WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 3, 1794-1812. Review Article ISSN 2277–7105

PERIPHERAL IMMUNE TOLERANCE

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Article Received on 05 Jan. 2026,
Article Revised on 25 Jan. 2026,
Article Published on 01 Feb. 2026,

https://doi.org/10.5281/zenodo.18481291

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How to cite this Article: *[1]Panchal Neha Rajkumar, [2]Mr. Sunil Dongre, [3]Dr. Ganesh Tolsarwad (2026). Peripheral Immune Tolerance. World Journal of Pharmaceutical Research, 15(3), 1794–1812.

ABSTRACT

Peripheral immune tolerance is a natural defense mechanism that helps the body control immune reactions outside the thymus. It prevents the immune system from attacking normal body cells and maintains immune balance. Tregs are synthesized in bone marrow and mature in the thymus. The main cells involved regulatory T cells (Tregs), which depend on the FOXP3 gene for their proper function. When this gene is disturbed then it cause immune disorders and uncontrolled inflammation can occur. Recent scientific progress, recognized by the 2025 Nobel Prize in Medicine, has explained how peripheral tolerance is controlled at the molecular level. Studies using Scurfy mouse model have shown that defects in FOXP3 lead to autoimmune diseases. Current research focuses on developing therapies that can strengthen or restore tolerance, which may help in treating autoimmune disorders and some types of cancer. This project aims to study the mechanism, role, and clinical applications of peripheral immune tolerance, highlighting its importance in drug development and disease management. The study also discusses new findings and future possibilities in immunotherapy based on tolerance regulation.

KEYWORDS: Peripheral immune tolerance, regulatory T cells, FOXP3 gene, autoimmunity, immunotherapy.

INTRODUCTION

The Immune System and Immune Tolerance

The human immune system is a highly organized defense mechanism designed to protect the body from harmful agents such as bacteria, viruses, fungi, and other pathogens. Its primary function is to identify and eliminate foreign substances, known as antigens, while leaving the body's own healthy cells unharmed. However, sometimes the immune system can mistakenly attack the body's own tissues, leading to autoimmune diseases such as rheumatoid arthritis, type 1 diabetes, and lupus.

To prevent such harmful reactions, the body relies on a process called immune tolerance, which allows the immune system to recognize self-cells and avoid attacking them. Immune tolerance is essential for maintaining immune balance and ensuring that the body is protected without causing self-damage.[1]

Types of Immune Tolerance

Immune tolerance can be broadly categorized into two types

1. **Central Tolerance**: This type occurs during the development of immune cells in primary lymphoid organs the thymus for T cells and the bone marrow for B cells. During central tolerance, self-reactive immune cells are either eliminated or inactivated before they enter the bloodstream.

2. **Peripheral Tolerance**: Some self-reactive immune cells may escape central tolerance and enter peripheral tissues. Peripheral tolerance acts as a secondary control system in organs such as the lymph nodes, spleen, and other peripheral tissues. It ensures that mature immune cells do not attack the body's own cells, thereby preventing autoimmune reactions.[2]

Regulatory T Cells (Tregs) and FOXP3 Gene

A key component of peripheral immune tolerance is the regulatory T cell (Treg). Tregs are a special type of T cells that suppress excessive immune responses and maintain immune system balance. They prevent self-reactive immune cells from attacking normal body tissues. The development and proper function of Tregs depend on the FOXP3 gene, which acts as a master regulator. Any defect in FOXP3 can lead to uncontrolled immune reactions and result in autoimmune diseases. Studies using the Scurfy mouse model have demonstrated that FOXP3 mutations lead to severe autoimmune conditions, highlighting its importance in maintaining immune homeostasis.[3]

The 2025 Nobel Prize in Physiology or Medicine, awarded to Mary E. Brunkow, Fred Ramsdell, and Shimon Sakaguchi. Their groundbreaking work elucidated how the immune system prevents self- damage through the action of Tregs and the FOXP3 gene.[4]

Shimon Sakaguchi discovered the existence of Tregs and demonstrated their importance in preventing autoimmune diseases.

Mary E. Brunkow and Fred Ramsdell identified the FOXP3 gene and revealed its critical role in the development and function of Tregs.

Their collective research has not only enhanced our understanding of immune regulation but also paved the way for new therapeutic strategies targeting Tregs to treat autoimmune diseases, improve transplant acceptance, and enhance cancer immunotherapy.

