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ROLE OF REGULATORY T-CELLS IN AUTOIMMUNE DISEASE

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ABSTRACT: Autoimmune diseases represent a major global health challenge, arising from the failure of the immune system to distinguish between self and non-self, leading to the destruction of healthy tissues. This breakdown of immune tolerance results in chronic inflammation, progressive tissue damage, and debilitating conditions such as rheumatoid arthritis, type 1 diabetes, and multiple sclerosis. Despite advances in conventional immunosuppressive therapies, current treatments often lack specificity and may cause systemic side effects, highlighting the need for targeted therapeutic strategies. Regulatory T cells (Tregs), a specialized subset of $CD4^+$ T lymphocytes characterized by the expression of CD25 and the transcription factor FOXP3, play a crucial role in maintaining immune homeostasis. They function as key immunological regulators by suppressing excessive immune responses through cytokine secretion (IL-10, TGF-β), direct cell-to-cell interactions, and modulation of cytokine availability such as IL-2. Dysfunction, deficiency, or imbalance of Tregs contributes significantly to the pathogenesis and progression of autoimmune diseases. This study explores the biological role of Tregs in immune regulation, their involvement in the development of autoimmune disorders, and the underlying mechanisms leading to immune dysregulation. Furthermore, it highlights emerging pharmacological approaches targeting Tregs, including cytokine-based therapies and adoptive Treg transfer, which offer promising and more specific alternatives to traditional treatments. Understanding Treg-mediated immune control provides a strong foundation for the development of innovative, targeted therapies aimed at restoring immune balance and improving clinical outcomes in autoimmune diseases.

INTRODUCTION: The immune system is a highly specialized defense network designed to protect the body against invading pathogens such as bacteria, viruses, and parasites. It functions by distinguishing between self and non-self antigens, thereby ensuring that harmful foreign substances are eliminated while the body's own cells are preserved.

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This process is known as immune tolerance. However, in certain conditions, this self-tolerance mechanism fails, leading to the development of autoimmune diseases. In such diseases, the immune system mistakenly recognizes self-antigens as foreign and initiates an immune response against the body's own tissues. This results in chronic inflammation, tissue damage, and loss of normal physiological function. Common examples include rheumatoid arthritis, type 1 diabetes, and multiple sclerosis [1].

A critical component in maintaining immune tolerance is a specialized subset of T lymphocytes known as Regulatory T cells (Tregs). These cells play a vital role in suppressing excessive or

inappropriate immune responses. They act as immune regulators by inhibiting the activation and proliferation of autoreactive T-cells that may otherwise attack self-tissues.

Tregs are primarily characterized by the expression of CD4, CD25, and the transcription factor FOXP3, which is essential for their development and function. They exert their immunosuppressive effects through multiple mechanisms, including the secretion of anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), as well as through direct cell-to-cell interactions [2].

In autoimmune diseases, either the number or the functional capacity of Tregs is reduced, leading to an imbalance between regulatory and effector immune responses. This imbalance contributes significantly to disease progression and severity.

In recent years, advances in immunology and pharmacology have highlighted the potential of targeting Tregs as a therapeutic strategy. Unlike conventional immunosuppressive drugs that broadly suppress the immune system, therapies aimed at enhancing Treg function offer a more specific and targeted approach. This can help restore immune balance while minimizing systemic side effects.

Therefore, understanding the biology and therapeutic potential of regulatory T cells is crucial for the development of novel and effective treatments for autoimmune diseases. This project focuses on exploring the role of Tregs in immune regulation, their involvement in autoimmune disorders, and the various strategies employed to utilize them as therapeutic targets.

Immune System: The immune system is a complex network of cells, tissues, and molecules that protects the body from harmful pathogens such as bacteria, viruses, and parasites. Its primary function is to recognize and eliminate foreign substances while maintaining tolerance toward the body's own cells, a process known as self–non-self discrimination. The immune system is broadly divided into two components: innate immunity and adaptive immunity. Innate immunity is the body's first line of defense against infections and is present from birth. It provides a rapid but non-specific response to pathogens using physical barriers like skin, immune cells such as macrophages and neutrophils, and processes like inflammation. It does not have memory, so it responds in the same way to repeated infections [3].

Adaptive immunity, on the other hand, is a specific and acquired defense mechanism that develops after exposure to antigens. It involves specialized cells such as T lymphocytes and B lymphocytes, which recognize specific pathogens and generate a targeted response. A key feature of adaptive immunity is immunological memory, which allows the body to respond more quickly and effectively upon subsequent exposures to the same pathogen.

Within adaptive immunity, T lymphocytes play a central role and are classified into different types,

1. Helper T Cells ($CD4^+$)

- Coordinate immune response
- Activate other immune cells

2. Cytotoxic T Cells ($CD8^+$)

- Kill infected or abnormal cells

3. Regulatory T Cells (Tregs)

- Suppress immune responses
- Maintain immune tolerance
- Prevent autoimmune diseases

Helper T cells ($CD4^+$) act as coordinators of the immune system. They do not directly kill pathogens but release chemical signals called cytokines, which activate and guide other immune cells like B cells and cytotoxic T cells. Cytotoxic T cells ($CD8^+$) are responsible for directly destroying infected or abnormal cells, such as virus-infected cells or cancer cells, by releasing toxic substances that lead to cell death. On the other hand, Regulatory T cells (Tregs) play a controlling role by suppressing excessive or unwanted immune responses. They ensure that the immune system does not overreact or attack the body's own tissues. This function is very important for maintaining immune homeostasis**,** which means keeping the immune system balanced and stable [4].

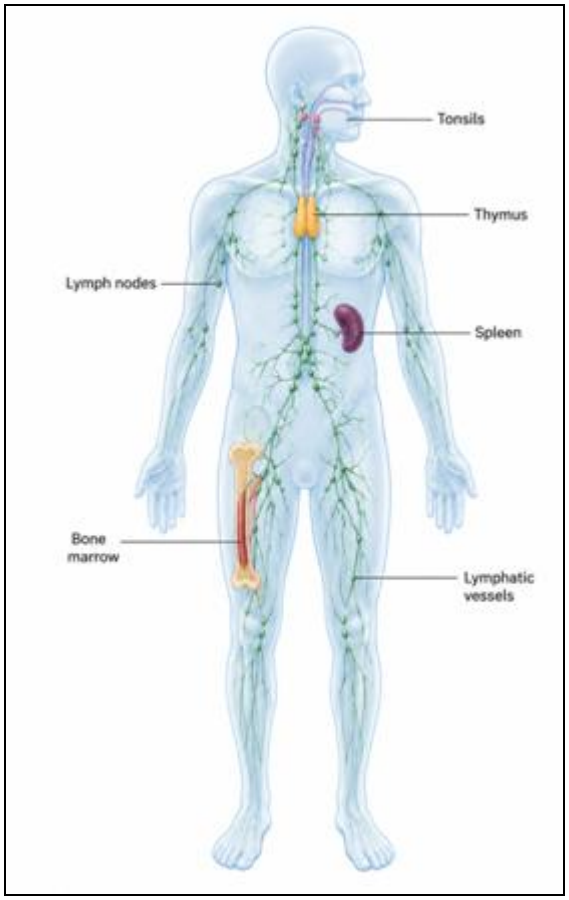

FIG. 1: IMMUNE SYSTEM

The immune response generally occurs in a stepwise manner. First, the immune system recognizes antigens (foreign substances). Next, immune cells become activated and start multiplying. Then, the pathogen is eliminated by immune actions. Finally, in the regulation phase, Tregs reduce and control the immune response to prevent excessive inflammation or tissue damage.

Thus, Regulatory T cells are especially important in the final stage, as they act like "brakes" on the immune system, preventing overreaction and protecting the body from autoimmune damage. If the immune system becomes overactive or fails to maintain tolerance, it can lead to autoimmune diseases, in which the body attacks its own tissues. Therefore, a balanced immune system is crucial for health. Understanding the immune system, especially the role of regulatory T cells, is important in pharmacology because it helps in developing targeted therapies for autoimmune diseases and improving immune-based treatments [5].

Regulatory T-Cells: $CD4^+$ T lymphocytes are a type of white blood cell that play a central role in the immune system by coordinating and regulating immune responses. They are called "$CD4^+$" because they possess a surface protein known as CD4, which helps them interact with other immune cells. These cells are commonly referred to as helper T cells, as they assist in activating B cells to produce antibodies, stimulate cytotoxic T cells to kill infected cells, and release cytokines that guide the overall immune response. $CD4^+$ T cells are:

- A type of immune cell
- Have CD4 protein on their surface
- Help in controlling immune responses [6].

Types within $CD4^+$ T Cells: $CD4^+$ T lymphocytes are not a single uniform group of cells but can differentiate into various functional subsets depending on the signals they receive from their environment, especially cytokines. The major subsets include helper T cells such as Th1, Th2, and Th17 cells, along with regulatory T cells (Tregs).

Helper T-Cells: T helper cells include different subsets with specialized immune functions. Th1 cells help fight intracellular pathogens such as viruses by activating macrophages and producing cytokines like interferon-gamma (IFN-γ), which strengthen the immune response. Th2 cells are mainly involved in defending the body against parasites and also assist B cells in producing antibodies; they play a significant role in allergic reactions as well. Th17 cells are associated with inflammation and help protect against bacteria and fungi, but when they become overactive, they can contribute to the development of autoimmune diseases.

Regulatory T Cells (Tregs): Regulatory T cells are a special subset of $CD4^+$ T cells that play an important role in suppressing immune responses and maintaining immune balance. They help prevent excessive immune activity that could damage the body's own tissues, thereby contributing to immune tolerance and overall immune system regulation.

In contrast to these effector T-cells, which generally enhance and promote immune responses, regulatory T-cells act to suppress immune activity.

Thus, CD4+ T cells include both immune-activating and immune-suppressing subsets, and a proper balance between these subsets is essential for maintaining a healthy immune system [7].

What Makes Tregs Different?: Regulatory T cells are unique among CD4+ T lymphocytes due to their distinct markers and specialized function of suppressing immune responses. They are characterized by the expression of CD4, high levels of CD25, and most importantly, the transcription factor FOXP3, which acts as a master regulator controlling their development and suppressive activity. Unlike other CD4+ T cells such as Th1, Th2, and Th17 cells that activate and amplify immune responses, Tregs perform the opposite role by limiting excessive or inappropriate immune reactions. They achieve this through several mechanisms, including the secretion of anti-inflammatory cytokines like IL-10 and TGF-β, direct inhibition of other immune cells through cell-to-cell contact, and by consuming IL-2, which reduces the growth of other T cells. This suppressive function is crucial for maintaining immune homeostasis and preventing the immune system from attacking the body's own tissues. Therefore, Tregs act as the "regulatory controllers" of the immune system, distinguishing them functionally and biologically from other CD4+ T cell subsets [8].

CD4+ Marker (Basic Identity): The CD4+ marker represents a surface protein found on certain T lymphocytes and serves as a basic identity feature of these cells. CD4 is a glycoprotein present on the outer membrane of helper T cells, and it plays an important role in helping these cells interact with other components of the immune system. It assists in the recognition of antigens by binding to molecules on antigen-presenting cells, thereby facilitating proper immune activation and communication. Because of this function, CD4+ T cells are essential in coordinating immune responses. Regulatory T-cells (Tregs) also express the CD4 marker, which means they belong to the same general category as helper T cells. However, unlike typical helper T-cells that activate immune responses, Tregs perform a regulatory role by suppressing excessive immune activity. Thus, the presence of CD4 indicates that Tregs originate from the helper T-cell lineage while having a specialized function in maintaining immune balance [9].

