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Autoimmune Diseases Primarily Mediated by Cellular Immunity—Mechanisms and Recent Treatment Advances

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Abstract

Autoimmune diseases primarily mediated by cellular immunity, classified as type IV hypersensitivity disorders, are driven by dysregulated T cell responses resulting in targeted tissue destruction. Unlike antibody-dominant autoimmune conditions, these disorders involve autoreactive $CD4^+$ and $CD8^+$ T cells that infiltrate tissues, amplify inflammatory cascades, and promote chronic organ damage through cytokine release and direct cytotoxicity. Representative diseases include type 1 diabetes mellitus (T1DM), multiple sclerosis (MS), rheumatoid arthritis (RA; with substantial T cell involvement), and inflammatory bowel disease (IBD). Their etiology reflects a multifactorial breakdown of central and peripheral tolerance, involving genetic susceptibility, environmental triggers, and regulatory T cell (Treg) dysfunction. Advancements in molecular immunology have accelerated the development of targeted therapies, ranging from Janus kinase (JAK) inhibitors and biologics to innovative chimeric antigen receptor (CAR) T cell-based strategies aimed at immune reset and durable remission. This editorial summarizes current mechanistic insights and highlights emerging therapeutic progress up to late 2025, with emphasis on strategies reshaping disease prognosis and management in refractory cases.

Keywords: Autoimmune diseases, Cellular immunity, T cells, Therapy, Treatment, CAR-T

Introduction

Autoimmune diseases collectively affect millions worldwide, with T cell-mediated immunity contributing substantially to the pathogenesis of many organ-specific and systemic disorders [1,2]. In contrast to classical antibody-mediated autoimmunity, cellular-mediated disease is characterized by delayed-type hypersensitivity reactions in which autoreactive T cells orchestrate inflammation and induce direct tissue destruction. Prototypical examples include type 1 diabetes mellitus (T1DM), multiple sclerosis (MS), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD), where pathogenic T cell subsets infiltrate target tissues, activate resident immune and stromal cells, and sustain chronic inflammation that progressively compromises organ function.

Disease onset reflects the convergence of genetic predisposition—frequently linked to HLA class I/II alleles and immune signaling variants—and environmental factors that disrupt immune tolerance [1,3]. Failures in both central tolerance (negative selection in the thymus) and peripheral tolerance mechanisms (Treg dysfunction, anergy defects, impaired deletion) allow autoreactive clones to persist and expand. Subsequent exposure to triggers such as infection, molecular mimicry, dysbiosis, or—less commonly—non-specific vaccination responses may precipitate clinical disease by intensifying effector T cell activity.

Recent advances in immunopathology have redefined our understanding of these processes, revealing a spectrum of pathogenic T cell phenotypes, including hyperinflammatory Th17 cells, cytotoxic $CD8^+$ populations, and tissue-resident memory T cells that sustain organ-specific autoimmunity. These insights are now directly informing therapeutic

innovation, enabling precision strategies that modulate defined pathways rather than broadly suppressing immune function. This editorial outlines the mechanistic basis of T cell-mediated autoimmunity and evaluates corresponding therapeutic progress, with emphasis on treatment paradigms shaping clinical practice.

Pathogenic Mechanisms

Breakdown of immune tolerance—refined

Under physiological conditions, autoreactive T cells are eliminated during thymic development (central tolerance) or controlled in the periphery through mechanisms including Treg-mediated suppression, anergy induction, and activation-induced cell death [1]. In cellular-mediated autoimmune diseases, these regulatory systems fail, permitting autoreactive clones to persist and expand. Contributing defects include impaired Treg function, altered antigen presentation, dysregulated co-stimulatory signaling, and molecular mimicry following environmental exposure [1–3].

1. **CD4⁺ T cells:** Autoreactive CD4⁺ subsets differentiate predominantly into Th1 and Th17 lineages. Th1 cells secrete IFN-γ and promote macrophage activation, whereas Th17 cells produce IL-17/IL-22 and recruit neutrophils to inflamed tissues [4–6]. Recent work highlights Th17 plasticity, with ex-Th17 cells acquiring IFN-γ expression and pathogenic profiles in MS and RA, bridging traditional Th1/Th17 classifications [5,6].

2. **CD8⁺ T cells:** Cytotoxic CD8⁺ T cells directly induce apoptosis of target cells via perforin/granzyme and Fas–FasL pathways. Emerging evidence suggests that perforin-mediated granzyme delivery is often the dominant mechanism in T1DM and neuroinflammatory models, enabling rapid cell killing and amplifying tissue destruction [7,8].