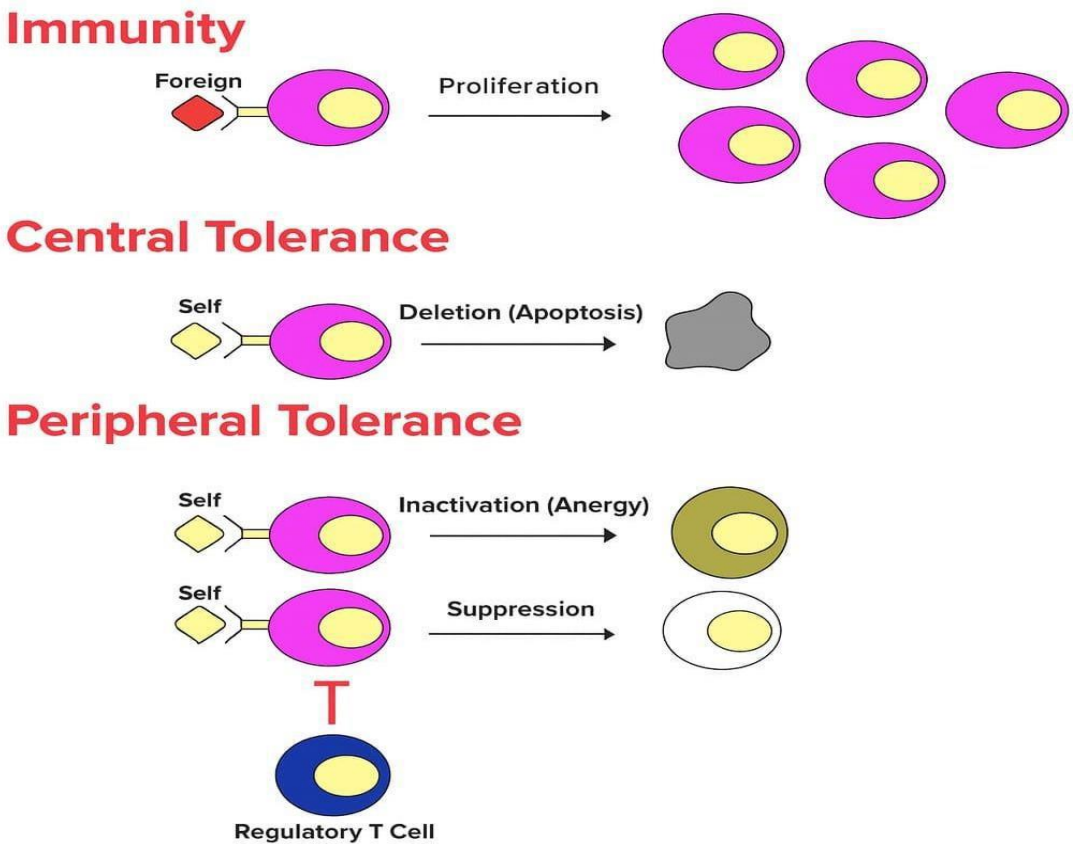


Figure No. 1: Mechanisms of immune tolerance.[5]

1. Immunity: The immune system detects foreign antigens (virus/bacteria).Immune cells become activated and multiply. These increased cells fight and remove the infection. (The immune system attacks foreign substances to protect the body.

2. Central Tolerance: Happens in thymus and bone marrow. Immature immune cells that react to self- antigens are destroyed (apoptosis).(Harmful self-reactive cells are removed early to prevent autoimmune diseases.)

3. Peripheral Tolerance: Some self-reactive cells escape central tolerance.

a. Anergy: Self-reactive cells are inactivated and cannot attack. They remain alive but stay switched off.

b. Suppression (Tregs): Regulatory T cells suppress harmful immune cells and stop damage. Tregs act like immune system police.

HISTORY

1. 1945 – Natural Tolerance Observed

R. D. Owen observed that dizygotic twin cattle sharing a placenta maintained a mixture of each other's red blood cells for life. This was the first evidence that the immune system can tolerate "foreign" cells under certain conditions.

2. 1945 – Beginning of Immune Tolerance Concept

Scientists like **Frank Macfarlane Burnet** introduced the idea that the immune system can learn to tolerate self-antigens. This was the foundation for understanding self vs. non-self recognition.

3. 1953 – Acquired Tolerance (Sir Peter Medawar)

Sir **Peter Medawar** and his team discovered that immune tolerance can be acquired experimentally in animals. Their transplantation studies explained why some grafts are accepted while others are rejected. This discovery earned Medawar the Nobel Prize in 1960.

4. 1987 – Discovery of CTLA-4 (Brunet et al.)

Pierre Golstein and **Philippe Brunet** identified CTLA-4, a molecule that acts as an immune "brake". It helps stop T cells from overreacting and maintains peripheral tolerance.

5. 1992 – Discovery of PD-1 (Tasuku Honjo)

Dr. Tasuku Honjo discovered PD-1, another inhibitory receptor on T cells. It plays a vital role in preventing autoimmunity and maintaining immune balance.

6. 1995 – Discovery of Regulatory T Cells (Dr. Shimon Sakaguchi)

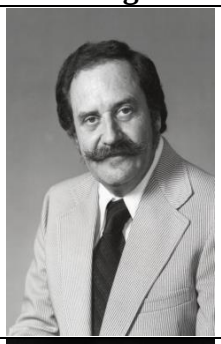
Dr. Shimon Sakaguchi identified $CD4^+CD25^+$ Regulatory T cells (Tregs) that suppress immune overactivation. These cells are essential for maintaining self-tolerance and preventing autoimmune diseases.

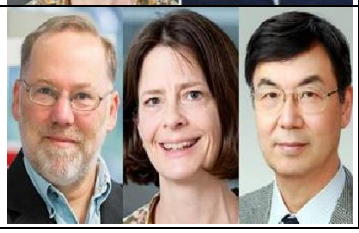
7. 2001–2003 – FOXP3 Gene Discovery (Bennett, Ramsdell & Chatila)

Bennett, Ramsdell, and **Chatila** linked the FOXP3 gene to the development of Tregs. Mutation in FOXP3 causes IPEX syndrome, proving its central role in immune regulation.

