Review

Biology

Dysfunction of Regulatory T Cells

The Fundamental Underlying Mechanisms Underpinning Autoimmune Diseases

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Regulatory T cells (Tregs) play a critical role in maintaining immune homeostasis by suppressing excessive immune responses and preventing autoimmune reactions. Dysregulation of Treg function has been identified as a key factor in the development and progression of various autoimmune diseases. Understanding the fundamental mechanisms underlying Treg dysfunction is essential for unraveling the complex pathogenesis of autoimmune disorders. This article delves into the intricate interplay between Tregs and autoimmune diseases, exploring the impact of Treg dysfunction on immune regulation and disease development. By examining the mechanisms of Treg dysfunction and therapeutic strategies aimed at restoring Treg function, we aim to shed light on this intricate aspect of autoimmunity and pave the way for innovative approaches to managing autoimmune conditions.

Keywords: Regulatory T Cells; Dysfunction; Autoimmune Diseases; Mechanisms; Therapeutic Potential

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Introduction

AUTOIMMUNE diseases represent a diverse group of disorders characterized by an aberrant immune response against self-antigens, leading to chronic inflammation and tissue destruction. These diseases, which include conditions such as rheumatoid arthritis (RA), type 1 diabetes (T1DM), multiple sclerosis (MS), and systemic lupus erythematosus (SLE), collectively affect millions worldwide and pose a significant burden on healthcare systems (Smith & Germolec, 1999). While the precise etiology of autoimmune diseases remains complex and multifactorial, emerging evidence highlights the dysfunction of regulatory T cells (Tregs) as a fundamental mechanism underlying their pathogenesis.

Regulatory T cells, particularly the forkhead box P3 (FoxP3)-expressing $CD4^+$ Tregs, play a crucial role in maintaining immune homeostasis by suppressing excessive immune activation and preventing autoimmunity (Deng et al., 2019). These cells mediate immune tolerance through multiple mechanisms, including the secretion of immunosuppressive cytokines (such as IL-10 and TGF-β), metabolic regulation, and direct

suppression of autoreactive T cells and antigen-presenting cells (Plitas & Rudensky, 2016). Under normal physiological conditions, Tregs ensure that immune responses are appropriately balanced, preventing both hyperinflammation and immune evasion by pathogens. However, in autoimmune diseases, defects in Treg function, stability, or differentiation can lead to unchecked immune activation and self-reactivity, thereby driving disease pathology (Honing et al., 2024).

The dysfunction of Tregs in autoimmunity can be attributed to several interrelated factors, including genetic predisposition, epigenetic modifications, environmental triggers, and alterations in cytokine signaling. Genetic mutations affecting FoxP3, CTLA-4, IL-2, and other key regulators of Treg function have been linked to impaired immunosuppressive capacity, predisposing individuals to autoimmune conditions (Sumida et al., 2024). Additionally, epigenetic modifications such as DNA methylation and histone acetylation can influence Treg stability and plasticity, potentially leading to their conversion into pro-inflammatory T cell subsets (Ajith et al., 2024). Environmental factors, including infections, diet, and gut microbiota composition, can further modulate Treg function, either promoting immune tolerance or exacerbating immune dysregulation (Zhang et al., 2023).

Cytokine imbalances also play a pivotal role in Treg dysfunction and autoimmune disease progression. Pro-inflammatory cytokines such as IL-6, TNF-α, and IFN-γ can disrupt Treg stability and function, shifting the balance towards effector T cell-mediated immune responses (Kennedy-Batalla et al., 2024). Furthermore, deficiencies in IL-2 signaling, which is essential for Treg survival and expansion, have been observed in various autoimmune diseases, further compromising immune regulation (Oparaugo et al., 2023). The interplay between these factors ultimately results in the failure of Tregs to control autoreactive immune responses, thereby facilitating chronic inflammation and tissue damage (Hardtke-Wolenski & Landwehr-Kenzel, 2024).