CD25+ Marker (High Expression): The CD25+ marker refers to the alpha chain of the interleukin-2 (IL-2) receptor present on the surface of T cells. IL-2 is an important growth factor that promotes the survival, proliferation, and activation of T lymphocytes. Regulatory T-cells (Tregs) express very high levels of CD25, which makes them highly efficient at binding and utilizing IL-2. This high expression allows Tregs to maintain their own growth and functional activity more effectively compared to other T-cells.

An important regulatory function of Tregs is their ability to absorb and utilize IL-2 from the surrounding environment. By doing so, they reduce the availability of IL-2 for other immune cells, especially effector T cells that rely on IL-2 for their activation and proliferation. As a result, this limits excessive immune cell growth and helps prevent overactivation of the immune response. In this way, the high expression of CD25 on Tregs plays a crucial role in controlling immune activity and maintaining immune balance [10].

FOXP3+ Marker (Master Regulator):

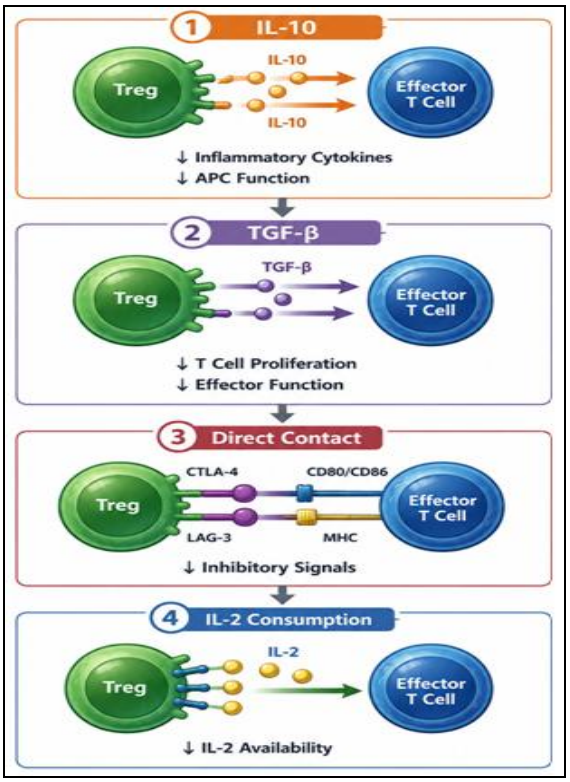

FIG. 2: METHODS OF TREGS IMMUNOSUPPRESSION

The FOXP3$^+$ marker is the most important and defining feature of regulatory T-cells (Tregs). FOXP3 is a transcription factor, which means it is a protein located inside the nucleus of the cell that controls the expression of specific genes. In Tregs, FOXP3 acts as a "master regulator" because it directs the cell to develop into a regulatory T cell and determines its functional behavior. It controls the activation of genes responsible for the suppressive activity of Tregs, enabling them to regulate immune responses effectively. FOXP3 is essential not only for the development of Tregs but also for maintaining their function and identity. It ensures that these cells continue to act as regulators rather than becoming normal effector T-cells. Through FOXP3-controlled mechanisms, Tregs are able to suppress excessive immune reactions and maintain immune tolerance. Without proper FOXP3 expression, Tregs lose their regulatory properties and cannot control immune responses effectively.

If FOXP3 is absent or defective, the consequences are severe. Tregs fail to develop properly or lose their suppressive function, leading to an overactive immune system. This can result in uncontrolled immune responses where the body begins to attack its own tissues, causing serious autoimmune diseases. Therefore, FOXP3 is considered the key factor that defines and maintains the regulatory function of T-cells [11].

Regulatory T-cells (Tregs) suppress immune responses through multiple coordinated mechanisms that help maintain immune balance and prevent excessive or harmful reactions. They act by releasing anti-inflammatory cytokines such as IL-10 and TGF-β, which reduce the activity of other immune cells, and by directly interacting with these cells to inhibit their activation and function. Additionally, Tregs can limit the availability of growth factors like IL-2, thereby restricting the proliferation of effector T-cells [12]. Through these combined actions, Tregs effectively control immune responses and ensure immune tolerance. Tregs use multiple methods:

Cytokine Secretion Mechanism by Tregs: Cytokines are small signaling proteins released by cells of the immune system that play a crucial role in communication between cells. They act as chemical messengers that help regulate and coordinate immune responses by sending signals from one cell to another. Cytokines can either stimulate or suppress the activity of immune cells, depending on the type and situation. For example, some cytokines promote inflammation to fight infections, while others reduce inflammation to prevent damage to the body's own tissues. Thus, cytokines are essential for maintaining a balanced and effective immune response.

What do Tregs do with Cytokines?- Regulatory T cells (Tregs) use cytokines as important tools to control and suppress immune responses. They primarily release anti-inflammatory cytokines, which act as signals to calm down overactive immune cells. These cytokines help reduce the activity of effector T cells, macrophages, and other immune cells that may otherwise cause excessive inflammation or tissue damage. By sending these "calming signals," Tregs ensure that the immune system does not overreact, especially in situations where the threat has already been controlled or when the body's own tissues might be mistakenly targeted. The main cytokines secreted by Tregs are interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). IL-10 works by inhibiting the production of inflammatory signals and reducing the activation of immune cells, while TGF-β suppresses the proliferation and function of T cells and also helps in maintaining immune tolerance [13]. Through the release of these cytokines, Tregs create an anti-inflammatory environment in the body, which is essential for preventing autoimmune reactions and maintaining overall immune balance.

TABLE 1: ROLE OF CYTOKINE

Aspect	Details
Function of Tregs	Suppress immune responses and maintain immune tolerance
Main cytokines released	IL-10, TGF-β
Action of IL-10	Inhibits inflammatory cytokine production and reduces activation of immune cells
Action of TGF-β	Suppresses T cell proliferation and function; promotes immune tolerance
Target cells affected	Effector T cells, macrophages, other immune cells
Overall effect	Decreased inflammation and immune activity
Clinical significance	Prevents autoimmunity and limits tissue damage

When Regulatory T cells (Tregs) become activated, they release anti-inflammatory cytokines such as IL-10 and TGF-β. These cytokines bind to receptors on other immune cells and send inhibitory signals inside those cells, which reduces their activity. As a result, the immune response becomes controlled, inflammation decreases, and body tissues are protected from excessive immune damage. This process is essential for maintaining immune balance and preventing harmful overreactions of the immune system.

Main Cytokines Released by Tregs:

IL-10 (Interleukin-10): Interleukin-10 (IL-10) is an important anti-inflammatory cytokine produced by various immune cells, especially regulatory T cells (Tregs). It acts as a key regulator of the immune system by limiting and controlling immune responses to prevent excessive inflammation and tissue damage. IL-10 works by inhibiting the activity of immune cells such as macrophages and helper T cells, and by reducing the production of pro-inflammatory cytokines. In this way, it helps to maintain immune balance and tolerance, ensuring that the immune system does not overreact or attack the body's own tissues [14].

Interleukin-10 (IL-10) is an anti-inflammatory cytokine that works by reducing the activity of immune cells and controlling inflammation. Interleukin-10 (IL-10) is mainly produced and released by Regulatory T cells (Tregs) into the surrounding environment. It binds to IL-10 receptors present on immune cells such as macrophages, dendritic cells, and helper T cells, functioning like a lock-and-key signaling interaction. After binding, IL-10 transmits signals inside the target cells by activating pathways such as the JAK-STAT pathway. These signals suppress immune activity by reducing the production of pro-inflammatory cytokines like IL-1 and TNF-α, decreasing antigen presentation, and inhibiting excessive T cell activation. As a result, inflammation is reduced, the immune response becomes controlled, and body tissues are protected from immune-mediated damage.

TGF-β: Transforming Growth Factor-beta (TGF-β) is an important anti-inflammatory cytokine produced by various cells of the immune system, including regulatory T cells (Tregs). It plays a key role in controlling cell growth, differentiation, and immune responses. In the immune system, TGF-β acts mainly as a suppressive signal that helps prevent excessive immune activation and maintains immune tolerance. It is essential for balancing immune reactions and protecting the body from damage caused by overactive immune responses [15].

Transforming Growth Factor Beta (TGF-β) is released by Regulatory T cells (Tregs) and other immune cells into the surrounding tissue environment. It binds to specific TGF-β receptors present on target cells such as T-cells, macrophages, and dendritic cells. This binding activates intracellular signaling pathways, mainly the SMAD pathway, which is an important signaling system involved in immune regulation. The activated SMAD proteins then move into the nucleus, where they regulate genes responsible for cell growth and immune suppression. As a result, TGF-β suppresses immune cell activity by reducing T-cell activation, T-cell proliferation, and the production of inflammatory cytokines. It also promotes the differentiation of naïve $CD4^+$ T-cells into Tregs, thereby increasing immune regulation. Overall, these actions lead to reduced inflammation, a controlled immune response, and the maintenance of immune tolerance.

Direct Cell-to-Cell Contact (by Tregs): Direct cell-to-cell contact is a mechanism by which Regulatory T cells (Tregs) suppress the activity of other immune cells through physical interaction rather than releasing cytokines. In this process, Tregs come into close contact with target immune cells such as effector T-cells, dendritic cells, and macrophages. Through specialized surface molecules, Tregs send inhibitory signals directly to these cells, reducing their activation and function [16]. This method is highly efficient because it allows Tregs to control immune responses in a precise and localized manner without affecting the entire immune system.

Regulatory T-cells (Tregs) suppress immune responses through direct cell-to-cell contact with overactive immune cells. They first recognize these activated immune cells and move close to them to form direct contact. Tregs use specific surface proteins, especially CTLA-4 (Cytotoxic T-Lymphocyte Antigen-4), which binds to CD80 and

CD86 receptors present on antigen-presenting cells such as dendritic cells. This interaction sends inhibitory signals to the target cells and reduces the activation of antigen-presenting cells. As a result, dendritic cells become less active and their ability to present antigens and activate other T-cells decreases. Consequently, effector T-cells receive weaker activation signals, leading to reduced proliferation and activity. This process helps reduce the immune response, prevents excessive inflammation, and maintains immune tolerance. In addition, Tregs may release inhibitory molecules at the contact site and can even induce apoptosis, or programmed cell death, in target cells.

Introduction to IL-2: Interleukin-2 (IL-2) is an important cytokine that acts as a growth factor for T lymphocytes**,** especially for their activation, proliferation, and survival. It is mainly produced by activated T-cells and plays a central role in expanding the immune response during infection or immune stimulation. IL-2 binds to its receptor on T-cells and promotes their multiplication, making it essential for an effective immune reaction. However, uncontrolled IL-2 activity can lead to excessive immune cell growth and overactivation, which may cause tissue damage or autoimmune responses.