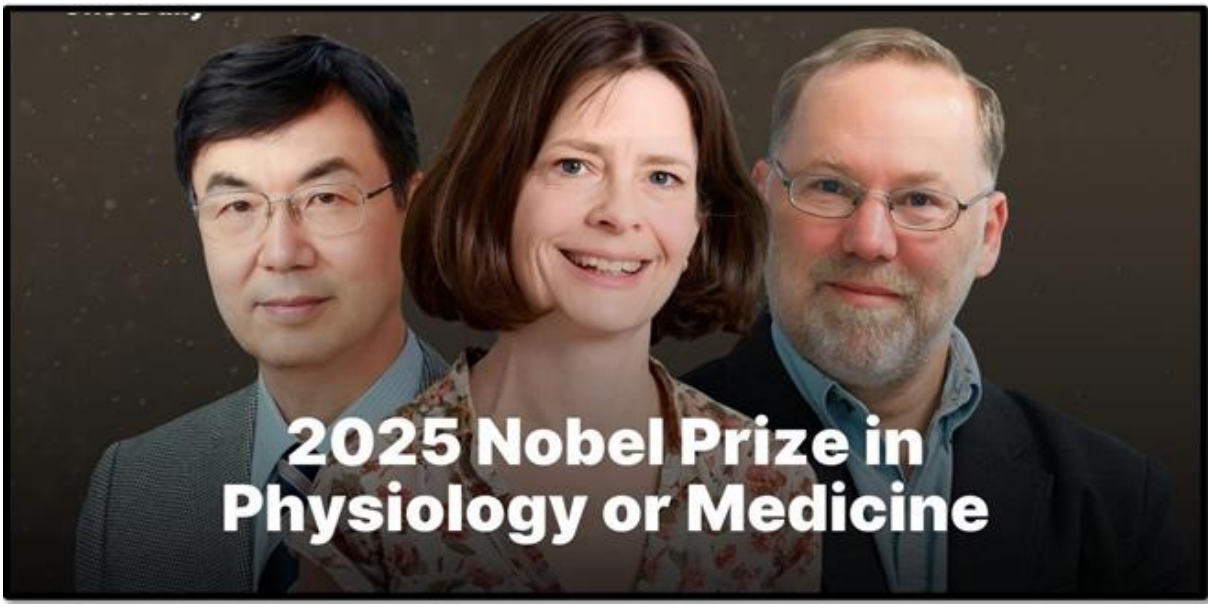
8. 2020–2025 – Modern Advances & Nobel Recognition Research continued linking Tregs, CTLA-4, and PD-1 to autoimmune diseases, infections, and cancer. In 2025, scientists working on Regulatory T cells and Peripheral Tolerance received the Nobel Prize, highlighting its major role in immunology and therapy.

Table No. 1: History of Peripheral Immune Tolerance.[1-6]

Year	Scientist name	Image	Discovery	Nobel prize
1945	R. D. Owen		Natural Tolerance Observed R.D. Owen observed that dizygotic twin cattle sharing a placenta maintained a mixture of each other's red blood cells for life. This was the first evidence that the immune system can tolerate "foreign" cells under certain conditions.	N/A
1949	Frank Macfarlane Burnet		Proposed Clonal Selection Theory, explaining how the immune system distinguishes self from non self.	Nobel Prize in Physiology or Medicine, 1960
1953	Peter Medawar		Demonstrated acquired immune tolerance in mice using skin grafts.	Nobel Prize in Physiology or Medicine, 1960
1970	Various immunologist		Concept of central and peripheral tolerance development.	N/A

1995	Shimon Sakaguchi		Identified Regulatory T cells (Tregs) that suppress autoimmune responses.	N/A (Later recognized widely)
2000	Mary Brunkow & Fred Ramsdell		Discovered FOXP3 gene, essential for Treg development and function.	N/A (Significant impact on autoimmune research)
2025	Mary Brunkow, Fred Ramsdell & Shimon Sakaguchi		Awarded Nobel Prize in Physiology or Medicine for discoveries on Peripheral Immune Tolerance, include Tregs and FOXP3.	Nobel Prize in Physiology or Medicine, 2025.

NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE 2025



In 2025, the Nobel Prize in Physiology or Medicine was awarded to Mary E. Brunkow, Fred Ramsdell, and Shimon Sakaguchi for their remarkable discoveries about Peripheral Immune Tolerance a vital process that keeps our immune system from attacking our own body.

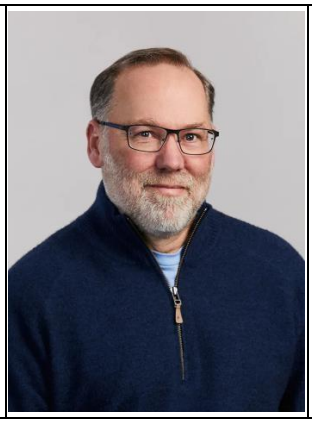
Their research explained how the immune system learns to “tolerate” our own tissues through specialized cells called Regulatory T cells (Tregs). These cells act like “police” of the immune system they control immune responses and prevent autoimmune reactions.