Understanding the molecular and cellular mechanisms underlying Treg dysfunction is crucial for developing targeted therapeutic strategies to restore immune tolerance in autoimmune diseases. Current therapeutic approaches, including low-dose IL-2 therapy, adoptive Treg transfer, and immune checkpoint modulation, aim to enhance Treg function and reestablish immune balance (Khare et al., 2025). Additionally, emerging research into metabolic and microbiome-based interventions offers promising avenues for modulating Treg activity and mitigating autoimmune pathology (Huang et al., 2025).

This review will delve into the fundamental mechanisms governing Treg dysfunction in autoimmune diseases, with a focus on genetic, epigenetic, environmental, and cytokine-mediated influences. By elucidating these mechanisms, we can pave the way for novel immunotherapies aimed at restoring Treg function and preventing the onset and progression of autoimmune disorders.

Role of Tregs in Immune Regulation

Tregs regulate immune responses through various mechanisms, including direct cell-cell interactions, secretion of immunosuppressive cytokines, modulation of antigen-presenting cells (APCs), metabolic regulation, and the control of immune cell activation. Defects in these regulatory pathways can lead to autoimmune diseases by allowing immune cells to become hyperactive, causing tissue damage and chronic inflammation (Chan & Mani, 2025).

Direct Cell-Cell Interactions and Inhibitory Receptors

One of the most prominent mechanisms by which Tregs exert their suppressive effects is through direct cell-to-cell interactions. Tregs utilize inhibitory receptors like CTLA-4 (Cytotoxic T-lymphocyte-associated protein 4) to suppress effector T cell activation. CTLA-4 competes with CD28 for binding to CD80/CD86 on APCs (Schwab et al., 2025). Unlike CD28, which activates T cells, CTLA-4 delivers inhibitory signals that dampen the activation of effector T cells. This prevents the overactivation of immune responses and maintains self-tolerance. CTLA-4 expression on Tregs has been shown to be critical for their ability to suppress autoimmunity, and deficiencies in CTLA-4 signaling are linked to autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis (Ezzedine et al., 2025).

Cytokine Secretion and Immune Suppression

In addition to direct interactions, Tregs also release immunosuppressive cytokines to control immune responses. Key cytokines produced by Tregs include IL-10 (Interleukin-10), TGF-β (Transforming Growth Factor Beta), and IL-35 (Interleukin-35). IL-10 is a potent anti-inflammatory cytokine that suppresses the production of pro-inflammatory cytokines such as IL-6 and TNF-α, thereby reducing inflammation. IL-10 also limits the activation of APCs, preventing the initiation of immune responses. TGF-β plays a critical role in peripheral tolerance by promoting the differentiation of induced Tregs (iTregs) and suppressing the proliferation of effector T cells (Yoshimura et al., 2003). IL-35, secreted by Tregs, contributes to immune regulation by inhibiting T cell activation and promoting the expansion of Tregs. Defects in the production or signaling of these cytokines can result in the breakdown of immune tolerance, contributing to autoimmune pathogenesis (Olson et al., 2013).

Metabolic Regulation by Tregs

Tregs also regulate immune responses through metabolic mechanisms. One of the central metabolic pathways involves the expression of CD39 and CD73, enzymes that degrade extracellular ATP into adenosine. ATP is typically released by dying or stressed cells and acts as a pro-inflammatory signal that can activate immune cells. Tregs use CD39 and CD73 to convert ATP into adenosine, which has potent anti-inflammatory properties. Adenosine inhibits the activation of effector T cells and promotes tissue repair. Additionally, Tregs also control the availability of IL-2 by expressing high levels of the IL-2 receptor alpha chain (CD25). By capturing IL-2, Tregs limit its availability to effector T cells, depriving them of the necessary growth factor for their expansion. This mechanism helps ensure that immune activation is tightly controlled and prevents the proliferation of autoreactive T cells that could cause tissue damage (Ohkura et al., 2011).

Modulation of Antigen-Presenting Cells

Tregs exert their suppressive effects by interacting with APCs, such as dendritic cells and macrophages, to inhibit their ability to activate naïve T cells. Through surface molecules like CTLA-4 and LAG-3 (Lymphocyte Activation Gene-3), Tregs inhibit the maturation of dendritic cells, reducing their ability to prime naïve T cells. This inhibition prevents the activation of self-reactive T cells and maintains immune tolerance. Additionally, Tregs can promote the differentiation of tolerogenic dendritic cells that support the expansion of additional Tregs, further amplifying the immunosuppressive effects within the immune system. This interplay between Tregs and APCs is crucial for the maintenance of immune homeostasis and preventing the onset of autoimmune diseases (Harris et al., 2022).