Regulatory T cells (Tregs) play a crucial role in controlling IL-2 levels in the immune system. They express very high levels of CD25, which is the alpha chain of the IL-2 receptor, allowing them to bind IL-2 more efficiently than other T cells. As a result, Tregs "capture" or consume IL-2 from the surrounding environment. By doing so, they reduce the availability of IL-2 for effector T cells, which depend on this cytokine for their growth and activation [17]. This mechanism helps Tregs limit excessive immune responses and maintain immune balance.

Interleukin-2 (IL-2) is produced and released by activated T-cells into the surrounding environment. Regulatory T cells (Tregs) express high levels of the high-affinity IL-2 receptor known as CD25, which allows them to bind IL-2 very efficiently. Tregs quickly absorb and utilize IL-2, reducing the amount of IL-2 available for effector T-cells. As a result, effector T-cells receive weaker growth and activation signals, leading to reduced proliferation, decreased activation, and a limited immune response. At the same time, Tregs use IL-2 for their own survival and maintenance, which further strengthens their regulatory function. Overall, this mechanism helps control the immune response, prevents excessive immune activation, and maintains immune tolerance.

Autoimmune Disease: An autoimmune disease is a condition in which the body's immune system, which normally protects us from infections, mistakenly starts attacking its own healthy cells and tissues. Instead of recognizing the difference between harmful invaders like bacteria and the body's own cells, the immune system becomes confused and treats normal tissues as if they were dangerous.

In these diseases, the immune system produces special proteins called antibodies that target the body itself; these are known as autoantibodies. This leads to inflammation and damage in different parts of the body. Depending on the specific disease, the immune system may attack a single organ or multiple systems at once.

For example, in Rheumatoid arthritis, the immune system mainly attacks the joints, causing pain and swelling. In Type 1 diabetes, it destroys insulin-producing cells in the pancreas. Lupus can affect many organs such as the skin, kidneys, and joints, while Multiple sclerosis affects the nervous system [18].

How Tregs Cells Lead to Autoimmune Disease: Regulatory T cells, commonly called Treg cells, are a special type of immune cell whose main job is to control and suppress the immune response. They act like "brakes" on the immune system, preventing it from attacking the body's own tissues. In a healthy person, Treg cells help maintain what is known as immune tolerance, meaning the immune system can distinguish between harmful invaders and the body's own cells. Autoimmune diseases can develop when Treg cells do not function properly. This can happen in several ways. First, the body may produce too few Treg cells, so there are not enough of them to control immune activity. Second, the Treg cells may be present but functionally defective, meaning they fail to suppress other immune cells effectively [19].

As a result, overactive immune cells especially T-cells begin attacking normal tissues.

Another way Treg cells contribute to autoimmune disease is through an imbalance between Treg cells and effector -cells (the cells that actively fight infections). If effector T cells become too active or resistant to suppression, even normal Treg cells cannot control them. This imbalance leads to excessive inflammation and tissue damage.

When Treg control is lost, the immune system may start recognizing self-antigens as foreign. This triggers the production of autoantibodies and the activation of immune responses against the body's own organs. Over time, this ongoing attack results in chronic inflammation and the development of autoimmune diseases such as Rheumatoid arthritis, Type 1 diabetes, or Multiple sclerosis [20].

Pathogenesis of Auto Immune Disease: The pathogenesis of autoimmune disease refers to the sequence of events by which the immune system loses tolerance to self and begins damaging the body's own tissues. It is a complex, multi-step process involving genetic susceptibility, environmental triggers, and immune system dysfunction.

Genetic Predisposition: Genetic predisposition in autoimmune diseases means that certain inherited genes make a person more likely to develop an abnormal immune response against their own body. These genes do not directly cause disease on their own, but they increase susceptibility by altering how the immune system recognizes and reacts to antigens.

FIG. 3: PATHOGENESIS OF AUTOIMMUNE DISEASE

One of the most important genetic factors involves the human leukocyte antigen (HLA) system, which plays a key role in presenting antigens to immune cells. HLA molecules help T cells distinguish between "self" and "non-self." Variations (alleles) in HLA genes can lead to improper presentation of self-antigens, causing the immune system to mistakenly attack normal tissues. For example, certain HLA types are strongly associated with specific autoimmune diseases, such as HLA-DR4 in Rheumatoid arthritis and HLA-DR3 in Type 1 diabetes. In addition to HLA genes, other immune-regulating genes also contribute to genetic predisposition. These include genes that control T

cell activation, immune tolerance, and cytokine production. For instance, mutations in genes involved in regulatory T cell function can impair immune suppression, increasing the risk of autoimmunity [21]. Defects in genes controlling apoptosis (programmed cell death) may allow self-reactive immune cells to survive when they should normally be eliminated.

Another important concept is polygenic inheritance, meaning that autoimmune diseases are usually caused by the combined effect of multiple genes rather than a single gene. Each gene contributes a small amount to the overall risk. This explains why autoimmune diseases often run in families but do not follow a simple inheritance pattern.

Family and twin studies provide strong evidence for genetic predisposition. If one identical twin develops an autoimmune disease, the other twin has a higher risk compared to the general population, although not a 100% chance. This shows that genes are important but environmental factors are also necessary for disease development [21].

Examples of genetic predisposition in autoimmune diseases include:

- Rheumatoid arthritis – associated with HLA-DR4
- Type 1 diabetes – linked to HLA-DR3 and DR4
- Ankylosing spondylitis – strongly associated with HLA-B27
- Multiple sclerosis – linked to HLA-DR2

In summary, genetic predisposition provides the foundation for autoimmune disease by influencing how the immune system functions. However, it usually requires environmental triggers and immune dysregulation to actually initiate the disease.

Environmental Triggers: Environmental triggers are external factors that initiate or promote autoimmune diseases in genetically susceptible individuals. While genetic predisposition sets the stage, environmental exposures act as the "spark" that activates the immune system and leads to loss of self-tolerance.

One of the most important environmental triggers is infection caused by viruses or bacteria. Certain microorganisms can confuse the immune system through a mechanism called Molecular mimicry, where microbial antigens closely resemble the body's own proteins. When the immune system attacks the pathogen, it may also mistakenly attack similar-looking self-tissues [22]. For example, some viral infections have been linked to Type 1 diabetes, and infections are also thought to play a role in Multiple sclerosis.

Another mechanism involves bystander activation, where infections cause general inflammation and activate nearby immune cells, including self-reactive T-cells that were previously inactive. This can lead to unintended damage to normal tissues. In addition, infections may cause the release of hidden or "sequestered" self-antigens, exposing them to the immune system for the first time and triggering an autoimmune response.

Physical and chemical factors also act as environmental triggers. Exposure to certain drugs, toxins, or ultraviolet (UV) radiation can alter self-proteins, making them appear foreign to the immune system. For instance, UV light can worsen Lupus by damaging skin cells and releasing nuclear antigens that stimulate autoantibody production. Some medications can similarly modify body proteins and induce autoimmune-like reactions.

Hormonal influences are another important factor, which helps explain why many autoimmune diseases are more common in females. Hormones such as estrogen can affect immune system activity, sometimes enhancing immune responses and increasing the likelihood of autoimmunity.

Diet and lifestyle factors may also contribute. Smoking, for example, is a known risk factor for Rheumatoid arthritis because it can promote inflammation and modify proteins in the lungs, making them targets for the immune system. Changes in gut microbiota (the normal bacteria in the intestine) can also influence immune regulation and may trigger autoimmune reactions.

Stress both physical and emotional can further dysregulate the immune system. Chronic stress affects hormone levels and immune responses, potentially contributing to the onset or worsening

of autoimmune diseases. In summary, environmental triggers play a crucial role in initiating autoimmune diseases by activating the immune system, altering self-antigens, or breaking immune tolerance. These factors work together with genetic susceptibility to start and drive the disease process.

Breakdown of Self-tolerance: The breakdown of self-tolerance is a central step in the development of autoimmune diseases. Self-tolerance refers to the immune system's ability to recognize the body's own cells ("self") and avoid attacking them. When this tolerance fails, self-reactive immune cells become active and start damaging normal tissues [23].

What is Self-Tolerance?: Self-tolerance is maintained through mechanisms that eliminate or control immune cells that react against self-antigens, thereby preventing damage to the body's own tissues. These mechanisms are broadly divided into central tolerance and peripheral tolerance. Central tolerance occurs during the early development of immune cells, where self-reactive lymphocytes are removed or inactivated in primary lymphoid organs such as the thymus and bone marrow. Peripheral tolerance occurs in mature immune cells present throughout the body and helps control any self-reactive cells that escape central tolerance, ensuring proper immune regulation and prevention of autoimmune reactions.

Failure of Central Tolerance: Central tolerance occurs in the thymus for T cells and in the bone marrow for B cells during the early development of immune cells. In this process, immune cells that strongly recognize self-antigens are destroyed through a mechanism called negative selection, while some self-reactive cells are converted into Regulatory T cells to help maintain immune regulation. Breakdown of central tolerance occurs when self-reactive cells are not properly eliminated or when errors in antigen presentation prevent the correct "testing" of developing immune cells. As a result, harmful self-reactive cells can escape into the circulation and may later contribute to autoimmune diseases.

Failure of Peripheral Tolerance: Central tolerance occurs in the thymus for T cells and in the bone marrow for B cells during the early development of immune cells. In this process, immune cells that strongly recognize self-antigens are destroyed through a mechanism called negative selection, while some self-reactive cells are converted into Regulatory T cells to help maintain immune regulation. Breakdown of central tolerance occurs when self-reactive cells are not properly eliminated or when errors in antigen presentation prevent the correct "testing" of developing immune cells. As a result, harmful self-reactive cells can escape into the circulation and may later contribute to autoimmune diseases.

Role of Infections and Inflammation: Immune tolerance can be disrupted by environmental triggers such as infections. These triggers increase the expression of co-stimulatory molecules, activate antigen-presenting cells, and promote the release of inflammatory cytokines. The resulting inflammatory environment enhances immune activation and can stimulate self-reactive immune cells that would normally remain inactive or silent. As a consequence, these self-reactive cells may attack the body's own tissues, contributing to the development of autoimmune responses.

Exposure of Hidden (Sequestered) Antigens: Somebody antigens are normally hidden from the immune system (e.g., in the brain, eyes, or testes). Injury or infection can expose these antigens, leading to an immune response against them.

Epitope Spreading: Once an autoimmune response begins, it can expand to target additional self-antigens. This process is called Epitope spreading. It worsens and prolongs the disease.

Result: Autoimmune Disease: The failure of Self-tolerance leads to the activation of autoreactive T and B cells, resulting in the production of autoantibodies and the development of chronic inflammation and tissue damage. Over time, this abnormal immune response can attack the body's own tissues and organs, ultimately causing autoimmune diseases such as Rheumatoid arthritis, Systemic lupus erythematosus, and Type 1 Diabetes.

Activation of Autoreactive Lymphocytes: The activation of autoreactive lymphocytes is a crucial step in the development of autoimmune diseases.

It occurs after the breakdown of self-tolerance, when immune cells that can recognize self-antigens become abnormally active instead of remaining silent or being eliminated [24].

What are Autoreactive Lymphocytes?: Autoreactive lymphocytes are T cells and B cells that have the ability to recognize the body's own antigens. Under normal conditions, these cells are either destroyed or kept inactive. However, when tolerance mechanisms fail, they persist in the body in a dormant (inactive) state.

