T-cell activation in autoimmune diseases: A double-edged sword.

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Introduction

T cells are pivotal to immune defense, responsible for identifying and eliminating pathogens. However, their activation is a tightly regulated process that, if dysregulated, can lead to autoimmune diseases. In such cases, T cells mistakenly target the body's own tissues, resulting in chronic inflammation and tissue damage. While T-cell activation is necessary for immune protection, its inappropriate activation becomes a double-edged sword—providing defense on one side and contributing to disease on the other. This article explores the mechanisms of T-cell activation, its role in autoimmunity, and how modern therapies aim to restore balance [1].

T-cell activation begins when antigen-presenting cells (APCs), such as dendritic cells, display antigens using major histocompatibility complex (MHC) molecules. This process involves: The T-cell receptor (TCR) recognizes a specific antigen presented by MHC on the APC. Costimulatory molecules (e.g., CD28 on T cells binding to CD80/86 on APCs) provide necessary activation signals [2].

Cytokines guide the differentiation of T cells into functional subsets (Th1, Th2, Th17, Treg, etc. If all three signals are present, T cells proliferate and perform effector functions. In the absence of regulatory mechanisms, this process can become pathogenic [3].

Autoimmune diseases such as multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and type 1 diabetes (T1D) are driven in part by autoreactive T cells that escape central and peripheral tolerance. The breakdown of tolerance mechanisms—such as thymic deletion of autoreactive cells or suppression by regulatory T cells—allows pathogenic T cells to persist and become activated [4].

In MS, for example, autoreactive CD4+ T cells target myelin proteins, leading to demyelination in the central nervous system (CNS). In T1D, cytotoxic CD8+ T cells destroy insulin-producing beta cells in the pancreas. In each of these cases, T-cell activation contributes to the pathology. Promote inflammation through interferon-gamma (IFN-γ) production and are implicated in RA and MS [5].

Secrete IL-17, driving chronic inflammation in psoriasis and inflammatory bowel disease (IIBD). Normally suppress immune responses. Reduced Treg function is common in many autoimmune. Genetic susceptibility (e.g., HLA-DR alleles) plays a key role in determining an individual's risk of autoimmunity. However, environmental factors such as infections, microbiota imbalance, stress, and toxins can also initiate or exacerbate T-cell activation against self-antigens [6].

Molecular mimicry where foreign antigens resemble self-antigens can cause T cells initially activated against pathogens to attack host tissues. This has been proposed as a mechanism in Guillain-Barré syndrome following Campylobacter infection [7].

Drugs like abatacept inhibit the CD28-CD80/86 interaction, preventing full T-cell activation in diseases like RA. IL-17 and IL-6 inhibitors have shown effectiveness in controlling Th17-driven inflammation in psoriasis and RA. While checkpoint inhibitors like anti-PD-1 enhance T-cell activation in cancer, the reverse approach enhancing checkpoints may suppress T cells in autoimmunity [8].

Emerging therapies aim to retrain T cells to tolerate specific self-antigens using peptide-based vaccines or tolerogenic dendritic cells. Suppressing T-cell activity to prevent autoimmunity risks impairing host defense against infections and tumors. This makes precise modulation rather than broad immunosuppression critical. The complexity of T-cell signaling pathways, plasticity of T-cell subsets, and individual variation in immune profiles complicate therapeutic strategies [9].

Restoring immune balance without compromising overall immunity remains the ultimate goal. This will likely require a combination of therapies tailored to the patient's immunological and genetic background. Advances in genomics, single-cell sequencing, and machine learning are helping to identify personalized biomarkers for predicting disease onset and treatment response. Novel agents targeting intracellular signaling molecules (e.g., JAK inhibitors) and cellular therapies using expanded Tregs are currently under investigation [10].

Conclusion

T-cell activation is a critical process for immune defense, but when misdirected, it becomes a potent driver of autoimmune disease. Understanding the dual role of T cells—as protectors and potential aggressors—has led to significant therapeutic advances. Ongoing research promises even more refined strategies to modulate T-cell activity, offering hope for better outcomes in autoimmune conditions.

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***Received:** 03-Apr-2025, Manuscript No. AAJCIT-25-163920; **Editor assigned:** 04-Apr-2025, Pre QC No. AAJCIT-25-163920(PQ); **Reviewed:** 17-Apr-2025, QC No AAJCIT-25-163920; **Revised:** 21-Apr-2025, Manuscript No. AAJCIT-25-163920(R); **Published:** 28-Apr-2025, DOI:10.35841/aajcit-8.2.264*

***Citation:** Han Y. T-cell activation in autoimmune diseases: A double-edged sword. J Cancer Immunol Ther. 2025;8(2):264*

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Citation: *Han Y. T-cell activation in autoimmune diseases: A double-edged sword. J Cancer Immunol Ther. 2025;8(2):264*