Treg Control of T Cell Differentiation

Tregs also regulate the balance between different T helper (Th) cell subsets, including Th1, Th17, and Th2 cells. Th1 and Th17 cells are primarily involved in driving inflammation and autoimmune responses. Tregs control the differentiation of these cells to prevent excessive inflammatory responses. They achieve this by secreting cytokines such as IL-10 and TGF-β, which inhibit the differentiation of Th1 and Th17 cells. Disruptions in the balance between Tregs and Th17 cells, in particular, have been implicated in the development of autoimmune diseases, such as inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis. In these conditions, a reduction in Treg numbers or dysfunction in Treg-mediated suppression allows Th17 cells to become dominant, promoting chronic inflammation and tissue damage (Richert-Spuhler & Lund, 2015).

Tregs and B Cell Regulation

Tregs also play a significant role in controlling B cell activation and antibody production. By interacting with B cells through CD40-CD40L signaling, Tregs limit excessive B cell activation. Furthermore, Tregs secrete IL-10, which inhibits B cell proliferation and the production of autoantibodies. This is particularly relevant in autoimmune diseases such as SLE, where dysfunctional Tregs allow B cells to become activated and produce autoantibodies that target self-antigens. The ability of Tregs to regulate B cells is an essential mechanism for preventing the development of autoimmune conditions that involve the production of pathogenic antibodies (Bayati et al., 2021).

Mechanisms of Treg Dysfunction

Genetic Factors Influencing Treg Dysfunction

Genetic factors play a significant role in Treg dysfunction, and various mutations or polymorphisms in genes responsible for Treg development and function have been linked to autoimmune disorders such as T1DM, RA, MS, SLE, and inflammatory bowel disease (IBD). Understanding the genetic basis of Treg dysfunction is crucial for developing targeted therapies that can restore immune tolerance in affected individuals.

FoxP3 Mutations and Their Role in Treg Dysfunction

FoxP3 is the master regulator of Treg differentiation and function, controlling the expression of immunosuppressive molecules such as CTLA-4, IL-10, and TGF-β. Any disruption in FoxP3 function severely impairs Treg-mediated immune suppression, leading to immune overactivation and self-reactivity. One of the most severe consequences of FoxP3 dysfunction is Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) syndrome, a rare but lethal autoimmune disorder characterized by early-onset type 1 diabetes, dermatitis, thyroiditis, and severe enteropathy. IPEX syndrome is caused by mutations in the FoxP3 gene, including missense mutations that impair its DNA-binding ability and transcriptional regulation, as well as frameshift and nonsense mutations that result in truncated, non-functional FoxP3 proteins. Without functional FoxP3, Tregs cannot develop properly, leading to a complete failure in immune regulation and widespread autoimmune damage (Perdigoto et al., 2016).

Beyond these severe mutations, single nucleotide polymorphisms (SNPs) in FoxP3 have been linked to common autoimmune diseases. For instance, the rs3761548 polymorphism is associated with RA and SLE and has been shown to reduce FoxP3 expression, thereby impairing Treg differentiation (Fasching et al., 2017). Another SNP, rs2232365, is linked to T1DM and is associated with a reduction in Treg suppressive activity, contributing to pancreatic β-cell destruction (Zhao et al., 2022).

IL-2 and IL-2R Signaling Defects in Treg Function

Interleukin-2 (IL-2) is a crucial cytokine required for Treg proliferation, survival, and function. Unlike conventional T cells, which rely on IL-2 for activation, Tregs depend on IL-2 signaling for their long-term maintenance. Genetic defects in the IL-2 signaling pathway, particularly in the IL2 and IL2RA genes, have been strongly linked to autoimmune diseases due to their direct impact on Treg homeostasis. IL2 gene variants such as rs2069762 and rs6822844 are associated with type 1 diabetes and multiple sclerosis, as they lead to reduced IL-2 production, impairing Treg survival (Malek & Castro, 2010). Similarly, SNPs in the IL2RA gene, which encodes the IL-2 receptor alpha chain (CD25), contribute to autoimmune susceptibility by reducing IL-2 binding efficiency. The rs2104286 variant, for example, is found in multiple sclerosis and type 1 diabetes patients and leads to decreased IL-2 responsiveness in Tregs (Maier et al., 2009).