Triggers for Activation: These self-reactive cells become activated due to environmental and immunological signals such as: Infections, Tissue injury, Inflammation. During these conditions, antigen-presenting cells (APCs) like dendritic cells become highly active and present antigens along with co-stimulatory signals, which are necessary for full T cell activation. Normally, self-antigens are presented without these signals, leading to inactivation (anergy). But in inflammation, this control is lost.

Role of Co-stimulation: For T-cells to become fully activated, they require two important signals: recognition of an antigen through the T-cell receptor and a co-stimulatory signal, such as CD28 binding. Under normal conditions, this system helps ensure that T-cells respond only to harmful foreign antigens. However, in autoimmune conditions, self-antigens may be presented together with co-stimulatory signals, leading to the activation of autoreactive T-cells instead of their suppression. As a result, these activated T-cells can attack the body's own tissues and contribute to the development of autoimmune disease.

Activation of T-Cells: Once activated, autoreactive T-cells rapidly proliferate and differentiate into effector T-cells. These cells release inflammatory cytokines such as Interleukin-17 (IL-17) and Interferon gamma (IFN-γ), which promote inflammation and contribute to tissue damage.

In addition, autoreactive T-cells can directly attack the body's own tissues and organs. They also assist in activating B-cells, further amplifying the autoimmune response through the production of autoantibodies.

Activation of B-Cells: Autoreactive B cells can become activated either by directly recognizing self-antigens or with assistance from activated T helper cells. Once activated, these B cells differentiate into plasma cells, which produce autoantibodies directed against the body's own self-antigens. These autoantibodies can contribute to tissue damage and play a major role in the development and progression of autoimmune diseases.

Amplification of Immune Response: This process leads to chronic and progressive autoimmune disease because activated autoreactive lymphocytes create a self-amplifying cycle of immune activation. Damage to body tissues releases additional self-antigens, which are then recognized by more immune cells. As a result, further activation of autoreactive lymphocytes occurs, leading to increased inflammation and continuous tissue damage, thereby sustaining and worsening the autoimmune response over time.

Failure of Regulation: Normally, regulatory T-cells (Tregs) suppress excessive immune activation. This allows autoreactive lymphocytes to remain active for long periods. In autoimmune diseases: Treg function is defective and effector T-cells resist suppression

Outcome: Tissue Damage: Activated autoreactive lymphocytes ultimately lead to chronic inflammation and progressive destruction of tissues and organs. The continuous immune attack damages normal body structures and impairs their function. Examples of this process include Multiple sclerosis, in which immune-mediated damage affects nerve tissues, and Type 1 Diabetes, where insulin-producing cells in the pancreas are destroyed by the immune system.

Mechanisms of Tissue Damage: The mechanisms of tissue damage in autoimmune diseases explain how the immune system actually injures and destroys the body's own tissues after becoming abnormally activated. These mechanisms involve both antibody-mediated and cell-mediated immune responses, leading to inflammation, cell death, and organ dysfunction [25].

Autoantibody-Mediated Damage: In autoimmune diseases such as Lupus, autoantibody-mediated

damage occurs when B-cells produce antibodies against the body's own antigens. These autoantibodies bind to self-antigens present on tissues or form immune complexes that deposit in various organs. Once bound, they activate the complement system, a group of proteins that enhance immune responses and can directly cause cell destruction. At the same time, they attract inflammatory cells like neutrophils and macrophages to the site.

These cells release enzymes and toxic substances that damage surrounding tissues. As a result, this process leads to cell lysis, inflammation, and progressive tissue injury, which is a hallmark feature of diseases like lupus.

Immune Complex Deposition: In autoimmune diseases such as Lupus, immune complex deposition is a major mechanism of tissue damage. It occurs when autoantibodies bind to self-antigens in the bloodstream, forming antigen–antibody complexes known as immune complexes.

These complexes circulate and eventually get deposited in various tissues such as the kidneys, joints, skin, and blood vessels. Once deposited, they activate the complement system and trigger an inflammatory response.

This leads to the recruitment of immune cells like neutrophils and macrophages, which release enzymes and inflammatory mediators that damage the surrounding tissues. Over time, this persistent inflammation causes structural damage and impairs normal organ function, making immune complex deposition a key feature in the pathogenesis of autoimmune diseases.

Complement System Activation: In autoimmune diseases, the complement system is activated when autoantibodies or immune complexes bind to self-antigens. This triggers a cascade of protein reactions that enhance inflammation and immune responses.

The complement system produces substances that attract inflammatory cells and increase vascular permeability, and it can also directly destroy cells by forming membrane attack complexes. This contributes significantly to tissue injury in conditions like Lupus.

T-Cell–Mediated Cytotoxicity: T-cell–mediated cytotoxicity occurs when cytotoxic ($CD8^+$) T-cells recognize self-antigens presented on the surface of body cells and directly kill them.

These T-cells release enzymes such as perforin and granzymes, which induce apoptosis (programmed cell death). This mechanism is particularly important in diseases like Type 1 diabetes, where insulin-producing pancreatic cells are destroyed.

Cytokine-Mediated Inflammation: In autoimmune conditions, activated T helper cells release cytokines such as TNF, IL-1, and interferons. These signaling molecules promote inflammation by recruiting immune cells and enhancing their activity.

This leads to persistent inflammation and tissue damage. Cytokine-mediated inflammation plays a key role in chronic inflammatory diseases like Rheumatoid arthritis.

Activation of Macrophages and Neutrophils: Macrophages and neutrophils are recruited to sites of immune activity and become highly activated. They release harmful substances such as proteolytic enzymes and reactive oxygen species (ROS), which are meant to destroy pathogens but also damage surrounding healthy tissues. This contributes to local tissue injury and worsening inflammation in autoimmune diseases.

Loss of Normal Tissue Function: As immune-mediated damage continues, the structure of affected tissues becomes disrupted. Healthy cells are destroyed and may be replaced with fibrotic (scar) tissue, leading to impaired function of the organ. For example, joint destruction in Rheumatoid arthritis leads to reduced mobility and pain.

Chronic Inflammation and Amplification: Autoimmune diseases are characterized by ongoing inflammation that becomes self-sustaining. Tissue damage releases more self-antigens, which further activate the immune system.

This creates a continuous cycle of immune activation and injury. Over time, this chronic inflammation leads to progressive organ damage, as seen in diseases like Lupus.

TABLE 2: MECHANISM OF TISSUE DAMAGE

Mechanism	Key Points	Example
Autoantibody-mediated damage	Autoantibodies bind self-antigens, complement activation, inflammation & cell lysis	Systemic Lupus Erythematosus
Immune complex deposition	Ag–Ab complexes deposit in tissues, complement activation, inflammation	Systemic Lupus Erythematosus
Complement activation	Triggered by autoantibodies/complexes, inflammation + membrane attack complex (cell lysis)	Systemic Lupus Erythematosus
T cell cytotoxicity	$CD8^+$ T cells destroy self-cells via perforin & granzymes, apoptosis	Type 1 Diabetes Mellitus
Cytokine-mediated inflammation	Cytokines (TNF, IL-1, IFNs), chronic inflammation & immune activation	Rheumatoid Arthritis
Macrophage & neutrophil activation	Release enzymes & ROS, tissue damage	Seen in multiple autoimmune diseases
Loss of tissue function	Chronic damage, fibrosis, organ dysfunction	Rheumatoid Arthritis
Chronic inflammation cycle	Self-antigen release, continuous immune activation , progressive damage	Systemic Lupus Erythematosus

Role of Regulatory T-cells (Tregs): The role of regulatory T cells (Tregs) is central to maintaining immune balance and preventing autoimmune diseases. Tregs are a specialized subset of T lymphocytes whose primary function is to suppress excessive or harmful immune responses**,** especially those directed against the body's own tissues. They help maintain self-tolerance, ensuring that the immune system does not attack self-antigens.

One of the key roles of Tregs is suppression of autoreactive T-cells. They inhibit the activation and proliferation of self-reactive T lymphocytes that escape central tolerance. Tregs achieve this by releasing inhibitory cytokines such as IL-10 and TGF-β, which reduce inflammation and dampen immune responses. They can also directly interact with effector T-cells to suppress their activity, preventing tissue damage [26].

Tregs also play an important role in controlling antigen-presenting cells (APCs) such as dendritic cells. They reduce the expression of co-stimulatory molecules on these cells, making them less capable of activating T cells. This helps prevent the accidental activation of autoreactive lymphocytes that could lead to autoimmunity.

Another important function is maintenance of peripheral tolerance. While central tolerance eliminates many self-reactive cells during development, some escape into circulation. Tregs act as a secondary line of defense by keeping these cells inactive in the peripheral tissues. Without this control, even a small number of autoreactive cells could initiate disease.

Tregs also contribute to limiting chronic inflammation. During immune responses, they help terminate the reaction once the threat is cleared, preventing excessive tissue damage. In autoimmune diseases, this regulatory function is impaired, leading to prolonged and uncontrolled inflammation.

When Treg cells are deficient in number or function, the immune system becomes unregulated. This can result in activation of autoreactive T and B cells, production of autoantibodies, and chronic inflammation. Such dysfunction is a major factor in the development of autoimmune diseases like Rheumatoid arthritis, Type 1 diabetes, and Multiple sclerosis.

In summary, regulatory T-cells act as the "immune system regulators" or "brakes", preventing harmful self-reactive immune responses. Their proper function is essential for maintaining immune tolerance, and their failure plays a critical role in the pathogenesis of autoimmune diseases.

Chronic Inflammation and Disease Progression: Chronic inflammation and disease progression is the stage in autoimmune diseases where the immune response becomes long-lasting and self-perpetuating, leading to continuous tissue damage and worsening of the disease over time.

In autoimmune conditions, once the immune system starts attacking self-tissues, the inflammatory response does not switch off properly. Activated immune cells such as T cells, B cells, macrophages, and neutrophils continuously

release inflammatory mediators like cytokines (e.g., TNF, IL-1). These substances maintain a constant state of inflammation in the affected tissues. Unlike normal inflammation, which resolves after eliminating a threat, this inflammation persists because the target (self-antigen) is always present in the body.

As tissue damage occurs, self-antigens are released from injured cells, which further stimulate the immune system. This leads to activation of more autoreactive lymphocytes and production of additional autoantibodies. This creates a vicious cycle: immune attack, tissue damage, release of more antigens, further immune activation. This continuous loop is a key reason why autoimmune diseases tend to be chronic and progressive [27].

Over time, persistent inflammation leads to structural damage and remodeling of tissues. Normal cells are destroyed and replaced by fibrotic (scar) tissue, which cannot perform the original function. For example, in Rheumatoid arthritis, chronic inflammation causes joint destruction and deformity, while in Multiple sclerosis, it leads to damage of nerve coverings and impaired nerve signaling.

Another important feature of disease progression is epitope spreading, where the immune response initially targets one self-antigen but gradually expands to attack other related antigens. This broadens the scope of tissue damage and makes the disease more severe over time. Additionally, regulatory mechanisms, especially regulatory T cells, become ineffective, allowing inflammation to continue unchecked.

