AUTOIMMUNE DISEASES: PATHOGENESIS AND THERAPEUTIC STRATEGIES

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Abstract: Autoimmune diseases pose significant challenges in both understanding their complex pathogenesis and developing effective treatments. This paper provides an overview of current therapeutic strategies, including conventional therapies such as anti-inflammatory drugs and immunosuppressive agents, as well as emerging approaches like biologics, targeted therapies, and cellular therapies. Challenges in autoimmune disease management, such as treatment resistance, side effects, and the need for personalized treatments, are discussed. The importance of continued research efforts, interdisciplinary collaboration, and innovation in advancing our understanding of autoimmune diseases and improving treatment outcomes is emphasized. Looking ahead, the future landscape of autoimmune disease management holds promise for more personalized, precise, and targeted approaches that optimize treatment outcomes while minimizing side effects. Advances in genomics, immunology, and therapeutic innovation are driving progress towards this goal, with the ultimate aim of enhancing the quality of life for individuals living with autoimmune diseases.

Keywords: Autoimmune diseases, pathogenesis, therapeutic strategies, conventional therapies, biologics, targeted therapies, emerging therapies, challenges, future directions, personalized medicine, precision medicine, research, treatment resistance, side effects, interdisciplinary collaboration, innovation.

АУТОИММУННЫЕ ЗАБОЛЕВАНИЯ: ПАТОГЕНЕЗ И ТЕРАПЕВТИЧЕСКИЕ СТРАТЕГИИ

Аннотация: Аутоиммунные заболевания создают серьезные проблемы как для понимания их сложного патогенеза, так и для разработки эффективных методов лечения. В этой статье представлен обзор современных терапевтических стратегий, включая традиционные методы лечения, такие как противовоспалительные препараты и иммунодепрессанты, а также новые подходы, такие как биологические препараты, таргетная терапия и клеточная терапия. Обсуждаются проблемы в лечении аутоиммунных заболеваний, такие как резистентность к лечению, побочные эффекты и необходимость индивидуального лечения. Подчеркивается важность продолжения научных исследований, междисциплинарного сотрудничества и инноваций для

углубления нашего понимания аутоиммунных заболеваний и улучшения результатов лечения. Забегая вперед, можно сказать, что будущее в области лечения аутоиммунных заболеваний обещает более персонализированные, точные и целенаправленные подходы, которые оптимизируют результаты лечения при минимизации побочных эффектов. Достижения в области геномики, иммунологии и терапевтических инноваций способствуют прогрессу в достижении этой цели, конечной целью которой является повышение качества жизни людей, страдающих аутоиммунными заболеваниями.

Ключевые слова: Аутоиммунные заболевания, патогенез, терапевтические стратегии, традиционные методы лечения, биологические препараты, таргетная терапия, новые методы лечения, вызовы, направления на будущее, персонализированная медицина, прецизионная медицина, исследования, устойчивость к лечению, побочные эффекты, междисциплинарное сотрудничество, инновации.

Introduction

Autoimmune diseases encompass a wide range of disorders in which the immune system attacks the body's own tissues, mistaking them for hostile invaders. This can lead to chronic inflammation, tissue damage, and serious morbidity. The pathogenesis of autoimmune diseases is due to a complex interplay of genetic predispositions, environmental factors, and immune system dysfunction. Genetic factors, such as certain variants of HLA genes, contribute to disease predispositions, and environmental factors, such as infections and toxins, can be triggering factors. Immune system dysfunction is manifested by impaired immunologic tolerance, leading to the formation of autoantibodies and activation of autoreactive T cells. Molecular and cellular mechanisms, including antigen presentation and epigenetic modifications, play an important role in the development of these diseases. The review discusses current concepts on the pathogenesis of autoimmune diseases as well as existing and new treatment strategies, emphasizing current research and future directions in this field [22].

Despite these achievements, challenges remain in developing effective and safe treatments and understanding the complex mechanisms underlying these diseases. This review summarizes current knowledge about the pathogenesis of autoimmune diseases and examines both existing and new therapeutic strategies, highlights current research and future directions in this area.