CTLA-4 Variants and Immune Regulation

CTLA-4 is a critical inhibitory receptor expressed on Tregs that plays a key role in maintaining immune tolerance. It binds to CD80/CD86 on APCs, preventing excessive immune activation and promoting self-tolerance. Variations in CTLA-4 have been strongly linked to autoimmune diseases, as they impair Treg function and allow effector T cells to become hyperactive. The rs231775 SNP, which results in a threonine-to-alanine substitution (Thr17Ala), has been associated with type 1 diabetes, rheumatoid arthritis, and Graves' disease. This polymorphism reduces CTLA-4 expression, leading to a weakened Treg-mediated suppression of immune responses (Hafler, 2007). Another SNP, rs3087243, is linked to multiple sclerosis and lupus and has been shown to impair CTLA-4 inhibitory signal-

ing, further compromising immune regulation (Hossen et al., 2023).

Other Key Genetic Factors Affecting Tregs

Beyond FoxP3, IL-2, and CTLA-4, several other genes play crucial roles in Treg function, and their polymorphisms have been associated with autoimmunity. PTPN2, which encodes Protein Tyrosine Phosphatase Non-Receptor Type 2, regulates T cell receptor (TCR) and cytokine signaling in Tregs. Variants in this gene, such as rs2542151, are associated with Crohn's disease and type 1 diabetes, as they impair IL-2 and STAT5 signaling, leading to reduced Treg stability (De La Rosa et al., 2004). Studies in animal models have shown that PTPN2 deletion results in spontaneous autoimmunity, underscoring its importance in immune regulation. Another key regulator of Treg function is STAT5 (Signal Transducer and Activator of Transcription 5), which is essential for IL-2 signaling and FoxP3 expression. Mutations in STAT5 impair IL-2 responses, reducing Treg survival and contributing to diseases such as lupus and type 1 diabetes. IL-6 also plays a role in Treg dysfunction, as increased IL-6 levels promote the differentiation of pro-inflammatory Th17 cells at the expense of Tregs. The rs1800795 polymorphism in IL6 has been associated with rheumatoid arthritis and is linked to increased IL-6 production, which leads to a Th17/Treg imbalance that exacerbates inflammation and tissue damage (Fasching et al., 2017; Li et al., 2014).

Environmental Triggers of Treg Dysfunction

Environmental factors play a crucial role in modulating the function and development of Tregs, and their dysfunction is often implicated in the pathogenesis of autoimmune diseases. These environmental factors can influence Treg activity through various mechanisms, including infections, diet, stress, toxins, and microbiota. One of the most significant environmental influences on Treg function is infection. Certain infections can trigger immune responses that either promote or impair the differentiation and function of Tregs, depending on the pathogen involved. For example, chronic viral infections, such as Epstein-Barr virus (EBV) or human cytomegalovirus (HCMV), have been shown to alter Treg dynamics, potentially leading to a failure in controlling self-reactive immune cells (Li et al., 2007). These infections can induce Treg dysfunction by either expanding Treg populations inappropriately or by causing Tregs to lose their suppressive function, contributing to the development of autoimmune diseases such as SLE or MS (Schlöder et al., 2022). On the other hand, some bacterial infections may promote Treg differentiation, which can have a protective effect against autoimmunity by enhancing immune tolerance (Gol-Ara et al., 2012).

Dietary factors are another important environmental influence on Treg function. The intake of certain nutrients, such as fatty acids, vitamins, and fiber, can have significant effects on the development and activity of Tregs. For instance, omega-3 fatty acids, commonly found in fish oil, have been shown to enhance Treg function and reduce inflammation, potentially offering protection against autoimmune diseases like rheumatoid arthritis and IBD (Simopoulos, 2002). Conversely, a diet rich in saturated fats and processed foods can lead to an imbalance in the immune system, impairing Treg function and promoting the development of autoimmune diseases. Deficiencies in certain vitamins, such as vitamin D, have also been associated with Treg dysfunction. Vitamin D is known to support the differentiation and stability of Tregs, and its deficiency has been linked to autoimmune diseases like multiple sclerosis and type 1 diabetes, where impaired Treg function contributes to disease progression (Issazadeh-Navikas et al., 2011).