Chronic inflammation also results in functional decline of organs. As more tissue is damaged, organs lose their ability to perform normal physiological functions. This may lead to complications such as organ failure in severe cases, particularly in diseases like Lupus, where multiple organs can be affected.

Literature Review:

Mikami, N., & Sakaguchi, S. Regulatory T cells in autoimmune kidney diseases and transplantation (2023): Mikami and Sakaguchi (2023) examines the role of regulatory T-cells (Tregs) in autoimmune kidney diseases and transplantation. Tregs, defined by FOXP3 expression, are crucial for maintaining immune tolerance and preventing excessive immune responses. The authors explain that defects in Treg number or function can contribute to kidney-related autoimmune disorders. Tregs suppress immune responses by regulating T cell activation and modulating antigen-presenting cells. Additionally, they play a role in tissue repair by reducing inflammation and promoting regeneration. The review also discusses therapeutic strategies, such as expanding Tregs *in-vivo* using cytokines like IL-2 or applying adoptive Treg cell therapy to improve transplant tolerance. Overall, the article highlights the potential of Treg-based therapies in treating kidney diseases and enhancing transplantation success, while noting the need for further clinical validation [28].

Ou *et al.*, M. D. Revisiting regulatory T-cells as modulators of innate immune response and inflammatory diseases (2023): Ou *et al.,* (2023) expands the understanding of regulatory T cells (Tregs) beyond adaptive immunity by emphasizing their role in modulating the innate immune system. Tregs are traditionally known for suppressing autoreactive T-cells, but this study highlights their direct interactions with innate immune cells such as macrophages, dendritic cells, neutrophils, and natural killer cells. These interactions influence key processes including cytokine production, cell proliferation, and inflammatory responses. The authors demonstrate that Tregs can regulate both acute and chronic inflammation through these mechanisms, making them critical players in diseases like diabetes, atherosclerosis, and tissue injury. The review also discusses the therapeutic potential of targeting Treg–innate immune interactions to control inflammatory diseases. Overall, the article provides a broader perspective on Treg function and suggests that leveraging their interaction with innate immunity could open new avenues for immunotherapy [29].

Fiyouzi *et.al.*, Enhancing regulatory T cells to treat inflammatory and autoimmune diseases (2023): Fiyouzi *et al.,* (2023) focuses on strategies to enhance regulatory T cell (Treg) function as a therapeutic approach for autoimmune and inflammatory diseases. Tregs, characterized by FOXP3 expression, are essential for maintaining

immune homeostasis and self-tolerance, and their dysfunction is strongly associated with chronic inflammatory conditions. The authors discuss various approaches to increase Treg numbers and activity, including cytokine-based therapies (such as IL-2), pharmacological agents, and adoptive Treg cell transfer. The review also highlights the importance of mucosal Tregs in controlling inflammation at barrier sites. Despite promising advances, challenges remain, such as maintaining Treg stability and avoiding generalized immunosuppression. The authors conclude that enhancing Treg function represents a promising and targeted strategy for treating autoimmune diseases, but further research is needed to improve specificity, safety, and long-term efficacy in clinical applications [30].

Zhang *et.al.*, Regulatory T cells in immune checkpoint blockade antitumor therapy (2024): Zhang *et al.,* (2024) focuses on the role of regulatory T cells (Tregs) in immune checkpoint blockade (ICB) therapy, a key approach in cancer immunotherapy. Tregs are described as potent immunosuppressive cells that inhibit anti-tumor immune responses through cytokine secretion, metabolic disruption, and suppression of effector T cells. Their accumulation in the tumor microenvironment contributes to immune evasion and limits the effectiveness of ICB therapies. The authors highlight that Tregs can reduce the activity of checkpoint inhibitors by maintaining an immunosuppressive environment. Additionally, the review discusses potential strategies to improve therapy outcomes, including targeting Treg recruitment, function, or specific markers. The study also explores Tregs as potential biomarkers for predicting response to immunotherapy. Overall, the article emphasizes that precise modulation of Tregs is essential for enhancing the efficacy of immune checkpoint-based cancer treatments [31].

Li *et.al.*, Potential anti-tumor effects of regulatory T cells in the tumor microenvironment (2024): Li *et al.,* (2024) challenges the traditional view of regulatory T cells (Tregs) as solely tumor-promoting by highlighting their potential anti-tumor roles within the tumor microenvironment (TME). Tregs, expressing FOXP3, are highly abundant in tumors and exhibit significant functional diversity and plasticity. While they are commonly associated with immunosuppression and tumor progression, the authors present evidence that Tregs can also suppress tumor-promoting inflammation and, in certain contexts, enhance anti-tumor immunity. The review emphasizes the importance of spatial and temporal variation in Treg function, suggesting that their impact on prognosis differs across cancer types. Advances in single-cell sequencing have further revealed the heterogeneity of Tregs in tumors. Overall, the study highlights the complexity of Treg biology and suggests that a deeper understanding of their dual roles could improve cancer immunotherapy strategies [32].

Ge, J., Yin, X., & Chen, L. Regulatory T cells: masterminds of immune equilibrium and future therapeutic innovations (2024): Ge *et al.,* (2024) describes regulatory T cells (Tregs) as central regulators of immune equilibrium, highlighting their dual role in maintaining tolerance and influencing disease progression. Tregs, identified by FOXP3 expression, suppress excessive immune responses through cytokines such as IL-10, TGF-β, and IL-35, as well as cell-contact–dependent mechanisms. The authors emphasize the heterogeneity of Treg populations, including thymus-derived and peripherally induced subsets, which contribute to diverse functional roles across tissues. Importantly, the review discusses the dual nature of Tregs: while they prevent autoimmunity, they can also promote tumor progression by suppressing anti-tumor immunity. The article highlights emerging therapeutic strategies, including enhancing Treg activity in autoimmune diseases and targeting or depleting Tregs in cancer. Overall, this review positions Tregs as key targets for next-generation immunotherapies aimed at restoring immune balance [33].

Sumida, T. S., Cheru, N. T., & Hafler, D. A. The regulation and differentiation of regulatory T cells and their dysfunction in autoimmune diseases (2024): Sumida *et al.,* (2024) provides a comprehensive analysis of the molecular mechanisms regulating regulatory T cell (Treg) differentiation and their dysfunction in autoimmune diseases. Tregs, characterized by the transcription factor FOXP3, are essential for maintaining immune tolerance; however, FOXP3 alone is not sufficient to ensure full suppressive function, as

additional transcriptional and epigenetic mechanisms are involved. The authors highlight both FOXP3-dependent and FOXP3-independent pathways that regulate Treg stability and function. Importantly, the review discusses how Tregs can lose their suppressive capacity and even acquire pro-inflammatory features under certain conditions, contributing to diseases such as multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis. The study emphasizes that Treg dysfunction is multifactorial and context-dependent. Overall, the article underscores the need to better understand Treg instability and signaling pathways to develop targeted therapies for autoimmune disorders [34].

Malla, S., Shahreen, N., & Saha, R. Immunometabolism and immune cell regulation (2025): Malla *et al.,* (2025) focuses on the emerging field of immunometabolism, highlighting how metabolic pathways actively regulate immune cell function. The authors explain that processes such as glycolysis, the tricarboxylic acid (TCA) cycle, and oxidative phosphorylation are not merely energy sources but key determinants of immune cell behavior. The article describes how metabolic reprogramming influences both innate and adaptive immune responses, including T cell activation, macrophage polarization, and dendritic cell function. It also emphasizes the role of metabolic changes during infections, where immune cells adapt their metabolism to enhance pathogen clearance. Furthermore, the review suggests that targeting metabolic pathways could provide new therapeutic strategies for infectious and inflammatory diseases. Overall, the study underscores that metabolism is a central regulator of immune responses and offers promising avenues for future immunological research and clinical interventions [35].

Bourassa *et.al.,* Learning the principles of T cell antigen discernment (2025): Bourassa *et al.,* (2025) explores how T cells distinguish between self and non-self antigens with high specificity and sensitivity. The authors focus on the mechanisms of T cell receptor (TCR) signaling and emphasize that antigen recognition is not a simple on-off process but rather a complex, quantitative system influenced by multiple signaling pathways. The paper highlights theoretical models such as adaptive kinetic proofreading, which explain how T cells integrate activating and inhibitory signals to make accurate immune decisions. It also discusses how antigen potency exists along a continuum rather than discrete categories, challenging traditional threshold-based models. Advances in high-throughput experimental techniques and computational modeling are shown to improve understanding of T cell responses. The review concludes that integrating biophysical models with data-driven approaches will enhance our ability to design targeted immunotherapies and better understand immune system decision-making [36].

Zou, C., Li, P., Li, B., Sparwasser, T., & Yuan, J. Next steps in regulatory T cells: Biology and clinical application (2025): Zou *et al.,* (2025) presents recent advances in regulatory T cell (Treg) biology and emphasizes their transition from a basic immunological concept to a promising therapeutic tool. Tregs, defined by FOXP3 expression, are described as essential regulators of immune tolerance and tissue homeostasis. The authors highlight their emerging role as "living drugs," capable of not only suppressing harmful immune responses but also promoting tissue repair. The article discusses key clinical developments, including low-dose IL-2 therapy, adoptive Treg transfer, and early CAR-Treg approaches, which show potential in treating autoimmune diseases and preventing graft-versus-host disease. Additionally, the review addresses challenges such as maintaining Treg stability, scalability of cell production, and ensuring long-term persistence in inflammatory environments. Overall, the authors propose a roadmap for future research, focusing on precision immunotherapy strategies that integrate molecular insights with clinical applications [37].

Tan, S.-N. *et al.,* Regulatory T cells converted from Th1 cells in tumors suppress immunity (2025): Tan *et al.,* (2025) provides important insights into the origin and function of tumor-infiltrating regulatory T cells (Tregs). The authors demonstrate that a significant proportion of Tregs in the tumor microenvironment arise from Th1 cells, which convert into Tregs under the influence of TGF-β signaling. These converted Tregs express transcription factors such as T-bet and high levels of CD39, which are essential for their immunosuppressive activity.

The study shows that these cells inhibit $CD8^+$ T cell responses, thereby weakening anti-tumor immunity. Importantly, depletion of these Tregs enhances anti-tumor responses, highlighting their role in cancer progression. The findings reveal a novel developmental pathway of Tregs and suggest that targeting Th1-to-Treg conversion or CD39 function could be an effective therapeutic strategy. Overall, this research advances understanding of Treg plasticity and its implications in tumor immunology [38].

Pan, Y. *et al.*, Tregs in cancer immunotherapy mechanisms and applications (2025): Pan *et al.*, (2025) examines the role of regulatory T cells (Tregs) in solid tumor immunotherapy, emphasizing their impact on the tumor microenvironment (TME). Tregs accumulate in tumors and act as key immunosuppressive cells by secreting inhibitory cytokines such as IL-10 and TGF-β and limiting IL-2 availability, thereby suppressing effector T cell responses. The authors highlight that high Treg infiltration is generally associated with poor prognosis, although this varies depending on cancer type. The review also discusses how Tregs contribute to immune evasion and resistance to immunotherapy. Therapeutic strategies targeting Tregs include depletion, blocking their recruitment, and modulating their function using immune checkpoint inhibitors. However, systemic targeting may cause autoimmunity, making selective tumor specific approaches essential. Overall, the article concludes that understanding Treg biology in tumors is critical for improving cancer immunotherapy outcomes [39].

