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Immunopathogenesis of Autoimmune Diseases: Diagnostic and Therapeutic Perspectives

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ABSTRACT

Autoimmune diseases (ADs) are a series of multifaceted conditions associated with loss of immune homeostasis, leading to self-inflicted destruction of self-tissues. The conditions arise from self-antigens mistakenly identified as foreign by the immune system, leading to chronic inflammatory responses, progressive tissue damage, and organ dysfunction. ADs like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), and type 1 diabetes mellitus (T1DM) impact millions of people globally, and this is a developing issue in population health. These disorders have a multifactorial pathogenesis, involving a combination of genetically predisposed factors, environmental factors, hormonal factors, and immune regulatory deficiencies. Immune homeostasis is maintained by central and peripheral tolerance mechanisms, which eliminate or suppress autoreactive T and B cells; when these mechanisms fail, autoimmune responses are driven by the survival of autoreactive T and B cells. Such immune abnormalities are linked to dysregulation of cytokine production, immune complex generation, complement activation (CA), and activation of chronic inflammatory signaling pathways.

Keywords: Autoimmune diseases, immunopathogenesis, immune tolerance, autoantibodies, cytokines, biomarkers

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Introduction

Autoimmunity is a pathological condition in which the immune system mistakenly identifies the body's own tissues as foreign and initiates immune responses against them. Under normal physiological conditions, immune tolerance mechanisms allow the immune system to distinguish between self and non-self antigens. However, when these regulatory processes fail, autoreactive immune cells become activated and attack host tissues, leading to inflammation and tissue damage [1]. Autoimmune diseases (ADs) represent a heterogeneous group of disorders, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), and type 1 diabetes mellitus (T1DM). These diseases arise from complex interactions among genetic predisposition, environmental factors, and immune dysregulation, ultimately disrupting immune homeostasis [2]. ADs collectively represent a major public health concern worldwide. Epidemiological studies indicate that ADs affect approximately 5–10% of the global population, and their incidence continues to increase in many countries [3]. These diseases are associated with significant morbidity, long-term disability, and substantial healthcare costs.

Recent advances in immunology and molecular medicine have improved understanding of AD mechanisms and facilitated the development of targeted therapeutic strategies such as cytokine inhibitors and monoclonal antibodies [4]. Self-tolerance is the ability of the immune system to avoid attacking the body's own tissues. This process is maintained through central and peripheral tolerance mechanisms that eliminate or regulate autoreactive lymphocytes during immune development and activation [5]. When these tolerance mechanisms fail, self-reactive T cells and B cells can escape immune regulation and initiate immune responses against host tissues. The breakdown of immune tolerance is therefore considered a central event in the development of ADs [6]. Despite considerable advances in understanding autoimmune diseases, many aspects of their pathogenesis remain unclear. Autoimmunity results from complex interactions between genetic susceptibility, environmental exposures, and immune regulatory pathways. A comprehensive understanding of these mechanisms is essential for improving diagnostic methods and developing effective therapeutic strategies.

The objective of this review is to explore the immunological mechanisms underlying ADs, including the loss of immune tolerance, genetic susceptibility, environmental triggers, and cellular and molecular processes involved in disease development.

Immunological Basis of Autoimmunity:

Central tolerance occurs during lymphocyte development in primary lymphoid organs such as the thymus and bone marrow. In the thymus, immature T cells undergo negative selection, during which T cells that strongly recognize self-antigens are eliminated through apoptosis. Similarly, developing B cells in the bone marrow undergo receptor editing or deletion if they exhibit strong autoreactivity [5]. Defects in central tolerance mechanisms may allow autoreactive lymphocytes to escape elimination and enter the peripheral circulation, thereby increasing susceptibility to ADs. Mechanisms of peripheral tolerance include immune cell anergy, activation-induced cell death, and immune checkpoint pathways that inhibit excessive immune activation [6].

Failure of these regulatory processes can result in persistent activation of autoreactive immune cells and the development of autoimmune pathology. Regulatory T cells (Tregs) play a critical role in maintaining immune homeostasis and preventing autoimmune responses. These cells suppress immune activation by producing anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) [7]. In several ADs, the number or function of Tregs is reduced, leading to impaired immune regulation and uncontrolled inflammatory responses [8].