Autoimmune diseases are a group of disorders in which the immune system attacks the body's own tissues. The pathogenesis of these diseases includes genetic predisposition, environmental factors, and immune system dysfunction. Genetic factors, such as HLA gene variants, affect predisposition to diseases, and infections

and toxins can cause their development. The dysfunction of the immune system is manifested by a violation of immune tolerance, which leads to the formation of antibodies and activation of autoreactive T cells. Molecular and cellular mechanisms, including antigen presentation and epigenetic changes, also lead to the development of the disease. Autoimmune diseases can affect any part of the body and lead to chronic inflammation and tissue damage, which causes a variety of symptoms and complications. Understanding the mechanisms of these diseases is key to developing effective treatments and improving the condition of patients.

Understanding the pathogenesis of autoimmune diseases is critical for several reasons. Firstly, it provides insights into the underlying mechanisms that drive these disorders, including genetic, environmental, and immunological factors. This knowledge is essential for identifying potential biomarkers for early diagnosis and for predicting disease progression. Secondly, a thorough understanding of disease mechanisms can reveal new therapeutic targets, enabling the development of more effective and specific treatments. Current therapies often focus on broadly suppressing the immune system, which can lead to significant side effects and increased susceptibility to infections. By targeting the specific pathways involved in autoimmune responses, it is possible to create therapies that are both more effective and have fewer adverse effects [11,15].

Moreover, as our understanding of the complex interactions within the immune system grows, it opens up possibilities for innovative treatments such as gene editing, personalized medicine, and cellular therapies. These advanced strategies hold promise for not only managing symptoms but potentially altering the course of the disease or achieving remission.

Autoimmune diseases are a category of disorders characterized by the immune system's failure to distinguish between self and non-self, leading to an immune response against the body's own tissues. Normally, the immune system protects the body from infections and diseases by identifying and attacking pathogens such as bacteria and viruses. However, in autoimmune diseases, this system malfunctions and begins to target healthy cells, tissues, and organs, resulting in chronic inflammation and tissue damage. This dysregulation can affect almost any part of the body, including joints, skin, brain, muscles, and other organs, leading to a wide range of symptoms and health complications. Common examples of autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes, and multiple sclerosis [7].

Genetic predisposition plays a crucial role in the development of autoimmune diseases. Numerous studies have demonstrated that individuals with a family history of autoimmune conditions are at a higher risk of developing such diseases themselves, indicating a significant hereditary component.

1. HLA Genes:

One of the most well-established genetic links to autoimmune diseases involves the human leukocyte antigen (HLA) genes, located on chromosome 6. These genes are essential for the regulation of the immune system. Specific HLA alleles have been strongly associated with various autoimmune diseases. For instance, HLA-DRB1 is linked with rheumatoid arthritis, while HLA-DQ2 and HLA-DQ8 are associated with celiac disease. The exact mechanism by which HLA genes influence autoimmunity involves their role in antigen presentation. Variations in these genes can affect the binding and presentation of self-antigens to T cells, potentially leading to an autoimmune response.

2. Non-HLA Genes:

In addition to HLA genes, several non-HLA genes have been implicated in autoimmune diseases. These include genes involved in immune regulation and response, such as PTPN22, which is associated with multiple autoimmune diseases including type 1 diabetes and rheumatoid arthritis, and CTLA4, which is linked to autoimmune thyroid diseases and type 1 diabetes. These genes can affect various immune functions, such as T cell activation and immune checkpoint regulation, contributing to the breakdown of self-tolerance [16].

3. Genome-Wide Association Studies (GWAS):

The advent of genome-wide association studies (GWAS) has significantly advanced our understanding of the genetic basis of autoimmune diseases. GWAS have identified numerous genetic loci associated with increased risk of autoimmune conditions. For example, in multiple sclerosis, over 200 genetic variants have been identified that contribute to disease susceptibility. These studies have highlighted the polygenic nature of autoimmune diseases, where multiple genetic factors, each contributing a small effect, collectively increase disease risk [20].

4. Epigenetics:

Epigenetic modifications, such as DNA methylation and histone modification, also play a role in the pathogenesis of autoimmune diseases. These modifications can influence gene expression without altering the DNA sequence. Environmental factors, including diet, infections, and stress, can affect epigenetic marks, potentially triggering autoimmune responses in genetically predisposed individuals. For instance, changes in DNA methylation patterns have been observed in patients with systemic lupus erythematosus and rheumatoid arthritis, suggesting that epigenetic regulation is an important factor in these diseases [10].