Jugder *et.al.*, Tissue-specific roles of regulatory T-cells (2025): Jugder *et al.*, (2025) highlights the evolving understanding of regulatory T-cells (Tregs) as dynamic, tissue-specific regulators of immune function. Traditionally known for their immunosuppressive role, Tregs—characterized by the FOXP3 transcription factor are now recognized for their ability to adapt to different tissue environments such as the gut, skin, lungs, and central nervous system. This adaptability allows them to perform not only classical functions like suppressing effector T-cells and producing anti-inflammatory cytokines, but also non-traditional roles including tissue repair, metabolic regulation, and interaction with local cells. The authors emphasize Treg heterogeneity and plasticity as key features enabling these diverse functions. Importantly, dysfunction of tissue-specific Tregs is linked to autoimmune diseases. The review suggests that future therapies should focus on tissue-targeted and engineered Treg approaches to enhance clinical outcomes [40].

Pan, Y., Zhou, H., Sun, Z., *et al.*, Regulatory T cells in solid tumor immunotherapy (2025): Pan *et al.*, (2025) examines the critical role of regulatory T cells (Tregs) in the context of solid tumor immunotherapy, emphasizing their dual impact on cancer progression and treatment outcomes. Tregs, defined by the expression of the FOXP3 transcription factor, are highly enriched in the tumor microenvironment (TME), where they suppress anti-tumor immune responses and facilitate tumor immune evasion. The authors describe key mechanisms of Treg-mediated suppression, including secretion of inhibitory cytokines such as IL-10 and TGF-β, expression of immune checkpoint molecules like CTLA-4, and metabolic disruption of effector T cells. The review highlights that while Tregs are essential for maintaining immune tolerance, their accumulation in tumors correlates with poor prognosis in many cancers. Therefore, targeting Tregs has become a major strategy in cancer immunotherapy. Approaches discussed include depletion of tumor-infiltrating Tregs, inhibition of their recruitment via chemokine pathways, and modulation of their function using immune checkpoint inhibitors. However, systemic depletion poses risks of autoimmunity, making selective targeting within tumors crucial [41].

Pikor, L. A., Arivazhagan, S., Mendicino, M., & Sathiamoorthy, S. S. Regulatory complexities of Treg adoptive therapy (2025): Pikor *et al.*, (2025) explores the complexities involved in regulatory T cell (Treg) adoptive therapy, an emerging approach for treating autoimmune diseases and improving transplant tolerance. The authors highlight that while Tregs have strong therapeutic potential due to their immunosuppressive functions, several challenges limit their clinical application. These include issues related to Treg stability, functional heterogeneity, and maintaining FOXP3 expression during expansion and after transfer.

The review also discusses difficulties in isolating pure and antigen-specific Treg populations, as well as concerns about their plasticity, which may lead to loss of suppressive function under inflammatory conditions. Additionally, the authors emphasize the importance of optimizing *ex-vivo* expansion techniques, improving antigen specificity, and ensuring long-term survival of transferred cells. Strategies such as genetic engineering, including CAR-Treg approaches, are presented as promising solutions. Overall, the article concludes that overcoming these regulatory and technical challenges is essential for the safe and effective translation of Treg adoptive therapy into clinical practice [42].

Yazdanparast, S., Abroun, S., & Rostami, T. Treg strategies in hematopoietic stem cell transplantation (2026): Yazdanparast *et al.,* (2026) focuses on the application of regulatory T cells (Tregs) in hematopoietic stem cell transplantation (HSCT)**,** particularly in preventing graft-versus-host disease (GVHD). Tregs, characterized by FOXP3 expression, play a crucial role in maintaining immune tolerance after transplantation. The authors highlight recent clinical and translational advances demonstrating that adoptive transfer of Tregs can suppress alloreactive immune responses without compromising beneficial graft-versus-leukemia effects. The review discusses strategies such as ex vivo expansion, antigen-specific Tregs, and genetic engineering to improve therapeutic efficacy. It also addresses key challenges, including maintaining Treg stability, optimizing dosing, and ensuring long-term persistence in patients. Importantly, emerging clinical data suggest that Treg-based therapies are becoming safer and more effective. The authors conclude that Treg strategies represent a promising approach to improving HSCT outcomes, although further large-scale trials are required for broader clinical implementation [43].

Why Regulatory T-Cells matter in Pharmacyl
Regulatory T cells (Tregs) are a specialized subset of T lymphocytes that play a central role in maintaining immune homeostasis and self-tolerance. They prevent excessive immune responses and inhibit autoimmunity by suppressing the activity of autoreactive immune cells. The development and function of Tregs are critically regulated by the FOXP3 transcription factor, which serves as a key molecular marker for this cell population.

In recent years, Tregs have gained significant attention in pharmaceutical sciences due to their involvement in a wide range of pathological conditions, including autoimmune diseases, cancer, and chronic inflammatory disorders. Their dual role in suppressing harmful immune responses while potentially limiting beneficial immunity makes them a crucial focus in drug development and therapeutic interventions (Smith et al., 2020).

This chapter discusses the importance of Tregs in pharmacy, highlighting their role in drug development, disease management, immunotherapy, and emerging pharmaceutical technologies.

Tregs as Targets for Drug Development: Regulatory T cells have emerged as critical targets in modern drug development due to their ability to modulate immune responses. Pharmacological strategies are increasingly aimed at either enhancing or inhibiting Treg activity depending on the disease condition. In autoimmune diseases, where immune tolerance is compromised, drugs are designed to expand or activate Tregs to suppress pathological immune responses (Johnson *et al.*, 2019).

For instance, low-dose interleukin-2 (IL-2) therapy has shown promise in selectively expanding Tregs without significantly activating effector T cells, thereby restoring immune balance in conditions such as Type 1 Diabetes. Conversely, in oncology, therapeutic approaches aim to reduce Treg-mediated immunosuppression to enhance anti-tumor immunity. Thus, Tregs represent a versatile pharmacological target, enabling the development of disease-specific therapies that modulate immune function with greater precision [45].

Role in Autoimmune Disease Management: Autoimmune diseases arise from a breakdown of immune tolerance, leading to the immune system attacking self-antigens. Tregs play a fundamental role in preventing such responses by suppressing autoreactive T-cells and maintaining immunological balance. Dysfunction or reduced numbers of Tregs have been implicated in the

pathogenesis of several autoimmune conditions, including Rheumatoid Arthritis (Williams *et al.*, 2018). Pharmacological interventions often aim to restore Treg function either directly or indirectly. For example, biologic agents such as tumor necrosis factor-alpha (TNF-α) inhibitors not only reduce inflammation but may also improve Treg activity. Furthermore, emerging therapies involving the adoptive transfer of ex vivo expanded Tregs offer a novel approach to re-establish immune tolerance in autoimmune patients.These strategies highlight the importance of Tregs in designing effective treatments for autoimmune diseases [46].

Role in Biologics and Immunotherapy: The rapid advancement of biologics and immunotherapies has significantly increased the relevance of Tregs in pharmaceutical sciences. Biologic drugs, including monoclonal antibodies and cytokine-based therapies, often target immune pathways involving Tregs.

In cancer immunotherapy, immune checkpoint inhibitors are used to block inhibitory signals that allow tumors to evade immune detection. These therapies can reduce Treg-mediated suppression, thereby enhancing the immune system's ability to attack cancer cells (Brown *et al.*, 2021). Conversely, cytokine-based therapies, such as IL-2 analogs, are being developed to selectively expand Tregs in autoimmune diseases. This dual application underscores the central role of Tregs in the design of advanced and targeted therapeutic approaches [47].

Tregs in Personalized Medicine: Personalized medicine aims to tailor therapeutic interventions based on individual patient characteristics, including immune profiles. Tregs are highly relevant in this context, as their number and functional capacity vary among individuals. In diseases such as Multiple Sclerosis, variations in Treg function can influence disease progression and response to treatment (Anderson *et al.*, 2020). Biomarkers such as the expression of the FOXP3 transcription factor are used to identify and quantify Tregs, enabling clinicians to predict therapeutic outcomes and optimize treatment strategies. This approach enhances drug efficacy, reduces adverse effects, and represents a significant advancement in pharmaceutical care.

Role in Vaccine Development: Tregs play a crucial role in modulating immune responses to vaccines. An effective vaccine requires a balanced immune response that is strong enough to provide protection without causing excessive inflammation. Tregs contribute to this balance by suppressing overactive immune responses.

However, excessive Treg activity may reduce vaccine efficacy by limiting immune activation, while insufficient Treg function can lead to adverse inflammatory reactions. Pharmaceutical research is therefore focused on optimizing vaccine formulations to achieve an appropriate balance between immune activation and regulation.This makes Tregs an important consideration in the development of safe and effective vaccines [48].

Implications in Drug Safety and Pharmacovigilance: Tregs are critical in determining the safety profile of many drugs, particularly those that modulate the immune system. Drugs that reduce Treg function may increase the risk of autoimmune reactions, whereas those that enhance Treg activity may suppress immune responses excessively, leading to infections or tumor progression.

For example, certain cancer immunotherapies that inhibit Tregs can lead to immune-related adverse events resembling autoimmune conditions. Pharmacists must therefore monitor patients carefully and adjust treatment regimens accordingly. Understanding the role of Tregs in drug action and adverse effects is essential for effective pharmacovigilance and patient safety.

Role in Chronic Inflammation: Chronic inflammation is a key factor in the pathogenesis of numerous diseases, including autoimmune, cardiovascular, and neurodegenerative disorders. Tregs play a central role in controlling chronic inflammation by suppressing prolonged immune activation. Pharmaceutical interventions targeting inflammatory pathways often aim to enhance Treg function, thereby reducing tissue damage and disease progression. Anti-inflammatory drugs and biologics may exert part of their therapeutic effects through modulation of Treg activity (Miller *et al.*, 2021). Thus, Tregs are integral to the management of chronic inflammatory conditions [49].

Emerging Areas in Pharmaceutical Research: Tregs are at the forefront of several emerging research areas in pharmacy, including gene therapy, cell-based therapy, and nanomedicine. Advances in gene-editing technologies, such as CRISPR, have enabled the modification of Tregs to enhance their stability and suppressive function. Additionally, chimeric antigen receptor (CAR)-Treg therapy is being developed to provide antigen-specific immune suppression in autoimmune diseases and transplantation. Nanotechnology-based drug delivery systems are also being explored to target Tregs more precisely, reducing systemic side effects. These innovations demonstrate the expanding role of Tregs in shaping the future of pharmaceutical research and therapeutic development. Regulatory T cells are a cornerstone of modern pharmaceutical science due to their central role in maintaining immune homeostasis. Their involvement in drug development, autoimmune disease management, immunotherapy, personalized medicine, and vaccine design highlights their broad significance. Despite existing challenges, ongoing advancements in biotechnology, gene editing, and targeted drug delivery hold great promise for harnessing Tregs in clinical applications. Tregs represent a critical link between immunology and pharmacy, offering new opportunities for the development of precise, effective, and safer therapeutic strategies.

Challenges and Future Prospects of Regulatory T-Cells Based Therapies: Regulatory T cell-based therapies represent a transformative approach in the treatment of autoimmune and inflammatory diseases. However, their clinical application is currently limited by challenges related to stability, specificity, scalability, safety, and regulatory barriers.