Psychological stress is another environmental factor that can significantly impact Treg function. Chronic stress has been shown to alter immune responses by increasing the production of pro-inflammatory cytokines and reducing the number and suppressive function of Tregs. Stress can elevate cortisol levels, which, in turn, may impair Treg stability and function, promoting the development or exacerbation of autoimmune conditions such as rheumatoid arthritis and psoriasis (Elenkov & Chrousos, 2002). Furthermore, stress-induced changes in the hypothalamic-pituitary-adrenal (HPA) axis can influence immune cell trafficking and the production of immune-modulating hormones, further affecting Treg activity.

Toxins and environmental pollutants also play a role in Treg dysfunction. Exposure to certain chemicals, such as heavy metals, pesticides, and air pollution, can have detrimental effects on the immune system, including Treg cells. Studies have shown that exposure to environmental pollutants, such as cigarette smoke, can decrease the number and function of Tregs, promoting inflammatory responses and increasing the risk of autoimmune diseases. Heavy metals like mercury and lead have also been shown to impair Treg differentiation and function, potentially contributing to autoimmune diseases such as lupus and rheumatoid arthritis. These toxins may affect Tregs by altering immune signaling pathways or inducing oxidative stress, which impairs the suppressive functions of Tregs (Yang, 2023).

The gut microbiota is another key environmental factor that influences Treg development and function. The gut microbiome plays an essential role in shaping the immune system, and dysbiosis (an imbalance in the microbiota) can lead to Treg dysfunction. Studies have shown that certain bacterial species promote the differentiation of Tregs, which helps maintain immune tolerance and prevent autoimmune diseases (Luo et al., 2017; Omenetti & Pizarro, 2015). Conversely, an imbalance in the gut microbiota, often triggered by factors such as antibiotic use, poor diet, or infection, can lead to reduced Treg numbers and function, increasing the susceptibility to autoimmune diseases like inflammatory bowel disease and type 1 diabetes (Lehto & Groop, 2018). The microbiota influences Treg function through various mechanisms, including the production of metabolites like short-chain fatty acids, which support Treg differentiation and stability.

In sum, environmental factors, including infections, diet, stress, toxins, and microbiota, have a profound impact on Treg function and are strongly associated with the development and progression of autoimmune diseases. These factors can either promote Treg dysfunction by altering immune responses or directly impair Treg differentiation and stability. Understanding how environmental factors influence Tregs is critical for identifying potential therapeutic targets and strategies to restore immune homeostasis in individuals with autoimmune diseases.

Interventions aimed at modulating these environmental factors, such as dietary modifications, stress management, and microbiota-based therapies, may hold promise in preventing or treating autoimmune diseases by restoring proper Treg function.

Epigenetic Factors Contributing to Treg Dysfunction in Autoimmune Diseases

Epigenetic factors play a critical role in the regulation of Treg function, and alterations in these mechanisms are increasingly recognized as contributing to the dysfunction of Tregs in autoimmune diseases. Epigenetics refers to heritable changes in gene expression that do not involve changes in the DNA sequence itself, and these changes can be influenced by environmental factors, aging, and various disease conditions (Loh et al., 2019). In Tregs, epigenetic modifications regulate the expression of key genes, such as FoxP3, which is essential for Treg development and function. One of the most significant epigenetic mechanisms is DNA methylation, which can either silence or activate genes. In Tregs, the FoxP3 locus undergoes complex DNA methylation modifications that govern its expression. Aberrant methylation of the FoxP3 gene can lead to the loss of Treg function, and studies have shown that altered DNA methylation patterns at the FoxP3 promoter are associated with several autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, and type 1 diabetes (Lal et al., 2009). For instance, in these diseases, Tregs often exhibit reduced expression of FoxP3, resulting in impaired suppressive activity and the failure to regulate self-reactive immune cells effectively.

