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Regulatory T Cell Plasticity in Rheumatoid Arthritis: Mechanisms, Pathogenic Roles, and Therapeutic Implications

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent inflammation, progressive joint damage, and functional disability. The plasticity of regulatory T cells (Tregs) plays a central role in the immunopathogenesis of RA by disrupting immune tolerance and promoting pro-inflammatory T helper (Th) 17 (Th17)-like responses. In this review, a comprehensive literature search was conducted in the PubMed, Scopus, and Web of Science databases up to May 2025, using the keywords "rheumatoid arthritis," "regulatory T cells," "regulatory T Cell plasticity," and "immune system regulation." Reference lists of retrieved publications were manually screened to identify additional relevant studies. Priority was given to peer-reviewed experimental and clinical studies addressing Treg biology, molecular mechanisms of plasticity, and therapeutic implications. Only English-language articles were included, and quality was assessed based on study design, sample size, and reproducibility of findings. Evidence indicates that inflammatory cytokines, metabolic alterations, and epigenetic reprogramming disrupt the stability of forkhead box protein 3 (Foxp3) and promote the conversion of Tregs into Th17-like cells. This shift diminishes suppressive capacity and increases interleukin (IL) 17 (IL-17) production, thereby exacerbating synovial inflammation and joint destruction. Clinical data demonstrate that unstable Foxp3+RORγt+ Tregs correlate with disease activity and radiographic progression in RA. Current therapeutic strategies—including IL-6 receptor inhibitors, Janus kinase (JAK) inhibitors, rapamycin, and epigenetic modulators—show potential in preserving Treg stability. Moreover, emerging approaches such as chimeric antigen receptor (CAR)-Treg cells and microRNA-based interventions represent innovative directions for targeted immunotherapy. Treg plasticity plays a pivotal role in the pathogenesis of RA and offers novel opportunities for therapeutic intervention. Stabilizing Treg identity and preventing their pathological conversion have the potential to restore immune tolerance, reduce inflammation, and halt disease progression. Clinicians could consider the implications of Treg-targeted strategies as adjuncts to conventional immunomodulatory therapies.

Key words: Rheumatoid arthritis, Regulatory T cells, Regulatory T cell plasticity, Immune system regulation

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by progressive joint inflammation, destruction of cartilage and bone, and motor disability (1). It affects approximately 1% of the global population and is associated with impaired self-tolerance and abnormal activation of the immune system (2). The pathophysiology of RA involves a complex interplay among immune cells, pro-inflammatory cytokines, and dysfunctional regulatory mechanisms, which lead to an immune response against self-antigens (3, 4). Among lymphocyte subsets, regulatory T lymphocytes (Tregs) are recognized as the guardians of self-tolerance; thus, any impairment in their function or numbers plays a crucial role in the initiation and progression of RA (5, 6). Tregs, characterized by the expression of specific markers such as forkhead box protein 3 (Foxp3), CD25, and CD4, play a crucial role in inhibiting autoimmune responses. They achieve this through cell contact-dependent suppressive mechanisms and the secretion of anti-inflammatory cytokines, including interleukin (IL) 10 (IL-10) and transforming growth factor-beta (TGF-β) (7, 8). Recent studies have indicated that in patients with RA, a reduction in the number or functionality of Tregs correlates with an increase in the pathological activity of T helper (Th) 17 lymphocytes (Th17) and the production of pro-inflammatory cytokines such as IL-17 and tumor necrosis factor-alpha (TNF-α). This imbalance between Tregs and Th17 cells is considered a key feature in the pathogenesis of RA (9-13).

An emerging concept in RA immunology is T-cell plasticity, which refers to the ability of these cells to alter their phenotype and function in response to environmental cues (14). Treg plasticity is particularly significant in RA, as under inflammatory conditions, some Tregs may lose their suppressive properties and even transform into pro-inflammatory effector cells (15). This phenomenon not only elucidates the dysfunction of Tregs in RA but also presents a potential target for immunomodulatory therapies (16, 17). Emerging evidence indicates that environmental factors, such as cytokines, cellular metabolites, and adhesion signals, play a crucial role in regulating Treg plasticity in RA (6, 17, 18).