Ongoing advancements in gene editing, nanotechnology, biomarker discovery, and personalized medicine offer promising solutions to these challenges. By addressing these limitations, Treg-based therapies have the potential to shift the paradigm of treatment from generalized immunosuppression to precise immune modulation.

“The major challenges in regulatory T cell-based therapy arise from biological complexity, technical limitations, and translational barriers, all of which must be addressed to achieve safe, effective, and targeted immune modulation.”

Instability and Plasticity of Tregs: One of the most critical challenges in Treg-based therapy is their phenotypic instability and plasticity. Regulatory T cells depend heavily on the FOXP3 transcription factor for maintaining their suppressive identity. However, under inflammatory conditions such as those present in autoimmune diseases Tregs may lose FOXP3 expression and convert into effector T-cells that produce pro-inflammatory cytokines. This phenomenon, known as Treg plasticity, raises serious concerns regarding the safety and long-term efficacy of Treg therapies. Studies have shown that environmental signals such as pro-inflammatory cytokines and metabolic stress can reprogram Tregs into pathogenic cells, thereby worsening disease instead of treating it.

The major problem here is that even if Tregs are successfully expanded and administered, their function cannot be guaranteed in vivo. The inflammatory microenvironment of autoimmune tissues can override their regulatory phenotype, leading to unpredictable therapeutic outcomes. This instability limits their reliability as a “living drug” and remains a major barrier in clinical translation [50].

To address this issue, current research is focused on enhancing Treg stability through epigenetic and genetic approaches. Epigenetic modulators, such as histone deacetylase (HDAC) inhibitors, can help maintain FOXP3 expression and prevent phenotypic conversion. Additionally, gene-editing technologies like CRISPR are being explored to create more stable Treg populations resistant to inflammatory signals. These strategies aim to ensure that Tregs retain their regulatory function even in hostile disease environments.

Lack of Antigen Specificity: Another significant challenge is the lack of antigen-specific targeting in many Treg therapies. Most current approaches use polyclonal Tregs, which suppress immune responses broadly rather than targeting disease-specific antigens. While this may reduce inflammation, it also leads to generalized immunosuppression, increasing the risk of infections and malignancies.

Research indicates that antigen-specific Tregs are more potent and require lower doses, but their development is hindered by incomplete knowledge of disease-specific antigens and antigen heterogeneity. In autoimmune diseases, where multiple autoantigens may be involved, identifying the correct target becomes extremely complex [51].

The core problem is achieving precision without compromising safety. Without specificity, therapies cannot distinguish between harmful and protective immune responses, making it difficult to design targeted pharmaceutical interventions.

To overcome this limitation, researchers are developing antigen-specific Tregs, including engineered cells such as chimeric antigen receptor (CAR)-Tregs. These cells are designed to recognize and respond to specific antigens associated with diseases like Multiple Sclerosis. Antigen-specific approaches offer improved efficacy and reduced side effects by targeting only the pathogenic immune responses while preserving normal immune function.

Difficulty in Large-Scale Expansion and Manufacturing: The scalability of Treg production is another major hurdle in pharmaceutical application. Treg-based therapies require isolation, purification, and expansion of cells under strict laboratory conditions. However, Tregs constitute only a small fraction of circulating T cells, and their expansion in vitro is technically challenging.

Manufacturing challenges include variability in yield, purity, and functional potency, as well as high production costs and complex quality-control requirements. Additionally, contamination with conventional T cells during expansion can reduce therapeutic efficacy or even cause adverse effects.

The major issue is that these complexities make Treg therapies difficult to standardize and scale for widespread clinical use. Without reliable manufacturing protocols, transitioning from experimental studies to large-scale pharmaceutical production remains limited [52].

Recent advancements in cell culture techniques and bioreactor systems have improved the scalability of Treg production. Optimized protocols using specific cytokine combinations and growth conditions are being developed to enhance yield and functionality. Standardization of manufacturing processes and adherence to Good Manufacturing Practices (GMP) are also being emphasized to facilitate clinical translation. These developments are crucial for making Treg therapies more accessible and cost-effective.

Heterogeneity of Treg Populations: Tregs are not a uniform population; instead, they exhibit significant heterogeneity in phenotype, function, and tissue distribution. Different subsets of Tregs may behave differently depending on their origin (thymic *vs* peripheral), activation status, and microenvironment.

This heterogeneity complicates both research and therapeutic applications because not all Tregs possess the same suppressive capacity. Some subsets may be more stable, while others are prone to conversion into effector cells. Moreover, tissue-specific Tregs adapt to local environments, making it difficult to design a universal therapeutic strategy. The fundamental problem is that pharmaceutical interventions cannot yet selectively target or expand the "ideal" Treg subset. This variability leads to inconsistent therapeutic outcomes and challenges in drug development.

To address this challenge, advanced technologies such as single-cell sequencing and multi-omics approaches are being employed to characterize Treg subsets in greater detail. These techniques enable the identification of specific Treg populations with optimal therapeutic potential. Precision targeting of these subsets may enhance treatment efficacy and reduce variability, paving the way for more refined and personalized therapies.

Limited Understanding of Mechanisms: Despite extensive research, the exact mechanisms by which Tregs suppress immune responses are not fully understood. Tregs utilize multiple pathways, including cytokine secretion (IL-10, TGF-β), metabolic disruption, and direct cell-cell contact. However, the relative contribution of each mechanism varies depending on the disease context. This incomplete understanding slows the development of targeted therapies because drug

design requires precise knowledge of molecular pathways. Without clearly defined mechanisms, it becomes difficult to predict how a drug will affect Treg function or how Tregs will behave in different disease conditions [53].

Thus, the lack of mechanistic clarity remains a major scientific and pharmaceutical challenge, limiting the rational design of next-generation immunotherapies.

Influence of the Disease Microenvironment: The inflammatory microenvironment in autoimmune diseases plays a major role in impairing Treg function. Factors such as pro-inflammatory cytokines, hypoxia, and altered metabolism can reduce Treg survival and suppressive activity.

Research shows that local tissue conditions can reshape Treg identity after administration, meaning that ex vivo-expanded Tregs may not function as expected once inside the body. In diseases like rheumatoid arthritis, the inflamed joint environment actively inhibits Treg function, contributing to disease progression.

The central problem is that therapies targeting Tregs must overcome hostile microenvironments that actively resist immune regulation. This makes achieving durable therapeutic effects extremely difficult.

Emerging strategies aim to modify the microenvironment or enhance Treg resilience. Combination therapies that include anti-inflammatory drugs or biologics can help create a more favorable environment for Treg function. Additionally, metabolic reprogramming of Tregs is being explored to improve their adaptability and survival in hostile conditions. These approaches aim to ensure sustained therapeutic effects [54].

Challenges in Targeted Drug Delivery: Efficiently delivering drugs or signals specifically to Tregs remains a significant pharmaceutical challenge. Most current drugs affect multiple immune cell types, leading to off-target effects and reduced specificity. For example, cytokines such as IL-2 can expand Tregs but may also activate effector T cells at higher doses, causing unwanted immune activation. Developing delivery systems that selectively target Tregs such as nanoparticle-based approaches is still in early stages. The key problem is achieving cell-specific targeting within a highly complex immune system. Without precise delivery mechanisms, therapeutic interventions may produce unintended systemic effects.

Nanotechnology-based drug delivery systems offer a promising solution by enabling the targeted delivery of drugs, cytokines, or genetic material directly to Tregs. These systems can improve therapeutic precision, reduce systemic toxicity, and enhance treatment efficacy. Continued research in this area is expected to significantly advance the field of Treg-based therapeutics.

Safety Concerns and Risk of Immunosuppression: While enhancing Tregs is beneficial for autoimmune diseases, excessive Treg activity can suppress protective immune responses. This creates a risk of increased susceptibility to infections and reduced anti-tumor immunity. Studies highlight that systemic expansion of Tregs may allow tumor cells to evade immune surveillance or promote chronic infections.

The fundamental challenge is maintaining a delicate balance between immune suppression and immune competence. Overcorrection can be just as harmful as under-treatment, making safety a critical concern in Treg-based therapies. Future approaches focus on controlled and localized modulation of Tregs rather than systemic enhancement. Antigen-specific therapies and targeted delivery systems are expected to minimize unwanted side effects. Careful patient monitoring and dose optimization will also play a key role in ensuring safety.

Lack of Reliable Biomarkers: Another major limitation is the absence of robust and specific biomarkers to monitor Treg function and therapeutic outcomes. Although FOXP3 is widely used as a marker, it is not entirely specific, as some activated non-regulatory T cells may transiently express it. This lack of reliable biomarkers makes it difficult to accurately measure Treg activity, predict patient response and monitor long-term efficacy. Without precise biomarkers, clinical trials and therapeutic monitoring become less reliable, slowing the advancement of Treg-based treatments [55]. Advances in multi-omics technologies, including genomics, proteomics, and

metabolomics, are enabling the discovery of more accurate biomarkers. These tools can provide detailed insights into Treg function and help in monitoring treatment responses. Improved biomarker identification will enhance clinical decision-making and accelerate the development of Treg-based therapies.

Regulatory and Clinical Translation Barriers: Finally, translating Treg therapies from research to clinical practice faces significant regulatory and logistical challenges**.** Cell-based therapies require strict compliance with Good Manufacturing Practices (GMP), extensive safety testing, and standardized protocols. Additionally, high costs, complex production processes, and lack of standardization hinder large-scale clinical implementation. Regulatory approval processes for gene-edited or engineered Tregs (e.g., CAR-Tregs) are even more stringent due to potential safety risks.

The core problem is that despite promising research results, these therapies are not yet easily accessible or scalable for routine clinical use, limiting their impact in real-world healthcare. To address these challenges, efforts are being made to standardize protocols, reduce production costs, and streamline regulatory pathways. Collaboration between academic institutions, pharmaceutical companies, and regulatory agencies is essential to facilitate the clinical implementation of these therapies [56].

CONCLUSION: Regulatory T cells (Tregs) have emerged as a fundamental component in understanding immune regulation and its application in pharmaceutical sciences. This study highlights the critical role of Tregs in maintaining immune homeostasis by preventing excessive immune responses and preserving self-tolerance. Their dysfunction is strongly associated with the development and progression of autoimmune diseases, where the immune system mistakenly targets healthy tissues, leading to chronic inflammation and tissue damage. The document emphasizes that Tregs are not only essential in disease pathogenesis but also serve as promising therapeutic targets. In autoimmune conditions, strategies aimed at enhancing or restoring Treg function can help re-establish immune balance, whereas in cancer, reducing Treg-mediated immunosuppression can improve anti-tumor immune responses. This dual role makes Tregs highly significant in the development of biologics and immunotherapies, including immune checkpoint inhibitors and cytokine-based treatments.