Their findings opened up new areas of research and helped in developing new treatments for many diseases such as

- Autoimmune disorders (e.g., Type 1 diabetes, rheumatoid arthritis)
- Cancer (by regulating immune checkpoints)
- Transplant rejection prevention

This discovery has greatly improved our understanding of how the body maintains immune balance (homeostasis) and protects itself from self-destruction.[7]

Table No. 2: Scientist information.[7]

Scientist			
Scientist Name	Mary E. Brunkow (American)	Fred Ramsdell (American)	Shimon Sakaguchi (Japanese)
Discovery Contribution	Studied genetic factors (like FOXP3 gene) affecting RegulatoryT cells.	Showed how FOXP3 controls the development and function of Tregs.	Discovered Regulatory T cells (Tregs) and their role in preventing autoimmune reactions.
Importance	Helped explain how immune tolerance is genetically controlled.	Key to understanding the mechanism of peripheral immune tolerance.	Foundation of the field of peripheral immune tolerance; important for disease treatment.

Awarded

Mary E. Brunkow (USA), Fred Ramsdell (USA), Shimon Sakaguchi (Japan)

INTRODUCTION

The human immune system is a highly advanced defense network. It continuously protects the body from invading microorganisms like bacteria, viruses, and parasites. However, it must also be able to distinguish between “self” and “non-self”. If this distinction fails, the immune system may begin to attack the body’s own cells and tissues, leading to autoimmune diseases such as type 1 diabetes, rheumatoid arthritis, or multiple sclerosis. To prevent this, the body has mechanisms called immune tolerance which help in recognizing and accepting

self-antigens.

There are two main types

Central Tolerance – occurs in the thymus.

Peripheral Tolerance – occurs outside the thymus, in peripheral tissues.

The 2025 Nobel Prize in Physiology or Medicine was awarded to Mary E. Brunkow, Fred Ramsdell, and Shimon Sakaguchi for their discoveries explaining how peripheral immune tolerance functions, through the identification and understanding of Regulatory T cells (Tregs) and the FOXP3 gene.

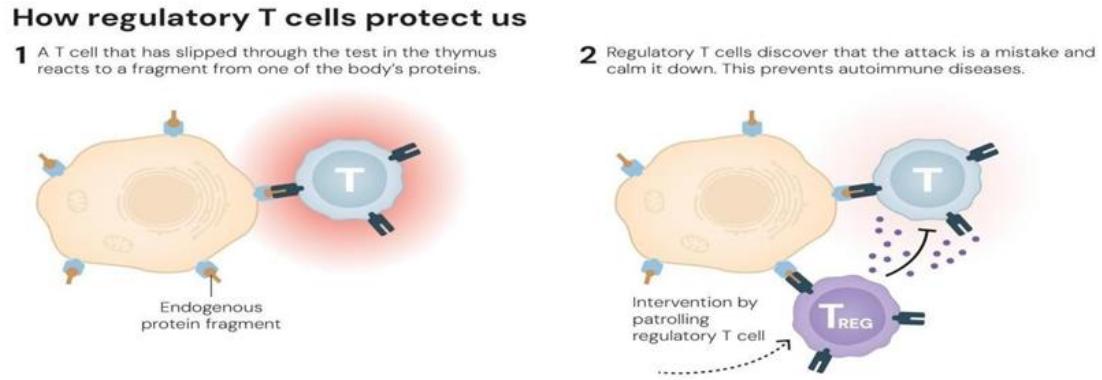


Figure No. 2: Tregs are white blood cells that regulate your immune system response.[8]

Background of Discovery

Earlier, scientists believed that self-reactive T cells were completely removed during their development in the thymus. This is known as central immune tolerance. However, researchers observed that some T cells that react to self-antigens still exist in healthy individuals. This observation raised a critical question why doesn't the immune system attack our body continuously? This question led to the discovery of an additional safety mechanism — Peripheral Immune Tolerance, which acts as a second checkpoint to control self-reactive T cells outside the thymus.

Shimon Sakaguchi's Discovery: – Regulatory T Cells

In the early 1980s, Shimon Sakaguchi from Japan observed something unusual in mice experiments. When the thymus gland was removed from newborn mice, their immune system became hyperactive, leading to severe autoimmune disorders. Sakaguchi hypothesized that there must be a special type of T cell that prevents such immune overreaction "security guard" cells that keep other immune cells under control. After several years of work, in 1995,

Sakaguchi discovered a new subset of T cells, which had both CD4 and CD25 proteins on their surface. He named them Regulatory T Cells.[9]

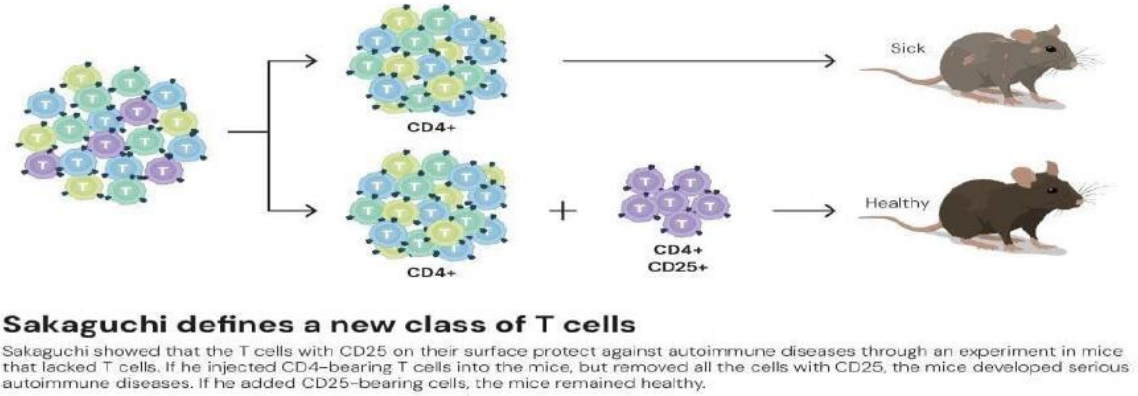


Figure No. 3: Cells regulating the immune system.[8]