Evidence Acquisition

Given the critical role of Tregs and their plasticity in the pathophysiology of RA, a more comprehensive understanding of the regulatory mechanisms and factors influencing the differentiation and function of these cells may yield novel therapeutic strategies aimed at restoring immune balance and inhibiting disease progression. In this study, a comprehensive literature search was conducted in the PubMed, Scopus, and Web of Science databases up to May 2025, using the keywords “rheumatoid arthritis,” “regulatory T cells,” “regulatory T Cell plasticity,” and “immune system regulation.” Reference lists of retrieved publications were manually screened to identify additional relevant studies. Priority was given to peer-reviewed experimental and clinical studies addressing Treg biology, molecular mechanisms of plasticity, and therapeutic implications. Only English-language articles were included, and quality was assessed based on study design, sample size, and reproducibility of findings.

Review of Evidence

Tregs: Types and Role of Foxp3

Tregs are a crucial subset of T cells that play a vital role in maintaining self-tolerance and preventing autoimmune responses (8). These cells are categorized into two primary groups: natural Tregs (nTregs) and induced Tregs (iTregs). Natural Tregs differentiate in the thymus and undergo central selection to recognize self-antigens. In contrast, iTregs are generated in the peripheral environment from conventional T cells under the influence of cytokines such as TGF-β and IL-2 (19, 20) (Figure 1).

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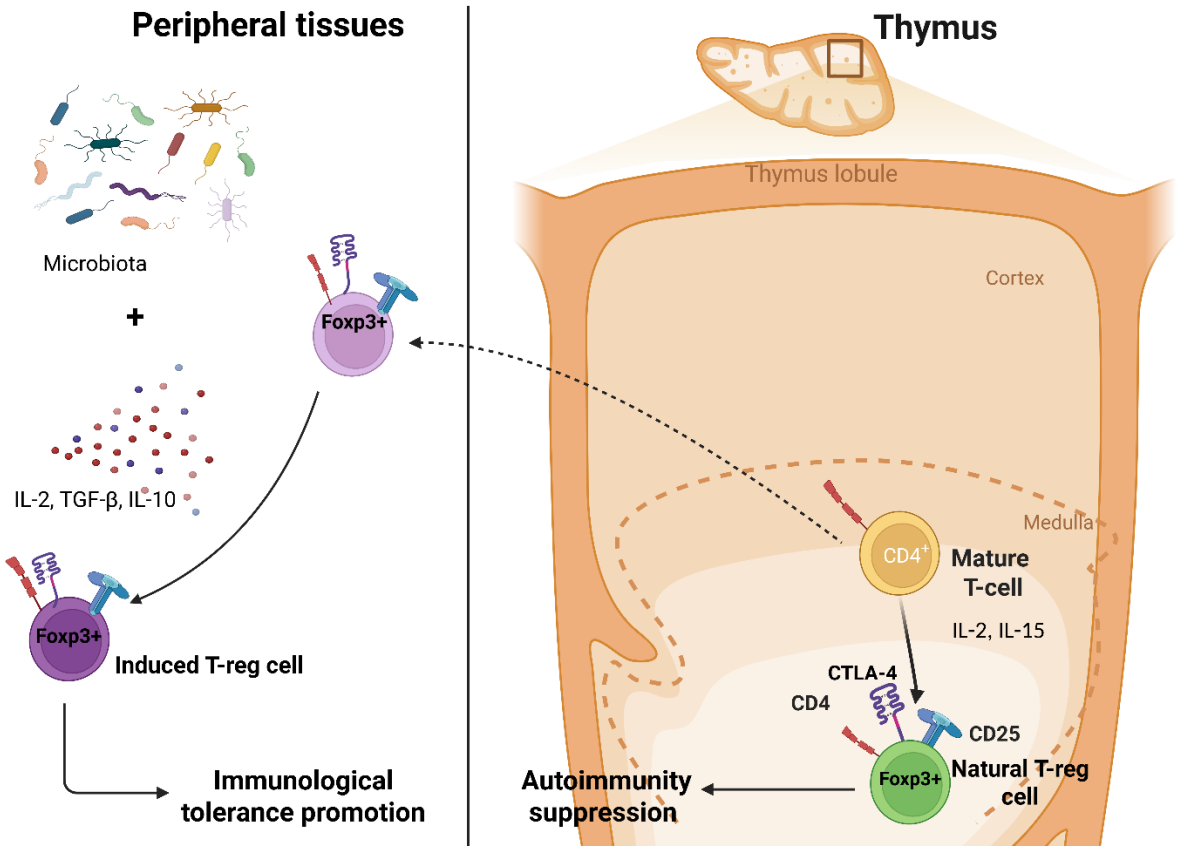