3. **Cytokine network dysregulation:** Excess proinflammatory cytokines—such as IFN-γ, TNF-α, IL-6, and IL-17—augmented by insufficient counter-regulatory IL-10 and TGF-β from Tregs, create a self-sustaining inflammatory microenvironment that perpetuates disease [4–7].

Role of infection and vaccination

External immune stimuli can modulate disease course in individuals with established or latent autoimmune predisposition. Infectious agents containing high epitope diversity may stimulate robust Th1-dominant responses and generate cross-reactive T cells through molecular mimicry, often precipitating disease onset or exacerbation in susceptible hosts [9–11]. In parallel, certain whole-pathogen vaccines (e.g., attenuated or inactivated formulations) may induce broad immune activation, particularly when paired with potent adjuvants designed to enhance cellular immunity [12–14]. While this is advantageous for pathogen-specific protection, it may contribute to heightened immune reactivity in individuals with pre-existing autoimmune tendencies.

Antigen-focused vaccines (e.g., subunit, peptide, or recombinant platforms) reduce exposure to non-essential proteins and thereby limit off-target immune stimulation, though adjuvant-mediated enhancement of T cell responses remains an area of careful evaluation [11–14]. Current evidence does not support vaccination as a direct causal factor for autoimmune disease in the general population; however, the interaction between genetic predisposition, immune activation intensity, and temporal immune responses continues to be investigated [11–15]. Clinical decisions should therefore consider individual disease status, treatment regimen, and infection risk to balance protective benefit against potential immunological perturbation.

Disease-Specific Mechanisms

Type 1 diabetes mellitus (T1DM)

Insulitis is characterized by CD8⁺ T-cell infiltration into pancreatic islets, supported by Th1/Th17-biased CD4⁺ T cells. Autoreactive clones target β-cell antigens, including proinsulin and GAD65, leading to progressive insulin deficiency [1,7]. Environmental factors—including viral infection and microbiome imbalance—may accelerate disease in genetically susceptible individuals.

Multiple sclerosis (MS)

Th1 and Th17 cells cross the blood–brain barrier and target myelin antigens (MBP, MOG), while CD8⁺ T cells and microglia contribute to axonal injury and neurodegeneration [1,16]. IL-17 induces barrier disruption and promotes leukocyte entry into the CNS, reinforcing chronic inflammatory cycles.

Rheumatoid arthritis (RA)

Synovial inflammation involves CD4⁺ T-cell activation of macrophages and fibroblast-like synoviocytes via TNF-α, IL-6, and GM-CSF. Th17 cells and peripheral helper T cells promote B-cell maturation and autoantibody production against citrullinated proteins, linking cellular and humoral pathology [17].

Inflammatory bowel disease (IBD)

Crohn's disease shows predominant Th1/Th17 polarization with elevated IL-17, IL-22, and TNF-α; ulcerative colitis displays atypical Th2 skewing with IL-13 and IL-5 from NKT cells [18]. Barrier dysfunction and dysbiosis perpetuate aberrant responses to luminal microbiota.

These mechanisms overlap with shared cytokine pathways (e.g., IL-6, TNF-α) and genetic risks (e.g., PTPN22, IL23R) [1,19]. Genome-wide studies identify PTPN22 and IL23R variants as common susceptibility factors across multiple autoimmune diseases, influencing T cell signaling, Th17 differentiation, and proinflammatory cytokine production like TNF-α and IL-6 [5,19].

Treatment Progress

Traditional immunosuppressive agents—such as corticosteroids and broad-spectrum cytotoxic drugs—remain foundational but act non-selectively, increasing susceptibility to infection and metabolic toxicity. Over the past decade, therapeutic development has shifted toward precision strategies that modulate discrete signaling pathways or re-establish immune tolerance, offering improved disease control with more favorable long-term outcomes [20].

Established and High-Efficacy Therapies

Multiple sclerosis (MS)

Modulators of sphingosine-1-phosphate receptors (e.g., fingolimod, ozanimod) sequester circulating T cells within lymph nodes, reducing CNS infiltration and relapse frequency. B-cell depletion with anti-CD20 antibodies (ocrelizumab) indirectly attenuates T cell responses by dampening antigen presentation.

Bruton's tyrosine kinase (BTK) inhibition has recently emerged as a novel therapeutic approach. The phase 3 HERCULES trial demonstrated that tolebrutinib, an oral CNS-penetrant BTK inhibitor, reduced the risk of 6-month confirmed disability progression by 26.38% (hazard ratio 0.69; 95% CI 0.55–0.88; p=0.003) in patients with non-relapsing secondary progressive MS, marking the first therapy to significantly decelerate disability accrual in this population [21].