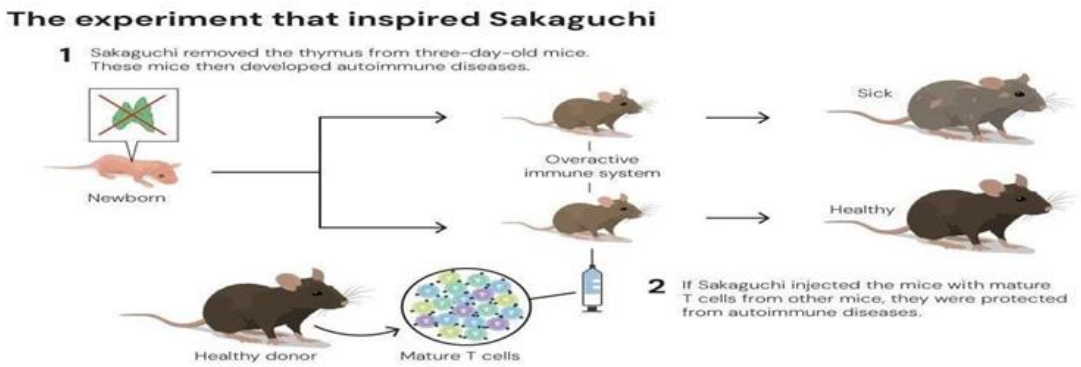


Figure No. 4: The Experiment That Inspired Sakaguchi.[8]

Function

Tregs suppress overactive immune responses.

They prevent normal immune cells from attacking self-tissues. They maintain immune homeostasis and self-tolerance.

This discovery provided the foundation for understanding peripheral immune tolerance.

Mary Brunkow and Fred Ramsdell's Contribution

The FOXP3 Gene during the 1990s, two American scientists, Mary E. Brunkow and Fred Ramsdell, studied a strange strain of mice called Scurfy mice. These mice had scaly skin, enlarged lymph nodes, and died young due to uncontrolled autoimmune disease. Brunkow and Ramsdell found that the disease was caused by a mutation in a gene on the X chromosome, which they later named FOXP3 (Forkhead Box P3). They later discovered that

mutations in the human version of this gene cause a severe autoimmune disorder known as IPEX Syndrome (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome). This proved that FOXP3 is essential for immune regulation in both mice and human.[8-9]

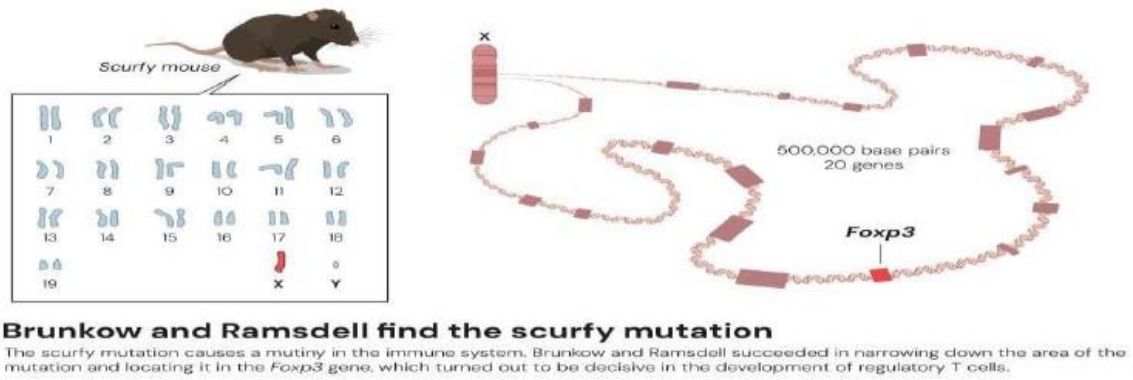


Figure No. 5: Brunkow and Ramsdell find the scurfy mutation.[8]

Connection between FOXP3 and Regulatory T Cells

In 2003, Sakaguchi and other scientists established that the FOXP3 gene is the master control gene for the development and function of Regulatory T Cells. Without FOXP3, Tregs cannot develop properly. As a result, the immune system loses its control and begins attacking self-tissues. Thus, FOXP3 and Tregs together form the biological basis of Peripheral Immune Tolerance.[10]

Table No. 3: Mechanism of Peripheral Immune Tolerance.[11]

Step	Process	Explanation
1	Central tolerance (in thymus)	Most self-reactive T cells are destroyed during maturation.
2	Escape of some self-reactive T cells	A few harmful T cells survive and enter the bloodstream.
3	Regulatory T cells (Tregs) activation	Tregs detect and suppress these self-reactive T cells in peripheral tissues
4	FOXP3 gene control	FOXP3 directs the development and suppressive function of Tregs.
5	Immune balance maintained	Tregs ensure the immune system attacks pathogens but not self-tissues.