5. Gene-Gene and Gene-Environment Interactions:

The pathogenesis of autoimmune diseases often involves complex interactions between multiple genetic factors and environmental triggers. Gene-gene interactions, where the effect of one gene is modified by the presence of another gene, can significantly influence disease susceptibility. Similarly, gene-environment

interactions, where environmental factors such as infections, smoking, and hormonal changes interact with genetic predisposition, can trigger or exacerbate autoimmune responses. Understanding these interactions is crucial for developing personalized approaches to prevention and treatment [6,15].

The pathogenesis of autoimmune diseases is strongly influenced by genetic factors, with specific genes playing pivotal roles in disease susceptibility and progression. Among these genes, the Human Leukocyte Antigen (HLA) genes stand out prominently due to their significant associations with various autoimmune conditions.

Table 1. Role of HLA Genes in Autoimmune Diseases [2,3,4,14]

Gene	Autoimmune Diseases	Role
HLA Class I	Ankylosing Spondylitis, Psoriasis	Encode cell surface proteins presenting peptide antigens to cytotoxic T cells
HLA Class II	Rheumatoid Arthritis, Systemic Lupus Erythematosus, Celiac Disease, Multiple Sclerosis	Express antigens to CD4+ T helper cells
HLA-DQB1, HLA-DRB1	Rheumatoid Arthritis	Strongly associated with disease susceptibility, especially shared epitope in HLA-DRB1
HLA-DQB102, HLA-DQA105	Celiac Disease	Major determinants of celiac disease susceptibility, involved in gluten peptide presentation to T cells
HLA-DQ2, HLA-DQ8	Celiac Disease	Strongly associated with disease susceptibility, involved in presenting gluten-derived peptides to T cells
HLA-B27	Ankylosing Spondylitis, Reactive Arthritis, Psoriatic Arthritis	Strongly associated with disease susceptibility,

		exact mechanism under investigation
HLA-DRB1, HLA-DQA1	Systemic Lupus Erythematosus	Linked to increased susceptibility to SLE, though associations are less pronounced compared to other autoimmune diseases

Genetic research plays an important role in understanding autoimmune diseases. Genome-wide association studies (GWAS) have helped to elucidate the genetic architecture of these diseases and to discover specific genes and genetic variants associated with their development. For example, GWAS in rheumatoid arthritis revealed associations in the HLA region and other genes associated with immunity. In systemic lupus erythematosus, more than 100 genetic loci are associated with a predisposition to the disease, including genes that regulate immunity. Multiple sclerosis is associated with more than 200 genetic variants, including genes that activate T cells. In type 1 diabetes, many genetic variants associated with predisposition have also been found. In celiac disease, key genetic variants are associated with HLA-DQ2 and HLA-DQ8 and genes involved in immune regulation. However, much of the heredity of these diseases remains unexplained, so further research is needed to understand the complex interactions between genetic and environmental factors and develop improved diagnostic and treatment methods [20].

Environmental triggers such as infections, toxins, and lifestyle play an important role in the development and exacerbation of autoimmune diseases. Some viral infections, including Epstein-Barr virus infection, are associated with an increased risk of developing systemic lupus erythematosus and multiple sclerosis. Bacterial infections, especially those with molecular mimicry with self-antigens, can cause autoimmune reactions such as rheumatic fever.

Exposure to environmental toxins such as heavy metals and pollutants can also increase the risk of autoimmune diseases. Some medications can cause autoimmune reactions, and dietary factors such as gluten can also be triggers for some autoimmune diseases. Smoking is a risk factor for various autoimmune diseases, and psychological stress can affect the immune system and lead to an exacerbation of autoimmune diseases. Understanding environmental triggers is an important step in developing strategies for the prevention and management of autoimmune diseases [9,22].

The development of autoimmune diseases depends on the interaction of genetic predisposition and the environment. Genetic factors cause autoimmune diseases, and the environment can be the initiator or aggravator of this process. Environmental

factors can influence epigenetic modifications that regulate gene expression. This can alter the immune response and contribute to the development of autoimmunity. In addition, the environment may interact with specific genetic variants, increasing the risk of disease. Understanding this interaction can help identify people at high risk and develop personalized prevention and treatment strategies. To do this, it is necessary to take into account both genetic predisposition and environmental influences. Thus, environmental triggers play an important role in the pathogenesis of autoimmune diseases by interacting with genetic predisposition, and understanding this interaction is necessary for effective treatment and prevention of these diseases [22].