Figure 1. The primary types of regulatory T cells (Tregs). Tregs are broadly categorized into natural Tregs (nTregs), which develop in the thymus through central selection and are specific for self-antigens, enabling them to maintain immune tolerance, and induced Tregs (iTregs), which differentiate from conventional $CD4^+$ T cells in peripheral tissues in response to cytokine signals such as TGF-β and IL-2.

The transcription factor Foxp3 is recognized as a master regulator and marker of Treg function. Stable expression of Foxp3 is crucial for preserving the suppressive phenotype and functional stability of Tregs (21). Research has demonstrated that mutations in the Foxp3 gene result in compromised Treg function and contribute to the development of autoimmune diseases, such as immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX syndrome) (21, 22). Furthermore, Foxp3 plays a vital role in maintaining immune balance by inhibiting the differentiation of pro-inflammatory effector cells, such as Th17 cells (8, 23).

Treg Plasticity: Phenotypic Changes and Pathological Consequences

Treg plasticity refers to the ability of Tregs to alter their phenotype and function in response to environmental signals (14, 18). Under inflammatory conditions, this property can result in the loss of Foxp3 expression and the transformation of Tregs into pro-inflammatory cells. in RA, certain Tregs, influenced by cytokines such as IL-6 and IL-23, can convert into Th17-like cells that secrete IL-17, thereby exacerbating joint inflammation (9, 24) (Figure 2). Treg plasticity not only contributes to the progression of autoimmune diseases but also presents challenges for Treg-based therapies.

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However, understanding the mechanisms that regulate plasticity, including metabolic pathways and epigenetic factors, could offer new strategies to enhance the stability of Tregs (25, 26).