Genetic factors play a crucial role in determining susceptibility to ADs. Among these factors, the human leukocyte antigen (HLA) gene complex is particularly important because it encodes proteins responsible for antigen presentation to T cells. Certain HLA alleles are strongly associated with specific ADs and influence how immune cells recognize antigens [1]. In addition to HLA genes, numerous non-HLA genetic variants contribute to AD risk. These genes regulate immune signaling pathways, cytokine production, and lymphocyte activation. Genome-wide association studies have identified multiple genetic loci that increase susceptibility to ADs [9]. Epigenetic mechanisms such as DNA methylation, histone modification, and microRNA regulation can influence gene expression without altering the DNA sequence. Environmental factors may induce epigenetic changes that disrupt immune tolerance and contribute to AD development [10].

Infectious agents are widely recognized as environmental triggers of ADs. Molecular mimicry occurs when microbial antigens resemble host proteins, leading to immune responses that cross-react with self-antigens. This mechanism has been implicated in several autoimmune conditions triggered by bacterial or viral infections [11]. The human microbiome plays an important role in immune system regulation. Dysbiosis, or an imbalance in the composition of gut microbiota, has been associated with several ADs. Alterations in microbial populations can promote pro-inflammatory immune responses and disrupt immune tolerance [9]. ADs occur more frequently in women than in men, suggesting that hormonal factors contribute to disease susceptibility. Hormones such as estrogen influence immune cell function and cytokine production, thereby affecting immune

tolerance and inflammatory responses [12]. Exposure to environmental pollutants, chemicals, and certain drugs may also trigger autoimmune responses. These factors can alter immune signaling pathways or induce epigenetic changes that disrupt immune regulation and promote inflammation [10]. Autoreactive T cells are key mediators of autoimmune pathology. These cells recognize self-antigens presented by antigen-presenting cells and initiate inflammatory immune responses that lead to tissue damage and organ dysfunction [6]. B cells contribute to ADs by producing autoantibodies (AAbs) directed against self-antigens. These AAbs can form immune complexes that deposit in tissues and activate inflammatory pathways, resulting in tissue injury [13].

Cytokines are important regulators of immune communication. In ADs, pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interferon-γ (IFN-γ) are often overproduced. These cytokines promote immune cell activation and sustain chronic inflammation [14]. For example, IL-6 promotes the differentiation of pro-inflammatory Th17 cells while inhibiting regulatory T cell development, thereby contributing to immune imbalance and ADs progression [7]. The complement system also contributes to AD pathogenesis. Activation of complement proteins by immune complexes leads to inflammatory cascades that damage tissues and contribute to disease severity, particularly in systemic autoimmune conditions such as lupus [15].

Immunopathogenesis in Major ADs:

SLE is a chronic, heterogeneous autoimmune disease with a strong female predisposition, characterized by multi-organ inflammation and damage. Its pathogenesis arises from a complex interplay of genetic susceptibility, epigenetic alterations, hormonal influences, and environmental triggers. This confluence drives a sustained loss of self-tolerance and profound immune dysregulation. Innate immune dysfunction, featuring unchecked type I IFN production and defective clearance of cellular debris, exposes autoantigens. Concurrent adaptive immune defects include breakdowns in B and T cell tolerance, leading to pathogenic autoantibody production, dysregulated cytokine networks, and aberrant lymphocyte interactions. These processes culminate in tissue injury via immune complex deposition and direct cellular effects [16]. SLE is a multifaceted AD characterized by chronic inflammation, tissue damage, accelerated cardiovascular disease (CVD), and the synthesis of AAbs that target nucleic acids and nuclear protein complexes. Emerging evidence underscores the key role of immune metabolic dysregulation in SLE, revealing how metabolic reprogramming during immune cell activation influences disease development and progression. Alterations in key metabolic pathways, such as glycolysis and oxidative phosphorylation, profoundly affect the activation, differentiation, and function of B and T cells, monocytes, neutrophils, and other immune cells, thereby driving inflammation and tissue injury. This review synthesizes current findings on immune cell metabolism in animal models of lupus and in patients with SLE, highlighting the interplay of metabolic disturbances, mitochondrial dysfunction, and disease pathogenesis [17]

RA is a chronic AD characterized by joint inflammation and the presence of AAbs. Progressive disability and a diminished quality of life may be the outcome of RA in the absence of treatment. MicroRNAs (miRNAs) are implicated in the diagnosis, prognosis, and monitoring of RA, according to multiple lines of evidence. MiRNAs are a class of small, single-stranded RNAs. They control gene expression by binding to target messenger RNA (mRNA). Besides, these molecules are involved in various processes. These include growth, differentiation, apoptosis, and response to stress [18].