Autoantibodies are antibodies produced by the immune system and directed against self-antigens that play a key role in the pathogenesis of autoimmune diseases. Autoantibodies can damage tissues through complement activation, antibody-dependent cell-mediated cytotoxicity, and the formation of immune complexes. Autoreactive T cells are T lymphocytes that recognize and respond to self-antigens, causing the activation of an immune response against their own tissues. Disruption of T cell tolerance mechanisms, such as central and peripheral tolerance, can lead to activation and expansion of autoreactive T cells, contributing to the development of autoimmune diseases. Cytokines and other immune mediators, including pro-inflammatory and anti-inflammatory cytokines, as well as chemokines and adhesion molecules, play a role in regulating immune responses and inflammation in autoimmune diseases. Understanding these mechanisms of immune dysregulation is important for the development of new therapeutic strategies for autoimmune diseases [19].

B cells and T cells are key players in the pathogenesis of autoimmune diseases, orchestrating immune responses against self-antigens and contributing to tissue damage:

1. B Cells:

- B cells play a central role in autoimmune diseases by producing autoantibodies against self-antigens. These autoantibodies can directly damage tissues through complement activation, antibody-dependent cell-mediated cytotoxicity (ADCC), and immune complex formation.
- Additionally, B cells can present autoantigens to T cells and produce pro-inflammatory cytokines, amplifying immune responses and promoting inflammation in autoimmune diseases.

2. T Cells:

- T cells are critical mediators of cellular immunity and play diverse roles in autoimmune diseases. Autoreactive T cells recognize self-antigens presented by antigen-presenting cells (APCs) and initiate immune responses against self-tissues.

- CD4+ T helper cells contribute to the activation and differentiation of B cells and cytotoxic CD8+ T cells, promoting antibody production and tissue destruction.
- CD8+ cytotoxic T cells directly attack target cells expressing self-antigens, leading to tissue damage and inflammation in autoimmune diseases [18,21].

Antigen presentation and molecular mimicry are mechanisms that can lead to impaired self-tolerance and the occurrence of autoimmune reactions. In autoimmune diseases, dysregulation of antigen presentation mechanisms by antigen-presenting cells (APC) can lead to activation of autoreactive T cells and the triggering of autoimmune reactions. Aberrant expression or processing of self-antigens, as well as defects in regulatory mechanisms that support immune tolerance, may also contribute to impaired self-tolerance and the development of autoimmune diseases.

Molecular mimicry is another mechanism that can lead to autoimmune reactions. In molecular mimicry, microbial antigens have structural similarities with self-antigens, which leads to cross-reactions of the immune system. Exposure to microbial antigens that share a common sequence or structural homology with self-antigens can cause autoimmunity through molecular mimicry. This means that cross-reactive T cells and B cells activated by microbial antigens can recognize and respond to self-antigens, which initiates autoimmune reactions and can damage tissues [17].

Epigenetic modifications such as DNA methylation, histone modification, and microRNA expression play an important role in the pathogenesis of autoimmune diseases. DNA methylation can lead to gene silencing, and dysregulation of this process contributes to impaired immune tolerance and activation of proinflammatory pathways. Histone modifications affect chromatin structure and gene expression, and their dysregulation is associated with autoimmune diseases. microRNA expression regulates gene expression by interacting with target mRNAs. Dysregulation of MRNA expression affects immune responses and inflammation. Conventional therapy for autoimmune diseases includes anti-inflammatory drugs such as NSAIDs and corticosteroids, as well as immunosuppressive agents such as methotrexate and azathioprine. These drugs are used to reduce inflammation, suppress the activity of the immune system and relieve symptoms of autoimmune diseases [13].

Biological therapies, also known as biologics, are a newer class of medications designed to target specific components of the immune system involved in autoimmune diseases. Here are two common types:

1. Monoclonal antibodies: These are laboratory-produced molecules that mimic the immune system's ability to fight off harmful pathogens or substances. Monoclonal antibodies can be engineered to target specific proteins or cells involved in autoimmune responses. Examples include:

- TNF inhibitors: These medications block the action of tumor necrosis factor (TNF), a protein involved in inflammation. They are used to treat autoimmune conditions such as rheumatoid arthritis, psoriasis, and Crohn's disease.