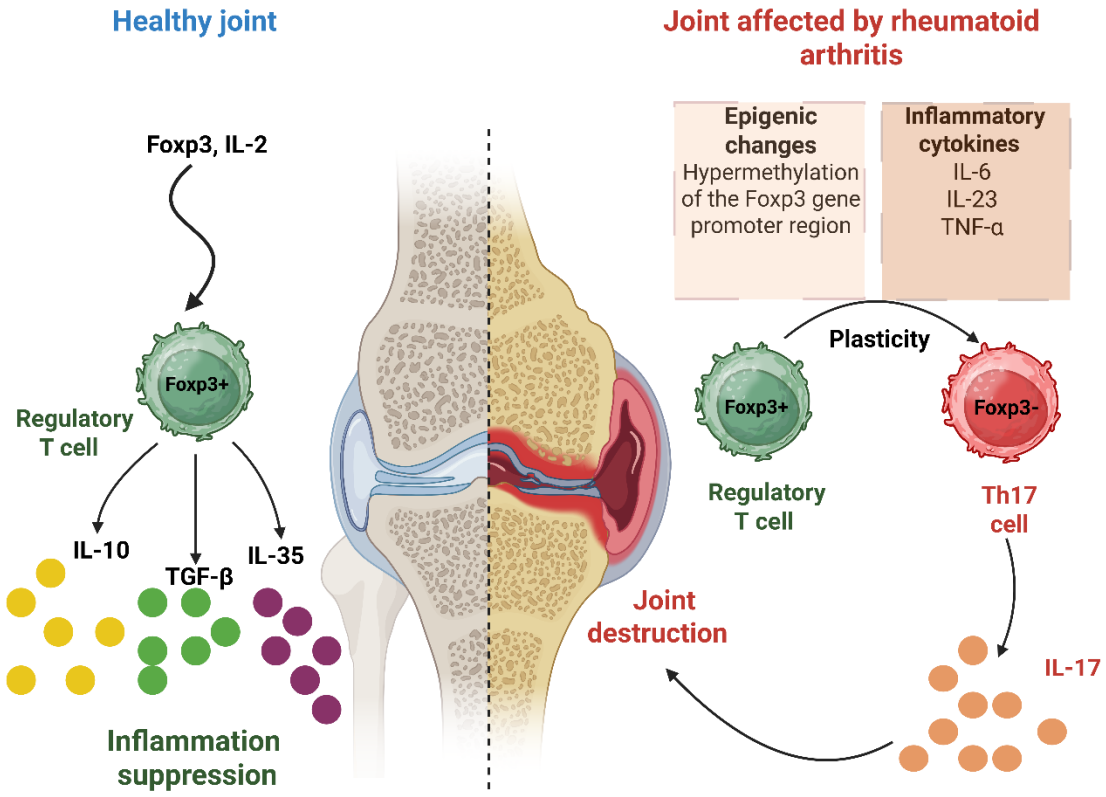

Figure 2. The plasticity and functional instability of regulatory T cells (Tregs) in Rheumatoid Arthritis (RA). In a healthy joint, stable forkhead box protein 3 (Foxp3) expression enables Tregs to suppress inflammation through the production of anti-inflammatory cytokines such as interleukin (IL) 10 (IL-10), transforming growth factor-beta (TGF-β), and IL-35. In RA, chronic inflammation driven by IL-6, IL-23, and tumor necrosis factor-alpha (TNF-α), combined with epigenetic silencing of the Foxp3 promoter, induces Tregs instability. This instability leads to the pathogenic conversion of Foxp3+ T cells into pro-inflammatory, IL-17-producing T helper (Th) 17 (Th17)-like cells, which contribute to joint destruction.

The Inflammatory Joint Environment in RA: Immunological and Metabolic Features

The joints of patients with RA exist in a highly inflamed environment, characterized by the extensive secretion of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, and IL-17. These cytokines not only sustain chronic inflammation but also play a crucial role in the abnormal activation of synovial fibroblast-like cells (FLS) (4, 27). In RA, activated FLS acquire invasive properties and contribute to the progressive destruction of cartilage and bone by producing matrix metalloproteinases (MMPs) and growth factors (1, 4). Macrophages in RA joints are the primary source of TNF-α and IL-1β production. These cells enhance T-cell hyperactivation by increasing the expression of costimulatory molecules such as CD80 and CD86. Dendritic cells (DCs) present in the synovial fluid also play a significant role in the expansion of Th17 responses and the reduction of Treg function by presenting self-antigens and producing IL-23 (4, 28). The metabolic environment of the RA joint is characterized by elevated glucose consumption and lactate

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accumulation, resulting from the activation of glycolytic pathways in inflammatory cells. These metabolic alterations profoundly affect the function of Tregs. Recent studies have demonstrated that in the hypoxic environment of the RA joint, decreased levels of glutathione and increased reactive oxygen species (ROS) contribute to impaired Treg function (6, 29, 30). Epigenetic changes also contribute to the impairment of Treg function in RA. Hypermethylation of the Foxp3 gene promoter region, along with modifications to histones that regulate the expression of this gene, results in decreased stability of the Treg phenotype. Notably, these epigenetic alterations may be induced by inflammatory cytokines present in the joint environment, promoting the transformation of Tregs into Th17-like cells (28, 31).

