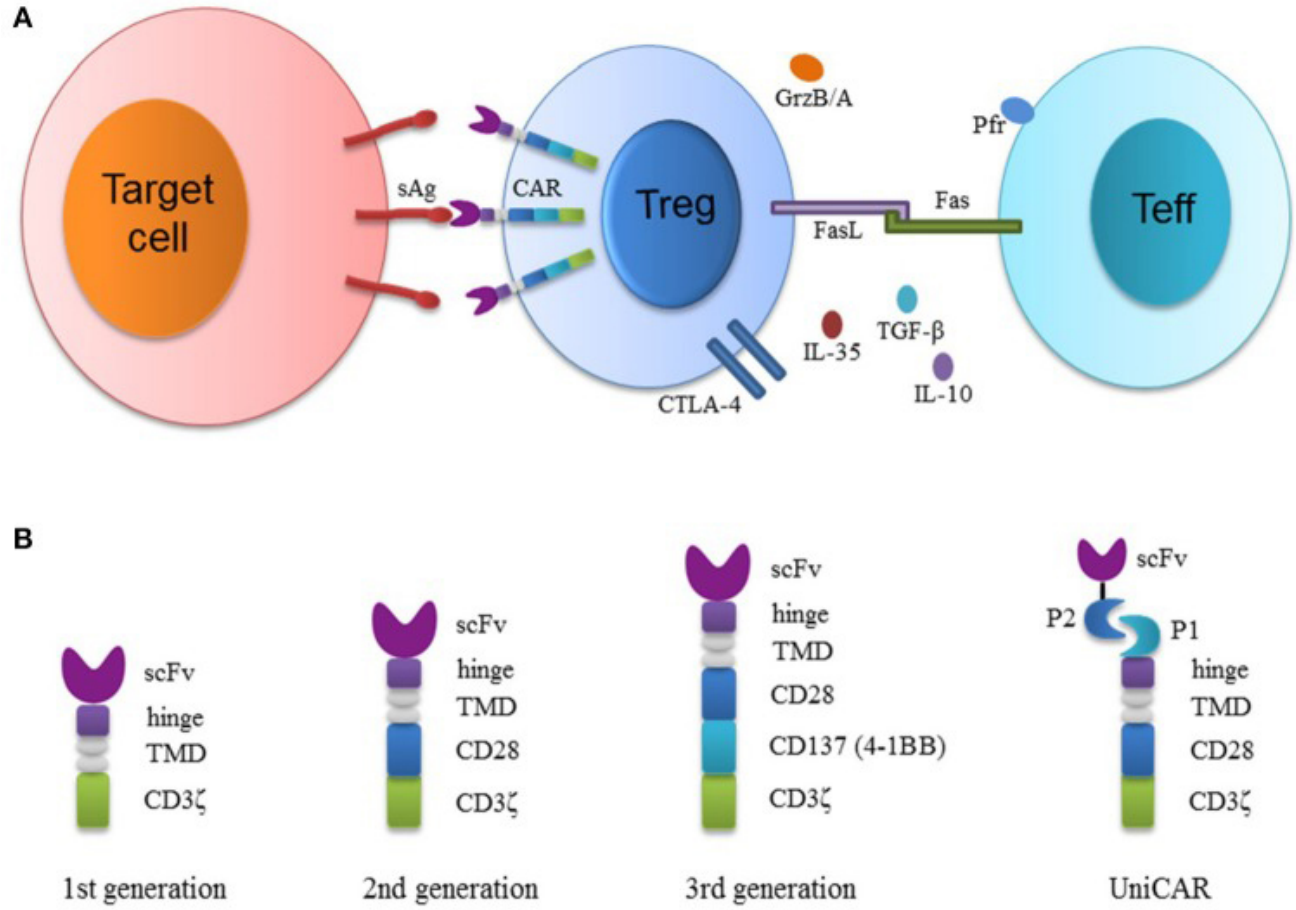

Fig. 2. Schematic diagram depicting the structure of chimeric antigen receptor-modified regulatory T cells (CAR-Tregs) and their suppression of effector T cells. (A) Tregs transduced with viral vectors overexpress CARs that specifically recognize surface antigens on target cells. CAR-Tregs suppress effector T (Teff) cells through various mechanisms. CAR-Tregs secrete immunosuppressive cytokines. CTLA-4 on activated Tregs also competes with CD28 on Teffs to bind CD80/CD86 on APCs. Granzyme B/A (GrzB/A) and perforin (Pfr) secreted by Tregs or their Fas-ligand can induce Teff apoptosis. (B) The construction of the first generation (1st CAR), second generation (2nd CAR), third generation (3rd CAR), and universal CAR (UniCAR) are presented. CARs consist of antigen binding scFv (single chain variable fragment), an extracellular hinge, a transmembrane domain (TMD), and intracellular signaling (CD28/CD137/CD3ζ) domains. The 1st CAR contains only CD3ζ signaling domain. The 2nd CAR contains an additional costimulatory domain (either CD28 or CD137). The 3rd CAR combines both costimulatory domains. Finally, the hinge of the universal CAR is attached to P1 (a peptide or protein), which binds to another peptide or protein P2 fused to an scFv recognizing surface molecules on target cells. Reproduced from Zhang *et al.* (2018) [50], licensed under CC BY.

sufficient specificity, as seen in early trials for SLE and transplantation [55]. Future prospects include optimizing Treg stability via epigenetic editing (e.g., CRISPR targeting TSDR demethylation) to lock in FOXP3 expression, enhancing durability in hostile microenvironments like tumors or inflamed grafts. Recent advances in Treg therapies, including CRISPR-edited antigen-specific Tregs, address stability challenged in autoimmunity [56]. Tissue-resident Treg therapies, tailored to skin, lung, or gut, could leverage local signals (e.g., AREG, IL-33) for precise suppression, with preclinical models showing efficacy in colitis and GVHD [57,58]. Combining CAR-Tregs with small molecules (e.g., PI3K inhibitors) or low-dose rapamycin may improve persistence and specificity, with phase I trials underway for kidney transplantation. Additionally, integrating AI-driven biomarker discovery could refine patient selection for Treg therapies, addressing heterogeneity in autoimmune and cancer responses. These advances promise to bridge current gaps, revolutionizing precision immunotherapy.

Conclusions

In conclusion, the field of immunoregulation has witnessed remarkable advancements since its inception, particularly through elucidating the roles of thymic selection, dendritic cell function, and regulatory T cells. These discoveries have not only deepened our understanding of im-

mune system dynamics but also opened new avenues for therapeutic strategies in treating immune-related disorders. The intricate balance between immune activation and tolerance, mediated by regulatory T cells and other regulatory cells, underscores the complexity and adaptability of the immune system. Continued research into the molecular mechanisms governing immunoregulation—including cytokine signaling, metabolic dependencies, and genetic engineering approaches like CAR-Tregs—promises to expand therapeutic options and improve clinical outcomes of immune-mediated diseases.

Availability of Data and Materials

This review article synthesizes data from published and does not generate new experimental data. All referenced studies are publicly available through their respective journals or repositories, as cited in the reference list. No additional datasets or materials were created for this manuscript.

Author Contributions

MR, NY, and JA conceptualized the review, conducted the literature search, and drafted the manuscript. JA and NY, together with MR, contributed to critical revisions, provided insights on Treg-based therapies, and edited sections on transplantation and autoimmunity. All authors reviewed and approved the final version of the manuscript. All authors agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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