- IL-6 inhibitors: These drugs target interleukin-6 (IL-6), a cytokine involved in inflammation and immune responses. They are used to treat conditions like rheumatoid arthritis and juvenile idiopathic arthritis.

2. Biological response modifiers: These are substances that modify the body's response to disease. They can include various types of molecules, such as cytokines or growth factors, that regulate immune function. Biological response modifiers are used to modulate immune responses in autoimmune diseases, often by either enhancing or suppressing specific immune pathways [5,12].

Targeted therapies for autoimmune diseases focus on interfering with specific molecules or pathways involved in the immune response.

1. Small molecule inhibitors: These are drugs that interfere with the activity of specific enzymes or proteins involved in immune signaling. One example is Janus kinase (JAK) inhibitors, which block the action of JAK enzymes involved in cytokine signaling. By inhibiting JAK enzymes, these medications can help reduce inflammation and control immune responses. JAK inhibitors are used to treat conditions like rheumatoid arthritis, psoriatic arthritis, and inflammatory bowel disease.

2. Specific pathway inhibitors: These drugs target specific pathways or signaling cascades involved in autoimmune diseases. For example, inhibitors of the Bruton's tyrosine kinase (BTK) pathway have been developed to treat conditions like rheumatoid arthritis and lupus by blocking B-cell activation and antibody production [1].

New treatments for autoimmune diseases present advanced approaches that promise more accurate and effective treatment. Some of these include cell therapy, which involves the genetic modification of a patient's T cells to express chimeric antigen receptors (CAR) to treat autoimmune diseases by destroying autoreactive immune cells. Another approach is stem cell therapy, which aims to suppress aberrant immune responses and repair tissues. Precision medicine offers an individualized approach to treatment based on the patient's genetic makeup and other specific characteristics, which makes it possible to develop targeted therapy for each patient. Gene editing technologies such as CRISPR-Cas9 are also in development, which can be used to alter immune cells or modulate immune pathways associated with the pathogenesis of autoimmune diseases. These new treatments promise more hope for patients with autoimmune diseases, although they are still in the early stages of research [8].

Lifestyle and complementary approaches play an important role in the treatment of autoimmune diseases, complementing medication and contributing to overall well-

being. An anti-inflammatory diet based on whole and unprocessed foods can reduce inflammation and support immune function. Some food triggers, such as gluten or dairy products, can exacerbate symptoms, so it's important to keep a food diary and experiment with elimination diets. Supplements such as vitamin D, omega-3 fatty acids and probiotics may have anti-inflammatory and immunomodulatory effects and may be beneficial for some people. Regular physical activity such as walking or yoga helps to promote health and reduce inflammation, and stress reduction techniques such as meditation promote a sense of calm. Alternative treatments, including acupuncture, probiotics and herbal supplements, can also alleviate the symptoms of autoimmune diseases, but it is necessary to seek the advice of medical professionals for safe and effective use [23].

Research in the field of autoimmune diseases continues and demonstrates various examples of successes and failures. Important achievements are stem cell therapy for multiple sclerosis, which has shown the potential to stop the progression of the disease, and CAR-T cell therapy for rheumatoid arthritis, which has led to a significant decrease in activity and inflammation. In addition, clinical trials of JAK inhibitors for the treatment of psoriasis and lupus gene therapy are underway. However, despite the successes, achieving sustained remission in autoimmune diseases is still a difficult task, and some promising treatments face challenges. Understanding the pathogenesis of autoimmune diseases remains a challenge for future research, including elucidating genetic and environmental interactions, as well as exploring the complexity of immune system dynamics. Solving these challenges will require collaboration, innovation and integration of data from different fields.

Conclusion

Autoimmune diseases are challenging to understand and treat. Key issues include pathogenesis, therapeutic strategies, challenges and future directions, and the importance of continuing research in this area. Autoimmune diseases occur due to the interaction of genetic predisposition and environmental factors, which leads to tissue damage and dysregulation of the immune response. Various methods are used in the treatment, from traditional to new, but there are problems with resistance and side effects. Continued research and collaboration are important to develop more effective treatments. Research on autoimmune diseases is crucial to meet the medical needs of patients and improve treatment outcomes. The future of autoimmune disease treatment promises a more personalized, accurate and targeted approach that optimizes results and minimizes side effects. Improvements in genomics, immunology, and therapeutic innovations will contribute to progress in understanding disease mechanisms and developing new treatments.

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