On the other hand, exosomes were implicated in the development and progression of inflammatory diseases, such as RA. Exosomes are nano-sized vesicles derived from endosomes inside cells. Depending on the cell of origin, exosomes contain a diverse array of components, including proteins, lipids, metabolites, DNA, and various ribonucleic acids, including mRNA. Exosomes act as intercellular messengers and play a key role in local and systemic communication between different cells. We aim to discuss dysregulated and circulating exosomal miRNAs in RA and present the current possibilities and future perspectives for using exosomal miRNAs as biomarkers and as specific targets for gene therapy in RA treatment. RA is a chronic inflammation that primarily affects the joints. RA usually results in synovial hyperplasia, expansion of "pannus," and destruction of cartilage. The etiology and pathogenesis of RA are not fully understood, but immunity has been shown to play an important role in the development of ADs such as RA [19].

MS is also an inflammatory disease determined by the degradation of oligodendrocytes, leading to demyelination and focal formation of pathognomonic plaques in the white matter of the brain and spinal cord [20]. In recent years, there has been a steady upward trend in the prevalence of MS. The new edition of the MS Atlas estimated that the number of people with MS worldwide increased to 2.8 million in 2020, using the same methodology as in 2013, an estimate that is 30% higher than in 2013. The global prevalence in 2020 was 35.9 per 100,000 people. High-quality epidemiological data worldwide are needed to understand the risk of the disease better and to support health policies aimed at meeting the diverse needs of people with MS [21] [37]. Preclinical and clinical studies have shown that MS is a disease that shows a predilection for females, with twice the risk. MS is mostly diagnosed in people between the ages of 20 and 40. Unfortunately, the number of diseases in children is increasing. It is currently estimated that in 3–5% of all people diagnosed with MS, the disease begins before the age of 16.

T1DM is a chronic AD characterized by the selective destruction of pancreatic islet β cells and consequent absolute insulin deficiency. The incidence of T1DM has increased markedly in recent years, particularly in developed countries. Global prevalence estimates indicated approximately 8.4 million individuals diagnosed with T1DM in 2021, and projections suggest a rise to 17.4 million by 2040. A combination of genetic predispositions and environmental triggers causes T1DM. Recognized environmental factors include dietary shifts, antibiotic overuse, and dysbiosis of the gut microbiota [23]. Despite insulin replacement therapy considerably extending patients' survival, its limitations remain significant. These encompass the burden of multiple daily injections impacting compliance, the inherent risk of hypoglycemia, substantial economic costs, and the therapy's inability to halt autoimmune progression or restore pancreatic β-cell function. [24]

Therefore, researchers have shifted their focus beyond insulin therapy to the underlying mechanisms, particularly immune dysregulation and metabolic imbalance. This shift in research focus has naturally led to increased interest in how environmental factors, such as the gut microbiota, influence disease initiation and progression. In recent years, the gut microbiota has emerged as a critical link between environmental factors and host immune-metabolic regulation. It is increasingly recognized for its role in the development of T1DM. [25]

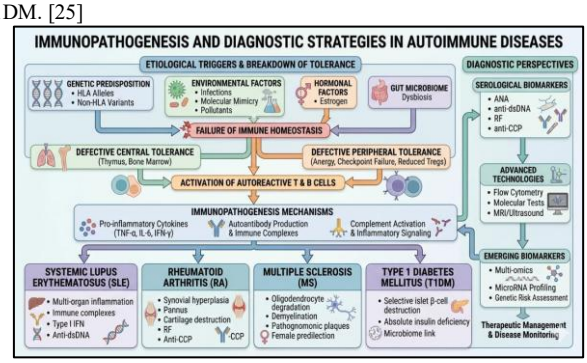

Figure 1: Autoimmune diseases: immunopathogenesis and diagnostic approaches

This figure shows how genetic vulnerability, environmental exposure, hormonal effects, and dysbiosis of the gut microbiome all play a role in the loss of immune tolerance, which triggers autoreactive T and B cells and inflammatory response. These processes supply the progression of autoimmune diseases, including SLE, RA, MS, and T1DM, whereas diagnostic methods comprise serological biomarkers, state of the art technologies, and new molecular markers.

Diagnostic Perspectives:

Accurate diagnosis of ADs requires integrating serological biomarkers, advanced diagnostic technologies, and emerging molecular markers. These tools help identify immune dysregulation, predict disease progression, and guide targeted therapies. Serological biomarkers remain the cornerstone of AD diagnosis because many ADs are characterized by the presence of AAbs against self-antigens [26]. Detection of these antibodies provides valuable information for disease classification, monitoring, and prognosis. Antinuclear antibodies (ANA) are widely used as a screening test for systemic ADs such as SLE, Sjögren's syndrome, and systemic sclerosis (SS). ANA targets nuclear antigens, including DNA, RNA, and nuclear proteins, reflecting loss of immune tolerance [27]. Anti-double-stranded DNA (anti-dsDNA) antibodies are highly specific for SLE and are often associated with disease activity and complications such as lupus nephritis (LN). In RA, RF and anti-cyclic citrullinated peptide (anti-CCP) antibodies are key diagnostic markers. Anti-CCP antibodies are highly specific for RA and may appear years before clinical symptoms, making them valuable for early diagnosis and prognosis [28].