Histone modifications are another key aspect of epigenetic regulation in Tregs. The addition or removal of various chemical groups, such as acetyl or methyl groups, to histone proteins can influence chromatin structure, affecting gene expression. In Tregs, certain histone modifications are required for the maintenance of FoxP3 expression and the suppressive function of these cells. For example, histone acetylation at the FoxP3 locus is associated with active gene expression and stable Treg function (Rao & Naqvi, 2011). Conversely, deacetylation of histones at key regulatory loci can lead to the downregulation of FoxP3 and the loss of Treg suppressive activity. Altered histone modification patterns in Tregs have been linked to autoimmune diseases, as these changes can impair Treg stability and their ability to maintain immune tolerance.

Non-coding RNAs, particularly microRNAs (miRNAs), are also involved in regulating Treg function through epigenetic mechanisms. miRNAs are small RNA molecules that can bind to messenger RNA (mRNA) and suppress gene expression. Specific miRNAs have been shown to regulate the differentiation, expansion, and stability of Tregs by targeting genes involved in immune responses (Schmitt & Williams, 2013). For example, miR-155, which is often upregulated in autoimmune diseases, can suppress Treg function by targeting key genes involved in Treg development and stability. Overexpression of miR-155 in Tregs leads to reduced FoxP3 expression and impaired immune suppression, contributing to the development of autoimmune disorders such as systemic lupus erythematosus and inflammatory bowel disease. On the other hand, miR-21, which is typically downregulated in Tregs during inflammation, has been shown to enhance Treg stability and function by inhibiting inflammatory signaling pathways (Hippen et al., 2018). These findings suggest that alterations in miRNA expression can have a profound impact on Treg function and contribute to immune dysregulation in autoimmune diseases.

The role of epigenetic factors in Treg dysfunction extends beyond genetic regulation and includes interactions between the immune system and environmental stimuli. Factors such as infections, diet, and stress can induce epigenetic modifications in Tregs, influencing their function in a way that may predispose individuals to autoimmune diseases. For example, inflammatory cytokines and microbial signals can lead to the activation of epigenetic regulators that modify histones or DNA methylation patterns in Tregs, resulting in a loss of immune tolerance (Omenetti & Pizarro, 2015). Furthermore, exposure to environmental toxins, such as cigarette smoke or pollutants, has been shown to alter the epigenetic landscape of Tregs, impairing their function and contributing to the development of autoimmune diseases. These environmental factors may act through the activation of specific signaling pathways that lead to epigenetic changes in Tregs, creating a feedback loop that exacerbates immune dysregulation (Schlöder et al., 2022).

As such, epigenetic factors play a critical role in the regulation of Treg function, and disturbances in these mechanisms can lead to Treg dysfunction and the development of autoimmune diseases. DNA methylation, histone modifications, and miRNA expression all contribute to the maintenance of Treg stability and their ability to suppress self-reactive immune cells. Alterations in these epigenetic processes, whether through genetic mutations or environmental influences, can impair Treg function, resulting in the breakdown of immune tolerance and the onset of autoimmune disease. Understanding the epigenetic regulation of Tregs offers potential therapeutic avenues for autoimmune diseases, as targeting epigenetic modifications could help restore Treg function and immune homeostasis.

Cytokine-Mediated Contribution to Treg Dysfunction in Autoimmune Diseases

Cytokines play a fundamental role in regulating Treg function, and disruptions in cytokine signaling are closely associated with Treg dysfunction in autoimmune diseases. Tregs rely on a delicate balance of pro-inflammatory and anti-inflammatory cytokines to maintain their suppressive functions and control immune responses (Oparaugo et al., 2023). One of the key cytokines involved in Treg regulation is interleukin-2 (IL-2), which is essential for the survival, expansion, and function of Tregs. IL-2 binds to the IL-2 receptor (CD25) on Tregs, activating intracellular signaling pathways that support their differentiation and stability. However, in autoimmune diseases, there is often an imbalance in IL-2 signaling, which can lead to insufficient Treg expansion and impaired function. For instance, in conditions like rheumatoid arthritis and multiple sclerosis, decreased IL-2 availability or signaling results in a reduced number of functional Tregs, allowing for the uncontrolled activation of effector T cells and the breakdown of immune tolerance (Humrich et al., 2009). Additionally, IL-6, a pro-inflammatory cytokine, can inhibit Treg differentiation and function. IL-6 promotes the dev-

Table 1. Genetic, Epigenetic, Environmental, and Cytokine-Mediated Factors Associated with Treg Dysfunction in Autoimmune Diseases.