MECHANISM OF PERPHERAL IMMUNE TOLERANCE

Peripheral immune tolerance involves several mechanisms that work together to prevent the immune system from attacking the body's own cells and tissues. It acts after lymphocytes (T and B cells) have fully matured and moved out of the central lymphoid organs such as the

thymus and bone marrow. The main goal of this mechanism is to inactivate or control those immune cells that mistakenly recognize self-antigens.

The mechanisms of peripheral immune tolerance can be broadly divided into three main processes.

1. Anergy (Functional Inactivation)

Anergy means the "non-responsiveness" of immune cells. When a T cell or B cell recognizes a self-antigen without receiving a proper second signal (co-stimulation), it becomes inactive or anergic.

In normal immune activation, two signals are needed

1) The first signal comes from the recognition of the antigen by the T-cell receptor (TCR).
2) The second signal comes from co-stimulatory molecules such as CD28 binding to B7 on antigen- presenting cells (APCs).

If the second signal is absent, the T cell does not become activated and enters a state of anergy. This mechanism helps ensure that self-reactive T cells in the periphery do not cause autoimmune reactions.

2. Clonal Deletion (Apoptosis of Self-Reactive Cells)

Clonal deletion is the process by which self-reactive immune cells are removed through programmed cell death (apoptosis).When T cells repeatedly recognize self-antigens without proper activation signals, they undergo apoptosis through pathways involving Fas–Fas ligand interactions. This deletion prevents self-reactive cells from surviving and damaging tissues. This mechanism is particularly important in maintaining tolerance toward self-antigens that are continuously present in the body.

3. Suppression by Regulatory T Cells (Tregs)

Regulatory T cells (Tregs) play the most crucial role in maintaining peripheral tolerance. These cells are identified by the presence of CD4, CD25, and FOXP3 markers. Tregs control the immune system by directly suppressing the activation and proliferation of self-reactive T cells.

They do this by

Releasing inhibitory cytokines such as IL-10, IL-35, and TGF-β, which reduce immune cell activity. Modifying antigen-presenting cells (APCs) to make them less stimulatory.

Consuming interleukin-2 (IL-2), a growth factor required for T-cell survival, which limits the growth of other T cells.

The FOXP3 gene is the master regulator of Treg cell development and function. Mutations in FOXP3 lead to a loss of Treg function, resulting in autoimmune diseases like IPEX syndrome (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome).[12]

4. Peripheral B Cell Tolerance

Although most studies focus on T cells, B cells also have peripheral tolerance mechanisms. Self- reactive B cells can become anergic, undergo apoptosis, or be controlled by regulatory T cells. These processes prevent the production of autoantibodies that could damage self-tissues.[13]

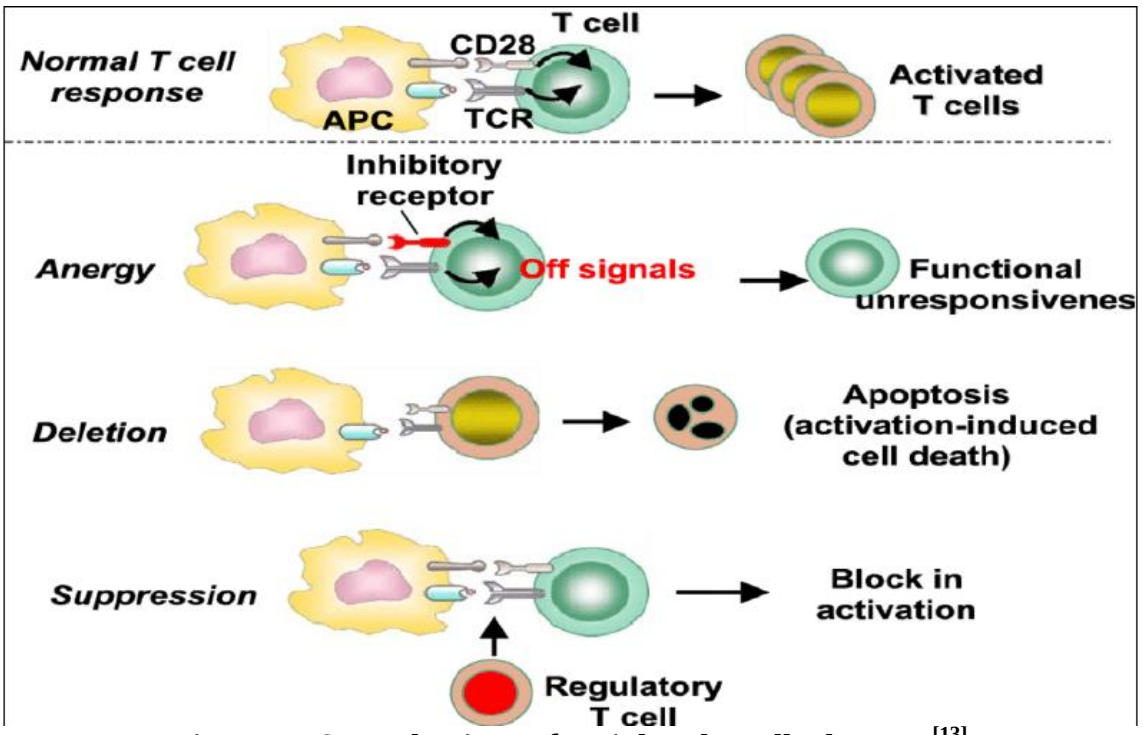


Figure No.6: Mechanisms of peripheral T cell tolerance.[13]