Furthermore, Tregs play an important role in various pharmaceutical domains such as personalized medicine, vaccine development, and pharmacovigilance. Their ability to modulate immune responses allows for the design of targeted therapies that are more precise and potentially safer than conventional treatments. Emerging approaches such as gene editing, CAR-Treg therapy, and nanotechnology-based drug delivery systems are expanding the therapeutic potential of Tregs and opening new avenues for clinical application. Despite these advancements, several challenges remain, including issues related to Treg stability, heterogeneity, targeted delivery, and safety concerns such as excessive immunosuppression. These limitations highlight the need for continued research to improve the specificity, efficacy, and scalability of Treg-based therapies. In conclusion, Tregs represent a crucial link between immunology and pharmacy, offering innovative opportunities for the development of advanced therapeutic strategies. With ongoing progress in biotechnology and precision medicine, Treg-based interventions hold great promise for transforming the treatment of autoimmune diseases, cancer, and other immune-related disorders, ultimately leading to more effective and personalized healthcare solutions.

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REFERENCES:

1. Abbas AK, Lichtman AH and Pillai S: Cellular and molecular immunology (latest edition). Cellular and molecular immunology. Elsevier.
2. Sakaguchi S, Miyara M, Costantino CM & Hafle DA: FOXP3^{+} regulatory T cells in the human immune system. Nature Reviews Immunology 2010; 10(7): 490–500.
3. Medzhitov R & Janeway CA: Innate immunity. New England Journal of Medicine 2000; 343(5): 338–344.
4. Sakaguchi S, Yamaguchi T, Nomura T & Ono M: Regulatory T cells and immune tolerance. Cell 2008; 133(5): 775–787.
5. Vignali DAA, Collison LW & Workman CJ: How regulatory T cells work. Nature Reviews Immunology 2008; 8(7): 523–532.

6. Luckheeram RV, Zhou R, Verma AD & Xia B: CD4+ T cells: differentiation and functions. Clinical and Developmental Immunology 2012; 2012: 925135.
7. Zhu J, Yamane H & Paul W: E Differentiation of effector CD4 T cell populations. Annual Review of Immunology 2010; 28: 445–489.
8. Josefowicz SZ, Lu LF & Rudensky AY: Regulatory T cells: mechanisms of differentiation and function. Annual Review of Immunology 2012; 30: 531–564.
9. Reinherz EL & Schlossman SF: The differentiation and function of human T lymphocytes. Cell 1980; 19(4): 821–827.
10. Malek TR & Bayer AL: Tolerance, not immunity, crucially depends on IL-2. Nature Reviews Immunology 2004; 4(9): 665–674.
11. Fontenot JD, Gavin MA & Rudensky AY: Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. Nature Immunology 2003; 4(4): 330–36.
12. Shevach EM: Mechanisms of foxp3+ regulatory T cell-mediated suppression. Immunity 2009; 30(5): 636–645.
13. Li MO & Flavell RA: TGF-β: a master of all T cell trades. Cell 2008; 134(3): 392–404.
14. Moore KW, de Waal Malefyt R, Coffman RL & O'Garra A: Interleukin-10 and the interleukin-10 receptor. Annual Review of Immunology 2001; 19: 683–765.
15. Letterio JJ & Roberts AB: Regulation of immune responses by TGF-β. Annual Review of Immunology 1998; 16: 137–161.
16. Wing K, Onishi Y, Prieto-Martin P, Yamaguchi T, Miyara M, Fehervari Z, Nomura T & Sakaguchi S: CTLA-4 control over Foxp3+ regulatory T cell function. Science 2008; 322(5899): 271–275.
17. Davidson A & Diamond B: Autoimmune diseases. New England Journal of Medicine 2001; 345(5): 340–350.
18. Buckner JH: Mechanisms of impaired regulation by CD4+CD25+FOXP3+ regulatory T-cells in human autoimmune diseases. Nature Reviews Immunology 2010; 10(12): 849–859.
19. Long SA & Buckner JH: CD4+FOXP3+ T regulatory cells in human autoimmunity: more than a numbers game. Journal of Immunology 2011; 187(5): 2061–2066.
20. Gough SCL & Simmonds MJ: The HLA region and autoimmune disease: associations and mechanisms of action. Current Genomics 2007; 8(7): 453–465.
21. Gregersen PK, Olsson LM & Forabosco P: Autoimmune disease genetics: a focus on genome-wide association studies. Annual Review of Genomics and Human Genetics 2012; 13: 43–65.
22. Goodnow CC, Sprent J, Fazekas de St Groth B & Vinuesa CG: Cellular and genetic mechanisms of self tolerance and autoimmunity. Nature 2005; 435(7042): 590–597.
23. Rose NR: Negative selection, epitope mimicry and autoimmunity. Current Opinion in Immunology 2016; 43: 51–55.
24. Davidson A & Diamond B: Autoimmune diseases. New England Journal of Medicine 2001; 345(5): 340–350.
25. Bluestone JA & Tang Q: How do CD4+CD25+ regulatory T cells control autoimmunity? Current Opinion in Immunology 2005; 17(6): 638–642.
26. Theofilopoulos AN, Kono DH & Baccala R: The multiple pathways to autoimmunity. Nature Immunology 2017; 18(7): 716–724.
27. Mikami N & Sakaguchi S: Regulatory T cells in human autoimmune disease and transplantation. Annual Review of Immunology 2023; 41: 593–620.
28. Ou Q, Power R & Griffin MD: Revisiting regulatory T cells as modulators of innate immune response and inflammatory diseases. Frontiers in Immunology 2023; 14: 1170548.
29. Fiyouzi T, Pelaez-Prestel HF, Reyes-Manzanas R, Lafuente EM & Reche PA: Enhancing regulatory T cells to treat inflammatory and autoimmune diseases. International Journal of Molecular Sciences 2023; 24(5): 4309.
30. Zhang A, Fan T, Liu Y, Yu G, Li C & Jiang Z: Regulatory T cells in immune checkpoint blockade antitumor therapy. Frontiers in Immunology 2024; 15: 1324567.
31. Li Y, Zhang C, Jiang A, Lin A, Liu Z and Cheng X: Potential anti-tumor effects of regulatory T cells in the tumor microenvironment. Frontiers in Immunology 2024; 15: 1345678.
32. Ge J, Yin X & Chen L: Regulatory T cells: masterminds of immune equilibrium and future therapeutic innovations. Frontiers in Immunology 2024; 15: 1357890.
33. Sumida TS, Cheru NT & Hafler DA: The regulation and differentiation of regulatory T cells and their dysfunction in autoimmune diseases. Nature Reviews Immunology 2024; 24: 123–138.
34. Malla S, Shahreen N & Saha R: Immunometabolism and immune cell regulation. Frontiers in Immunology 2025; 16: 1456789.
35. Bourassa FXP, Achar S, Altan-Bonnet G & François P: Learning the principles of T cell antigen discernment. Nature Reviews Immunology 2025; 25: 67–82.
36. Zou C, Li P, Li B, Sparwasser T & Yuan J: Next steps in regulatory T cells: Biology and clinical application. Nature Reviews Immunology 2025; 25: 145–160.
37. Tan SN, Jing Hao Jing Ge and Yazheng Yang: Regulatory T cells converted from Th1 cells in tumors suppress immunity. Nature Immunology 2025; 26: 210–222.
38. Pan Y, Zhou H and Sun Z: Tregs in cancer immunotherapy: mechanisms and applications. Frontiers in Immunology 2025; 16: 1567890.
39. Jugder BE, Park E, Du L, Jawale C, Popov N, Guo Z, Bednar KJ & Ort T: Tissue-specific roles of regulatory T cells. Nature Reviews Immunology 2025; 25: 201–218.
40. Pan Y, Zhou H, Sun Z, Zhu Y, Zhang Z, Han J, Liu Y & Wang Q: Regulatory T cells in solid tumor immunotherapy. Frontiers in Immunology 2025; 16: 1582345.
41. Pikor LA, Arivazhagan S, Mendicino M & Sathiamoorthy SS: Regulatory complexities of Treg adoptive therapy. Nature Reviews Immunology 2025; 25: 245–260.
42. Yazdanparast S, Abroun S & Rostami T: Treg strategies in hematopoietic stem cell transplantation. Frontiers in Immunology 2026; 17: 1678901.
43. Huang CH, Ku WT, Lin YC & Lin CY: Regulatory T cells: from concept to clinic. Nature Reviews Immunology 2026; 26: 85–102.
44. Saadoun D, Rosenzwajg M, Joly F, Six A, Carrat F, Thibault V, Sene D, Cacoub P & Klatzmann D: Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. New England Journal of Medicine 2011; 365(22): 2067–2077.
45. Ehrenstein MR, Evans JG, Singh A, Moore S, Warnes G, Isenberg DA & Mauri C: Compromised function of regulatory T cells in rheumatoid arthritis and reversal by anti-TNF-α therapy. Journal of Experimental Medicine 2004; 200(3): 277–285.
46. Plitas G & Rudensky AY: Regulatory T cells in cancer. Annual Review of Cancer Biology 2020; 4: 459–477.

47. Sakaguchi S, Mikami N, Wing JB, Tanaka A, Ichiyama K & Ohkura N: Regulatory T cells and human disease. Annual Review of Immunology 2020; 38: 541–566.
48. Smigiel KS, Srivastava S, Stolley JM & Campbell DJ: Regulatory T-cell homeostasis: steady-state maintenance and modulation during inflammation. Immunological Reviews 2014; 259(1): 40–59.
49. Zhou X, Bailey-Bucktrout S, Jeker LT, Penaranda C, Martinez-Llordella M, Ashby M, Nakayama M, Rosenthal W & Bluestone JA: Instability of the transcription factor Foxp3 leads to the generation of pathogenic memory T cells *in-vivo*. Nature Immunology 2009; 10(9): 1000–1007.
50. Tang Q & Bluestone JA: Regulatory T-cell therapy in transplantation: moving to the clinic. Cold Spring Harbor Perspectives in Medicine 2013; 3(11): 015552.
51. Putnam AL, Safinia N, Medvec A, Laszkowska M, Wray M, Mintz MA, Trotta E, Szot GL, Liu W, Lares A, Lee K, Laing A, Lechler RI, Riley JL, Bluestone JA, Lombardi G & Tang Q: Clinical grade manufacturing of human alloantigen-reactive regulatory T-cells for use in transplantation. American Journal of Transplantation 2013; 13(11): 3010–3020.
52. Vignali DAA, Collison LW & Workman CJ: How regulatory T cells work. Nature Reviews Immunology 2008; 8(7): 523–532.
53. Delgoffe GM, Kole TP, Zheng Y, Zarek PE, Matthews KL, Xiao B, Worley PF, Kozma SC & Powell JD: The mTOR kinase differentially regulates effector and regulatory T cell lineage commitment. Immunity 2009; 30(6): 832–844.
54. Miyara M, Yoshioka Y, Kitoh A, Shima T, Wing K, Niwa A, Parizot C, Taflin C, Heike T, Valeyre D, Mathian A, Nakahata T, Yamaguchi T, Nomura T, Ono M, Amoura Z, Gorochov G & Sakaguchi S: Functional delineation and differentiation dynamics of human $CD4^+$ T-cells expressing the FoxP3 transcription factor. Immunity 2009; 30(6): 899–911.
55. MacDonald KG, Hoeppli RE, Huang Q, Gillies J, Luciani DS, Orban PC, Broady R, Levings MK & Viswanathan S: Alloantigen-specific regulatory T cells generated with a chimeric antigen receptor. Journal of Clinical Investigation 2016; 126(4): 1413–1424.

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