Molecular Mechanisms of Treg Plasticity: The Role of Cytokines, Signaling Pathways, and Epigenetic Regulation

The inflammatory environment promotes Treg plasticity towards a Th17 phenotype by modulating the expression of key transcription factors. Research has demonstrated that IL-1β and IL-6 activate the signal transducers and activators of transcription 3 (STAT3) signaling pathway, leading to the downregulation of Foxp3 expression and the upregulation of retinoic acid-related orphan receptor gamma t (RORγt), a transcription factor specific to Th17 cells. Notably, TGF-β at low concentrations, in conjunction with IL-6, facilitates this conversion; however, at high concentrations, it exerts an inhibitory effect (5, 9, 13, 21). These findings indicate that the specific ratio of these cytokines within the microbial environment plays a crucial role in determining the fate of Tregs. At the molecular level, IL-6 induces the phosphorylation of Foxp3 via the STAT3 pathway, resulting in decreased stability of Foxp3. Concurrently, the activation of the RORγt pathway initiates the programming of Th17 genes. Recent studies have demonstrated that these alterations are accompanied by epigenetic modifications, including reduced DNA methylation in the promoter region of the RORC gene (which encodes RORγt) and increased acetylation of associated histones (4, 9, 31). STAT3, activated by IL-6/IL-23, suppresses Foxp3 and induces RORγt, promoting Th17-like conversion. Nuclear factor kappa B (NF-κB) signaling, sustained by TNF-α, enhances inflammatory gene expression and weakens Treg suppressive function. Hyperactivation of phosphoinositide 3-kinase (PI3K)–protein kinase B (Akt)–mechanistic target of rapamycin (mTOR) (PI3K–Akt–mTOR) links metabolic stress to lineage instability. Together, these pathways integrate cytokine and metabolic cues, amplifying loss of tolerance (32, 33). Additionally, microRNAs (miRs) play a crucial regulatory role in this process. For instance, miR-10a diminishes Foxp3 stability by targeting B-cell lymphoma 6 (BCL-6) and nuclear receptor co-repressor 2 (NCOR2). Conversely, miR-155 inhibits the conversion of Tregs to Th17 cells, highlighting the complex regulatory network of miRs involved in this process. Furthermore, studies have indicated that miR-326 enhances RORγt expression by inhibiting E26 transformation-specific sequence-1 (Ets-1) (34, 35). Extensive epigenetic changes occur during the conversion of Tregs to Th17. Hypomethylation of the IL17A enhancer region and hyperacetylation of histone H3 in the promoter region of this gene enhance the accessibility of transcription factors. Furthermore, alterations in the DNA methylation pattern of the Foxp3 gene result in its stable silencing (25, 31, 36). These findings suggest that Treg plasticity relies not only on changes in gene expression but also on enduring epigenetic modifications. In the inflamed synovial microenvironment, hypoxia promotes hypoxia-inducible factor 1-alpha (HIF-1α)–dependent

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glycolysis, which impairs Treg function and facilitates Th17 differentiation. Additionally, increased ROS and altered lipid metabolism further compromise Treg suppressive capacity (37, 38).