ROLE OF PERIPHERAL IMMUNE TOLERANCE IN AUTOIMMUNE DISEASE

Peripheral immune tolerance is crucial for preventing the immune system from attacking self-tissues. When these tolerance mechanisms fail, self-reactive lymphocytes can initiate immune responses against the body, leading to autoimmune diseases. Below are major examples and how peripheral tolerance affects them. Peripheral immune tolerance is the body's way of stopping the immune system from attacking its own tissues. When this system fails, immune cells can mistakenly attack the body, causing autoimmune diseases.[14]

1. Type 1 Diabetes Mellitus (T1DM)

What happens: Immune cells attack the insulin-producing β-cells in the pancreas, causing low insulin.

Role of peripheral tolerance: Normally, Tregs (regulatory T cells) stop immune cells from attacking β- cells. In T1DM, Tregs don't work well, or attacking cells resist control, leading to β-cell destruction.

Clinical importance: Treatments that boost Tregs or tolerance may help prevent or delay T1DM.

2. Rheumatoid Arthritis (RA)

What happens: Immune system attacks joints, causing inflammation and damage.

Role of peripheral tolerance: Loss of Treg control allows immune cells to produce too many inflammatory chemicals (like TNF-α and IL-6). Dendritic cells that usually promote tolerance are also not working properly.

Clinical importance: Drugs like abatacept work by improving tolerance signals to reduce joint inflammation.

3. Systemic Lupus Erythematosus (SLE)

What happens: Immune system attacks skin, kidneys, joints, and other organs.

Role of peripheral tolerance: Tregs don't work properly, and self-reactive immune cells aren't eliminated. This, plus an imbalance of cytokines (low anti-inflammatory IL-10, high inflammatory interferons), worsens disease.

Clinical importance: Treatments aim to restore Treg function or balance the immune system using special vaccines or cytokines.

4. Multiple Sclerosis (MS)

What happens: Immune cells attack the myelin covering nerves in the brain and spinal cord, causing nerve damage.

Role of peripheral tolerance: Tregs are low or not working properly, so attacking cells overreact. Other immune checkpoints also fail, letting disease progress.

Clinical importance: Therapies focus on increasing Treg numbers or improving their function to protect nerves.

5. Mechanisms Leading to Loss of Peripheral Tolerance in Autoimmune Diseases

- **Treg problems**: Too few Tregs or weak suppression of harmful cells.

- **Cytokine imbalance**: Too many inflammatory signals, too few calming signals.
- **Defective cell death**: Harmful self-reactive cells are not eliminated.
- **Weak tolerogenic dendritic cells**: They can't teach Tregs properly.
- **Checkpoint problems**: Pathways like CTLA-4 or PD-1 fail, allowing immune cells to attack freely.

ROLE OF PERIPHERAL IMMUNE TOLERANCE IN CANCER

Cancer cells have the ability to evade immune detection and destruction by exploiting peripheral immune tolerance mechanisms. While tolerance is essential to prevent autoimmunity, its dysregulation can allow tumor cells to survive and grow.

1. Tumor Immune Evasion via Tregs

Mechanism: Tumors attract regulatory T cells (Tregs) that stop killer T cells ($CD8^+$) and NK cells from attacking the cancer. Tregs release IL-10 and TGF-β to block the immune response.

Clinical Importance: More Tregs in tumors usually mean worse outcomes in cancers like breast, lung, and pancreatic cancer.

2. Immune Checkpoint Exploitation

Mechanism: Tumor cells use checkpoints like PD-1/PD-L1 and CTLA-4 to switch off T cells and help Tregs suppress immunity.

Clinical Importance: Drugs called checkpoint inhibitors can block these signals and reactivate T cells to fight cancer.

3. Tolerogenic Dendritic Cells (DCs) in Tumors

Mechanism: Tumors change dendritic cells so they encourage Tregs instead of attacking T cells. They show tumor antigens in a way that makes T cells "ignore" the tumor.

Clinical Importance: Targeting these DCs can help the immune system recognize and attack cancer.

4. Cytokine-Mediated Immune Suppression

Mechanism: Tumors release cytokines (IL-10, TGF-β, VEGF) that make the immune environment weak and support Tregs.

Clinical Importance: Blocking these cytokines can boost immune attack on the tumor.

5. Tumor Antigen-Specific Tolerance

Mechanism: Tumor antigens look like normal body proteins, so the immune system ignores them.

Clinical Importance: Breaking this tolerance is important for cancer immunotherapy.

