Technology Networks

Autoimmunity:

When Immune Defense Turns Inward

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The immune system protects the human body against infection by producing lymphocytes and antibodies in response to threats like bacteria, viruses, and fungi. In autoimmunity, the body's own healthy cells and tissues can come under attack, leading to chronic conditions known as autoimmune diseases.

An estimated 4.6% of the US population were diagnosed with an autoimmune disease between 2011 and 2022.

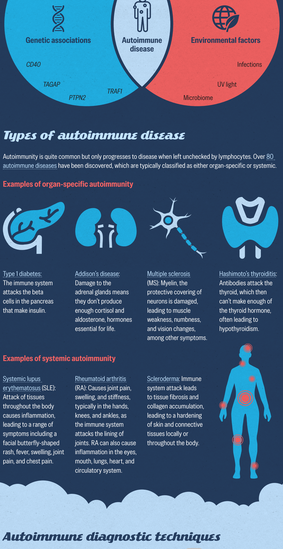
This infographic will explore how the immune system misfires in autoimmunity, the disorders that result, emerging therapeutic strategies, and autoimmune testing methods.

Immune tolerance and what goes wrong

Autoreactive T cells are present in healthy people and have been found to assist with beneficial functions including wound healing and maintaining homeostasis, but are typically prevented from causing damage to healthy cells and tissues by central and peripheral tolerance.

Central tolerance: once identified, highly autoreactive lymphocytes are destroyed, develop into regulatory T cells or undergo receptor change in the bone marrow or thymus.

Peripheral tolerance: autoreactive lymphocytes that avoid central tolerance mechanisms and escape into the periphery undergo suppression, anergy (inactivation), or deletion .

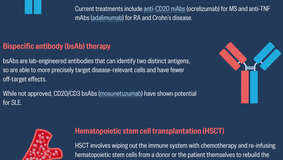


Defective regulation, genetic factors, and environmental stimuli are thought to promote activation and reduce control of autoreactive lymphocytes, leading to the development of autoimmune disease.

Types of autoimmune disease

Autoimmunity is quite common but only progresses to disease when left unchecked by lymphocytes. Over 80 autoimmune diseases have been discovered, which are typically classified as either organ-specific or systemic.

Examples of organ-specific autoimmunity



Type 1 diabetes: The immune system attacks the beta cells in the pancreas that make insulin.

Addison's disease: Damage to the adrenal glands means they don't produce enough cortisol and aldosterone, hormones essential for life.

Multiple sclerosis (MS): Myelin, the protective covering of neurons is damaged, leading to muscle weakness, numbness, and vision changes, among other symptoms.

Hashimoto's thyroiditis: Antibodies attack the thyroid, which then can't make enough of the thyroid hormone, often leading to hypothyroidism.

Examples of systemic autoimmunity

Systemic lupus erythematosus (SLE): Attack of tissues throughout the body causes inflammation, leading to a range of symptoms including a facial butterfly-shaped rash, fever, swelling, joint pain, and chest pain.

Rheumatoid arthritis (RA) Causes joint pain, swelling, and stiffness, typically in the hands, knees, and ankles, as the immune system attacks the lining of joints. RA can also cause inflammation in the eyes, mouth, lungs, heart, and circulatory system.

Scleroderma: Immune system attack leads to tissue fibrosis and collagen accumulation, leading to a hardening of skin and connective tissues locally or throughout the body.

Autoimmune diagnostic techniques

There are multiple approaches available for detecting autoimmune activity.

Antinuclear antibody (ANA) testing determines the presence of antibodies targeting the nucleus of cells. This test can help detect non-specific autoimmune disease, however healthy individuals can generate a positive result.

An extractable nuclear antigen (ENA) panel is often used after a positive ANA test and can detect specific autoantibodies present in SLE and scleroderma, among others.

Examples of other blood tests:

Disease	Diagnostic antibody tests
SLE	Anti-double-stranded DNA (anti-dsDNA) Anti-Smith (anti-Sm)
	Anti-ribonucleoprotein (Anti-RNP)
RA	Rheumatoid factor (RF)
	Anti-cyclic citrullinated peptide (Anti-CCP)
Scleroderma	Anti-centromere protein (Anti-CENP)
	Anti-topoisomerase I (Anti-Scl-70)
	Anti-ribonucleoprotein (Anti-RNP)
Sjögren's syndrome	Anti-Sjögren syndrome-A (anti-SSA/anti-Ro)
	Anti-Sjögren syndrome-B (anti-SSB/La)
Autoimmune hepatitis	Smooth muscle antibody (SMA)

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) tests are used to detect inflammation in the body.

Current and emerging therapeutic strategies

Conventionally, autoimmune disease treatment has focused on broad immunosuppression with corticosteroids, which can alleviate symptoms but often has significant side effects and does not target the underlying immune dysregulation. Advances are now allowing for the development of more targeted and effective treatments.

Monoclonal antibody (mAb) therapy

mAbs are lab-engineered antibodies used to target specific immune cells or proteins that drive autoimmune diseases. While they have high target specificity, mAbs can cause adverse events including risk of infection, and many patients relapse after treatment.

Current treatments include anti- CD20 mAbs (ocrelizumab) for MS and anti-TNF mAbs (adalimumab) for RA and Crohn's disease.

Bispecific antibody (bsAb) therapy

bsAbs are lab-engineered antibodies that can identify two distinct antigens, so are able to more precisely target disease-relevant cells and have fewer off-target effects.

While not approved, CD20/CD3 bsAbs (mosunetuzumab) have shown potential for SLE.

Hematopoietic stem cell transplantation (HSCT)

HSCT involves wiping out the immune system with chemotherapy and re-infusing hematopoietic stem cells from a donor or the patient themselves to rebuild the immune system. The therapy has the potential to achieve long-term remission and is most often used in MS, scleroderma, and Crohn's disease. However, HSCT comes with a significant risk of infection and relapse after transplantation, along with other potential complications.

Regulatory T-cell (Treg) therapy

Treg therapy aims to rebalance the immune system and induce long-term immune tolerance by modulating immune responses and reparative processes.
Tregs can be genetically engineered to express a chimeric antigen receptor (CAR) or T-cell receptor (TCR). TCR-Tregs and CAR-Tregs activate suppressive pathways to control autoimmune responses and inflammation, however, engineering CAR-Tregs comes with manufacturability, cost, and scalability challenges.
In a preclinical trial, CAR-Tregs were able to reverse type 1 diabetes in a clinically relevant mouse model.

CAR T-cell therapy

In CAR T-cell therapy, T cells are engineered to specifically recognize and eliminate autoreactive B cells and plasma cells. In a mouse model, anti-CD19 CAR T-cell therapy was found to be effective in the prevention and treatment of SLE. Clinical trials are ongoing.

As research continues to unravel the drivers of autoimmunity, increasingly precise diagnostic tools and targeted therapies are bringing the field closer to restoring immune tolerance rather than simply suppressing disease.