Type 1 diabetes mellitus (T1DM)

Immune modulation with teplizumab (anti-CD3) delays disease onset in high-risk individuals through induction of T cell exhaustion and partial immune reset. Antigen-specific therapies, including insulin-derived peptides, aim to preserve residual β-cell mass by reinforcing immune tolerance.

The PROTECT phase 3 trial evaluated two 12-day courses of teplizumab in children and adolescents with newly diagnosed stage 3 T1DM. The trial met its primary endpoint by preserving stimulated C-peptide levels, indicative of maintained β-cell function, while secondary outcomes—including insulin usage and HbA1c—did not significantly differ from placebo [5,20,22].

Rheumatoid arthritis (RA)

Janus kinase (JAK) inhibitors (tofacitinib, baricitinib, upadacitinib) effectively suppress T cell activation and proinflammatory cytokine signaling (e.g., IL-6, IFN family). These agents demonstrate comparable efficacy to biologics and may be used as monotherapy or in combination with disease-modifying agents. A 2024 evidence synthesis confirmed reductions in disease activity and joint damage progression, while emphasizing safety considerations including cardiovascular and infectious risks [17,23].

Inflammatory Bowel Disease (IBD)

Targeted biologics have expanded therapeutic options for Crohn's disease and ulcerative colitis:

- **Vedolizumab**, a gut-selective α4β7 integrin antagonist, prevents T cell homing to intestinal mucosa and demonstrates favorable safety with sustained response in induction and maintenance therapy [24].
- **Ustekinumab**, targeting IL-12/23, modulates Th1/Th17 polarization and shows durable remission in both Crohn's disease and ulcerative colitis, including postoperative prophylaxis [25–27].
- **Tofacitinib**, an oral JAK inhibitor, provides rapid clinical response in moderate-to-severe ulcerative colitis with efficacy supported by pivotal clinical trials and real-world validation [28].

Together, these agents exemplify a shift toward disease-specific immunomodulation, supporting long-term control with reduced systemic toxicity.

Emerging Advances (2020–2025)

CAR-T cell therapy

Adapted from oncology, CD19-directed CAR-T cell therapy induces deep B cell depletion and metabolic immune reset. Case series (2023–2025) reported remission in refractory systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and inflammatory myopathies, with investigational applications now extending to MS, RA, and IBD. Dual-targeted constructs (CD19/BCMA) and Treg-based CAR platforms represent next-generation refinements to enhance safety and antigen specificity [29–31].

Long-term follow-up indicates remission in select patients with manageable toxicities—including cytokine release syndrome—suggesting disease-modifying or possibly curative potential in selected cohorts.

Combination biologic and small-molecule therapy

In highly refractory disease, combination strategies are increasingly employed to target multiple inflammatory pathways. Observational studies (2024–2025) report improved

mucosal healing and symptom control in IBD using dual regimens, such as infliximab + ustekinumab and vedolizumab + anti-TNF therapy.

Although associated with increased infection risk, accumulation of real-world data indicates acceptable safety when applied selectively under specialist supervision [32].

Precision and tolerance-restoring approaches

Innovative strategies aim to restore immunological tolerance rather than suppress immunity [32,33]:

1. **Low-dose IL-2** selectively expands Tregs with clinical benefit observed in SLE and early-phase trials for additional autoimmune diseases.
2. **Antigen-specific therapy**, including nanoparticle-delivered autoantigens and engineered IL-2 variants, induces anergy or Treg differentiation without broad immunosuppression.
3. **Microbiome modulation** through targeted probiotics or fecal microbiota transplantation (FMT) shows therapeutic promise in IBD, MS, and RA by stabilizing mucosal immunity and restoring metabolic homeostasis.

Conclusion

Cellular immunity-mediated autoimmune diseases arise from dysregulated T-cell responses that bypass central and peripheral tolerance mechanisms, culminating in targeted tissue injury and progressive organ dysfunction. Insight into the roles of Th17 polarization, cytotoxic $CD8^+$ responses, and cytokine network imbalance has reshaped current therapeutic paradigms. As of 2025, advances in immunology have generated a spectrum of precision therapies—including JAK inhibitors, biologics, and CAR-T interventions—that offer the potential for sustained remission and, in select cases, functional immune re-establishment.

Continued integration of translational research, clinical trial evidence, and personalized care strategies will further refine the balance between efficacy and safety. The trajectory of current innovation suggests a gradual transition from disease suppression toward immune recalibration and tolerance restoration. Multidisciplinary management and long-term monitoring remain essential to optimize clinical outcomes and mitigate risks associated with advanced immunotherapies.

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