Clinical Implications of Treg Plasticity in RA

The plasticity of Tregs and their transformation into Th17-specific cells in RA has significant clinical implications. Studies have demonstrated that the reduction in both the number and function of stable Tregs in RA patients is directly correlated with the severity of the disease and the progression of joint destruction (3, 9, 13, 28). In the inflammatory environment of the RA joint, elevated levels of IL-6 and IL-23 activate the STAT3 pathway and decrease the expression of Foxp3, leading to a loss of regulatory properties and the acquisition of a pro-inflammatory phenotype (4, 9). Analysis of synovial samples from patients with RA has revealed a population of unstable Tregs that co-express Foxp3 and RORγt, which is positively correlated with disease activity and radiographic joint damage. These dual-positive cells not only lose their suppressive function but also contribute to chronic inflammation and tissue damage by producing IL-17 (9, 28, 39). From a therapeutic perspective, understanding the mechanisms underlying Treg plasticity has opened new avenues for intervention (36, 39). Epigenetic modulators, such as DNA methyltransferase (DNMT) and Histone deacetylase (HDAC) inhibitors, have demonstrated efficacy in animal models of RA by maintaining Foxp3 stability and preventing the conversion of Tregs to Th17 cells (40-42). Recent findings indicate that targeted therapeutic strategies based on Treg plasticity could help restore immune balance and prevent disease progression. However, significant challenges remain, including the need for accurate methods to identify and isolate stable and unstable Tregs in clinical settings (16, 26, 43). Beyond Treg instability, effector T-cell resistance to Treg-mediated suppression represents another critical mechanism in RA pathogenesis. Pro-inflammatory cytokines, such as TNF-α and IL-6, along with altered signaling pathways, diminish effector T-cell responsiveness, thereby sustaining inflammation despite the presence of stable Tregs. Therapeutic strategies targeting both Treg stability and effector T-cell sensitivity—such as TNF and IL-6 blockade—may therefore provide synergistic benefits in restoring immune tolerance (44, 45).

Novel Therapeutic Strategies for Regulating the Stability and Plasticity of Tregs

The functional stability of Tregs and the prevention of their undesirable plasticity towards pro-inflammatory phenotypes have been proposed as promising therapeutic strategies for autoimmune diseases, such as RA (17, 26, 38). Recent studies indicate that existing immunomodulatory drugs, including IL-6 receptor inhibitors (tocilizumab) and Janus kinase (JAK) inhibitors (tofacitinib), not only reduce inflammation but also enhance the stability of Tregs by maintaining Foxp3 expression and decreasing RORγt expression. These drugs exert their effects by inhibiting the STAT3 pathway, which plays a crucial role in the conversion of Tregs to Th17 cells (46-49). Novel therapeutic approaches that focus on the metabolic modification of Tregs are currently under development. Research has demonstrated that the inhibition of mTOR using rapamycin can enhance the functional stability of Tregs by shifting their metabolic programming from glycolysis to lipid oxidation. Additionally, epigenetic regulators, such as HDAC and DNMT inhibitors, help prevent the transformation of Tregs into pro-inflammatory effector cells by preserving the methylation pattern of the Foxp3 promoter region (50-52). One of the most promising therapeutic strategies is the use of chimeric antigen receptor (CAR)-Treg cells. In this approach, patient-derived Tregs are

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engineered with CARs to specifically recognize self-antigens in the joints (53). Preclinical studies have demonstrated that CAR-Tregs are not only more stable in inflammatory environments but also capable of locally suppressing inflammation and preventing joint destruction (54-56). In addition, targeting miRs that regulate Treg plasticity, such as miR-10a and miR-155, has emerged as a promising therapeutic strategy. These approaches can selectively inhibit the signaling pathways involved in the conversion of Tregs to Th17 cells, without compromising the overall suppressive function of the immune system. However, significant challenges remain, including the necessity for tissue-specific targeting systems and precise control of therapeutic dosages (34, 57-59).

Conclusion

A deeper understanding of Treg plasticity has significantly advanced our knowledge of RA pathophysiology. The disruption of Treg stability and their conversion into Th17-like cells play a crucial role in disease initiation and progression. Targeted strategies aimed at preserving Treg function—such as small molecules that enhance Foxp3 stability, CAR-Treg therapy, and epigenetic modulation—hold promise for restoring immune balance. Future research should prioritize the identification of patient-specific biomarkers of Treg stability to enable precision immunotherapy in RA.

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