Factors	Mechanisms	Diseases
FOXP3 mutations	FOXP3 mutations disrupt Treg differentiation and function by impairing their development and suppressive ability, leading to immune dysregulation.	IPEX, SLE, T1DM, AIH
IL-2RA mutations	Mutations in IL-2 receptor alpha (IL-2RA) impair IL-2 signaling, crucial for Treg survival and function, leading to reduced Treg numbers and impaired immune regulation.	T1DM, SLE
CTLA-4 polymorphisms	CTLA-4 polymorphisms reduce the inhibitory signals in Tregs, weakening their suppressive function and contributing to unchecked immune activation.	RA, SLE, T1DM, Graves'
RUNX1 mutations	RUNX1 mutations disrupt Treg lineage commitment and impair their suppressive functions, contributing to autoimmune conditions by promoting excessive inflammation.	RA, SS, IBD
DNA methylation	Altered DNA methylation patterns affect Treg-specific genes, leading to defective Treg function and loss of immune tolerance.	SLE, MS, RA
Histone modification	Changes in histone acetylation and methylation patterns can modulate the expression of key Treg-related genes, disrupting Treg function and differentiation.	SLE, RA, Psoriasis
MicroRNA regulation	Dysregulation of microRNAs (e.g., miR-155) affects the expression of key genes involved in Treg differentiation and function, resulting in Treg dysfunction.	RA, IBD, MS, SLE
Infections	Infections trigger immune responses that can lead to Treg dysfunction and failure to suppress autoimmunity, often through molecular mimicry or by directly activating Tregs.	MS, SLE, T1DM, RA
Diet and Gut Microbiota	An imbalance in gut microbiota or nutrient deficiencies (e.g., vitamin D) can alter Treg differentiation and function, contributing to immune dysregulation.	IBD, T1DM, RA, MS
Environmental toxins (e.g., pollutants)	Toxins can directly or indirectly impair Treg function by promoting pro-inflammatory pathways or disrupting immune homeostasis.	Asthma, Hashimoto's, RA, SS
Stress	Psychological or physiological stress alters immune responses by affecting Treg function through hormones like cortisol, leading to immune activation.	RA, MS, Psoriasis
IL-6	IL-6 impairs Treg function by promoting Th17 differentiation while inhibiting Treg differentiation and function, promoting inflammation.	RA, Psoriasis, SLE, IBD
TNF-α	TNF-α reduces Treg numbers and inhibits their suppressive function by activating inflammatory pathways that compete with Treg activity.	RA, IBD, Psoriasis
TGF-β	TGF-β is essential for Treg differentiation; dysregulated TGF-β signaling can result in impaired Treg function or promote pro-inflammatory responses, contributing to autoimmunity.	MS, SLE, IBD, RA
IL-2	Insufficient IL-2 signaling results in Treg depletion and dysfunction, impairing immune tolerance and allowing for autoimmunity.	SLE, RA, MS
IL-10	IL-10 deficiency disrupts Treg-mediated suppression, leading to inadequate regulation of inflammatory responses and autoimmunity.	IBD, SS, Psoriasis

AIH: Autoimmune Hepatitis; Hashimoto's: Autoimmune Thyroiditis; Graves': Graves' Disease; IBD: Inflammatory Bowel Disease; IPEX: IPEX Syndrome; MS: Multiple Sclerosis; Psoriasis; RA: Rheumatoid Arthritis; SLE: Systemic Lupus Erythematosus; SS: Systemic Sclerosis; T1DM: Type 1 Diabetes

elopment of Th17 cells, which are inflammatory T cells implicated in autoimmune diseases like IBD and psoriasis (Omenetti & Pizarro, 2015). High levels of IL-6 disrupt the balance between Tregs and Th17 cells, contributing to the pathogenesis of these diseases by impairing Treg-mediated suppression and promoting inflammatory responses (Ryba-Stanisławowska et al., 2013).