In addition to these markers, organ-specific AAbs help diagnose diseases affecting particular organs, such as anti-thyroid antibodies in autoimmune thyroid disease (ATD) and anti-GAD antibodies in T1DM [29]. Modern diagnostic approaches integrate immunological, molecular, and imaging technologies to improve the accuracy and sensitivity of ADs' detection. Flow cytometry enables detailed analysis of immune cell populations, including T-cell subsets, B cells, and regulatory immune cells. This

technique helps identify immune dysregulation and immune activation patterns associated with ADs [30]. Cytokine panels measure inflammatory mediators such as IL-6, TNF-α, and interferons, which play major roles in autoimmune inflammation and disease progression. Changes in cytokine profiles can reflect disease activity and treatment response. Molecular diagnostics, including PCR-based assays and next-generation sequencing, allow detection of genetic susceptibility factors and immune-related gene expression signatures that contribute to disease development [31] [38]. Imaging modalities such as MRI, ultrasound, and PET scanning are also used to detect tissue damage, inflammation, and structural changes in autoimmune disorders, particularly in conditions such as RA and MS [32]. Recent advances in omics technologies have led to the discovery of novel biomarkers that may enhance early detection and personalized medicine approaches in ADs [33]. miRNAs are small non-coding RNAs that regulate gene expression and immune responses. Altered miRNA expression profiles have been associated with ADs and may serve as potential diagnostic and prognostic biomarkers [34]. Proteomics and metabolomics analyze proteins and metabolic pathways involved in immune regulation. These approaches help identify disease-specific molecular signatures and improve understanding of disease mechanisms. Genetic risk profiling involves identifying susceptibility genes, such as HLA alleles and other immune-related polymorphisms, which contribute to AD development and progression [35]. These emerging biomarkers offer promising opportunities for precision medicine, enabling early diagnosis and individualized treatment strategies [36].

Future Perspectives:

Future studies on ADs will focus more on enhancing early detection and designing individual treatment strategies using molecular medicine and immunology. A combination of multi-omics technologies, such as genomics, transcriptomics, proteomics, metabolomics, and microbiome analysis, can provide a comprehensive picture of immune dysregulation in ADs. These methods can be used to discover new biomarkers to be used in early detection, disease surveillance, and forecasting treatment response. Moreover, using artificial intelligence and machine learning in biomedical research can improve the analysis of complex biological data and predict disease risk and progression, supporting precision medicine practices in the management of ADs [39].

Another avenue that suggests prospective success is the advancement of specific, novel therapeutic approaches that can restore immune tolerance. Biologic therapies, such as monoclonal antibodies that block cytokines and immune signaling pathways, have already been shown to improve outcomes in various ADs. The cell-based therapeutic strategies that might be used in the future are regulatory T cell (Treg) therapy, gene editing with Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) to correct immunologically based genetic defects, and microbiome-based therapy to tune the immune response [40] [41]. Also, nanotechnology-based drug delivery systems have the potential to increase treatment effectiveness by delivering immunomodulatory agents to affected tissues while reducing systemic side effects. These innovations will require continuous interdisciplinary study that integrates immunology, molecular biology, and clinical medicine to translate them into useful diagnostic and therapeutic interventions for ADs.

Conclusion

ADs arise from complex interactions between genetic susceptibility, environmental triggers, and immune dysregulation, leading to chronic inflammation and tissue damage. Advances in immunopathogenesis research have improved our understanding of the mechanisms underlying these disorders. Traditional serological biomarkers such as ANA, anti-dsDNA, RF, and anti-CCP antibodies remain essential tools for diagnosis and monitoring. However, newer technologies, including flow cytometry, cytokine profiling, molecular diagnostics, and advanced imaging techniques, are enhancing diagnostic precision. Furthermore, the identification of emerging biomarkers such as microRNAs, proteomic signatures, and genetic risk profiles may revolutionize the early detection and personalized management of autoimmune diseases. Future research should focus on integrating multi-omics approaches and clinical data to develop more accurate diagnostic tools and targeted therapies.

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