6. Therapeutic Implications

Understanding peripheral immune tolerance in cancer has led to novel therapies

- **Checkpoint Blockade Therapy:** Anti-PD-1, Anti-PD-L1, and Anti-CTLA-4 antibodies restore T cell activity.
- **Treg Depletion:** Drugs targeting Tregs or their suppressive cytokines can enhance anti-tumor immunity.
- **Tolerogenic Vaccine Strategies:** Manipulating dendritic cells or antigens to break tolerance selectively against tumor cells.
- **Combination Therapy:** Combining checkpoint inhibitors with chemotherapy, radiotherapy, or Treg-targetin agents improves efficacy.[15]

THERAPEUTIC APPLICATION OF PERIPHERAL IMMUNE TOLERANCE

Peripheral immune tolerance mechanisms are not only important for preventing autoimmunity but also play a key role in designing modern therapies for autoimmune diseases, cancer, and other immune- related disorders. Scientists have developed strategies to enhance or modulate peripheral tolerance for therapeutic benefit.

1. Treg-Based Therapies

Mechanism: Increase the number or function of regulatory T cells (Tregs) to suppress harmful immune responses.

Clinical Importance: Helps treat autoimmune diseases like Type 1 Diabetes, Rheumatoid Arthritis, and Multiple Sclerosis; also used to prevent organ transplant rejection.

2. Cytokine Modulation

Mechanism: Administer cytokines like IL-10, TGF-β, or drugs that boost their activity to enhance immune tolerance.

Clinical Importance: Low-dose IL-2 therapy selectively expands Tregs in autoimmune patients to reduce inflammation.

3. Immune Checkpoint Modulation

Mechanism: Enhance checkpoint signals (CTLA-4, PD-1) in autoimmunity to suppress T cells; block checkpoints in cancer to reactivate T cells.

Clinical Importance: Anti-CTLA-4 and Anti-PD-1 antibodies are used in cancer immunotherapy; potential use in autoimmune disease treatment.

4. Tolerogenic Vaccines

Mechanism: Teach the immune system to ignore specific antigens instead of attacking them.

Clinical Importance: Peptide-based tolerogenic vaccines for Type 1 Diabetes and allergy treatments are in clinical trials.

5. Tolerogenic Dendritic Cell (DC) Therapy

Mechanism: Modify DCs to promote Tregs and suppress autoreactive T cells.

Clinical Importance: Tested in clinical trials for Rheumatoid Arthritis and Multiple Sclerosis.

6. Small Molecule Drugs

Mechanism: Drugs like rapamycin increase Treg activity and reduce harmful effector T cells.

Clinical Importance: Enhances immune tolerance in autoimmune diseases.

7. Medical Importance

- **Autoimmune Diseases**: Boosting Tregs helps control diseases like Type 1 Diabetes, Multiple Sclerosis, and Rheumatoid Arthritis.
- **Cancer Immunotherapy**: Blocking Tregs around tumors helps the immune system attack cancer cells.
- **Organ Transplantation**: Increasing Tregs prevents organ rejection.
- **Gene Therapy**: Modifying FOXP3 or Tregs can correct immune imbalances in genetic immune disorders.[16-17]

FUTURE PROSPECTS

Peripheral immune tolerance is a critical mechanism that maintains immune balance, preventing the immune system from attacking the body's own tissues while allowing defense against pathogens and abnormal cells. Recent research (up to 2025) has significantly improved our understanding of how Tregs, tolerogenic dendritic cells, cytokines, and immune checkpoints work together to maintain this balance.

1. **New ways to control autoimmune diseases**

Researchers hope to use tolerance pathways to calm down only the harmful immune cells, so the body stops attacking itself without weakening the whole immune system.

2. **Improving Regulatory T cells (Tregs)**

In the future, doctors may boost or increase Tregs inside the body to help keep the immune system balanced and prevent unnecessary inflammation.

3. **Treg cell therapy**

Scientists may take a patient's Tregs, expand them in the lab, make them more powerful, and return them to the patient to control diseases caused by overactive immunity.

4. **Better organ transplant success**

By strengthening peripheral tolerance, doctors may reduce the chances of organ rejection so that patients need fewer long-term anti-rejection medicines.

5. **Smarter cancer therapies**

Tumors sometimes use tolerance mechanisms to hide from the immune system. Future treatments may block this "hiding," helping the immune system attack cancer cells more effectively.

6. **More personalized treatments**

As we understand tolerance better, each person may receive treatments tailored to their immune response, making therapies more effective and safer.[18-19]

CONCLUSION

The work of Mary Brunkow, Fred Ramsdell, and Shimon Sakaguchi showed how the body has a second line of immune control called Peripheral Immune Tolerance. They discovered that Regulatory T Cells (Tregs), controlled by the FOXP3 gene, protect the body from attacking itself. This understanding has changed immunology and helped develop new treatments for autoimmune diseases, cancer, and organ transplants.

How it works: Tregs stop harmful immune reactions and keep the immune system balanced. The FOXP3 gene is essential for making Tregs and keeping them functional. By studying Tregs and FOXP3, scientists hope to develop therapies for diseases like diabetes, arthritis, and lupus.

In cancer: Tumors can use Tregs to avoid being attacked by the immune system. Too many active Tregs can stop the body from fighting cancer. Learning how FOXP3 and Tregs work has helped create immunotherapies that reduce this suppression and strengthen anti-cancer responses.

In HIV/AIDS: The virus damages $CD4^+$ T cells, including Tregs, which disrupts immune balance and leads to chronic inflammation. HIV also affects FOXP3 and Treg function. Understanding these effects helps design treatments to restore immune regulation and improve health in HIV patients.

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