Another critical cytokine that influences Treg function is transforming growth factor-beta (TGF-β). TGF-β is crucial for the induction and maintenance of Tregs, and it helps sustain immune tolerance by promoting the differentiation of naïve T cells into induced Tregs (iTregs)(Huang & Sattler, 2011). However, in autoimmune diseases, TGF-β signaling can be dysregulated, leading to either an insufficient number of Tregs or an impaired ability of existing Tregs to suppress immune responses effectively (Miyake et al., 2020). In conditions like type 1 diabetes and SLE, defects in TGF-β signaling can result in the failure to properly induce Tregs, allowing autoreactive T cells to become activated and cause tissue damage (Bednar et al., 2022). Additionally, the dysregulation of IL-10, an anti-inflammatory cytokine secreted by Tregs, can further exacerbate immune dysfunction. IL-10 is important for maintaining peripheral tolerance and preventing excessive immune activation. However, in autoimmune diseases, IL-10 production is often compromised, impairing Treg-mediated suppression and leading to heightened immune responses. This disruption contributes to the development and progression of autoimmune diseases by allowing inflammatory cells, such as Th1 and Th17 cells, to proliferate and induce tissue damage.

Furthermore, the interaction between Tregs and other immune cells through cytokines is critical in the regulation of immune responses. In autoimmune diseases, an imbalance in these interactions can lead to Treg dysfunction. For example, in rheumatoid arthritis, elevated levels of pro-inflammatory cytokines, such as TNF-α (tumor necrosis factor-alpha), interfere with Treg function by disrupting their ability to suppress effector T cells and maintain immune homeostasis (Oparaugo et al., 2023). TNF-α can promote the differentiation of Th17 cells while suppressing Treg development, exacerbating chronic inflammation and tissue damage (Li et al., 2025). Similarly, interferon-gamma (IFN-γ), a cytokine produced by Th1 cells, can inhibit Treg function and impair their ability to suppress immune responses. In conditions like multiple sclerosis and autoimmune hepatitis, IFN-γ impedes Treg activity, leading to unrestrained immune

activation and damage to self-tissues (Hardtke-Wolenski & Landwehr-Kenzel, 2024).

The overall immune environment created by these cytokines is crucial for Treg function, and a dysregulated cytokine network often results in Treg dysfunction and autoimmune disease development. In many autoimmune diseases, the presence of high levels of pro-inflammatory cytokines combined with a lack of adequate anti-inflammatory cytokine production leads to the breakdown of immune tolerance and the emergence of chronic inflammation. The imbalance between cytokines such as IL-2, TGF-β, IL-6, IL-10, TNF-α, and IFN-γ can promote the activation of autoreactive T cells while impairing Treg-mediated suppression. This results in an environment where immune regulation is lost, and autoimmunity takes hold. Targeting cytokine signaling pathways offers a promising therapeutic strategy to restore Treg function and re-establish immune tolerance in individuals with autoimmune diseases. By modulating cytokine levels or blocking specific pro-inflammatory cytokines, therapies could potentially enhance Treg activity and prevent the pathological immune responses characteristic of autoimmune disorders.

Conclusion

The dysfunction of Tregs plays a central role in the development of autoimmune diseases (**Table 1**). The mechanisms behind Treg dysfunction are complex and involve a combination of genetic, epigenetic, cytokine, and environmental factors. Genetic mutations and epigenetic changes can disrupt Treg development and function, impairing immune tolerance and allowing self-reactive immune cells to cause damage. Environmental factors, including infections, diet, stress, and toxins, can further compromise Treg function by altering immune signaling pathways or destabilizing Treg cells. Additionally, imbalances in cytokines such as IL-2, TGF-β, and IL-6 disrupt the fine-tuned regulation of immune responses, promoting inflammation and autoimmunity. Understanding these underlying mechanisms provides critical insights into the pathogenesis of autoimmune diseases and highlights potential therapeutic avenues aimed at restoring Treg function and re-establishing immune tolerance.■

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