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Derleme / Review

The Interaction of Epigenetics in Autoimmune Diseases

Otoimmün Hastalıklarda Epigenetiğin Rolü

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Özet

Otoimmün hastalıkların sınıflandırılması, teşhisi ve yeni terapi yöntemlerinin bulunmasında birçok önemli gelişme olmuştur. Mevcut teoriler, otoimmün hastalıkların gelişiminin genetik yatkınlığı ve çevresel faktörlerden kaynaklanan epigenetik modifikasyonları içerdiğini ve özellikle doku hasarına neden olan kazanılmış bağışıklık sistemini tetiklediğini öne sürmektedir. Epigenetik modifikasyonlar ile genomik dizide bir değişiklik olmamasına rağmen gen ekspresyonu değişmektedir. Son yıllarda, tek gen hastalıkların patofizyolojisinde genetik yatkınlığın yanı sıra epigenetik modifikasyonların rol oynadığı tespit edilmiştir. Buradan yola çıkarak, otoimmün hastalıklara katkıda bulunan epigenetik faktörlerin anlaşılması, hedefe yönelik yeni terapilerin araştırılması ve uygulanmasına olanak sağlayabilecektir. Bu derlemede, otoimmün hastalıklarda patogenezinde epigenetik modifikasyonların önemi ve epigenetik değişikliklerin hastalığın ortaya çıkışı üzerindeki etkisi özetlenmiştir.
Anahtar Kelimeler: İmmün Tolerans, Epigenomik, Otoimmün Hastalıklar

Abstract

There have been many important developments in the classification, diagnosis, and finding of new therapies for autoimmune diseases. Current theories suggest that the development of autoimmune diseases involves genetic predisposition, and epigenetic modifications arising from environmental factors, that trigger mainly the adaptive immune pathways that eventually result in tissue destruction. Gene expression can be modified by epigenetic modifications without changing the sequence of the genome. In recent years, it has been identified that epigenetic modifications play role in the pathophysiology of single gene disease in addition to genetic predisposition. Therefore, understanding the epigenetic factors that contribute to autoimmune diseases may lead to new target-directed therapies. Here, the importance of epigenetic modifications in the pathogenesis of autoimmune diseases and the effect of epigenetic changes on the onset of the disease are summarized.
Keywords: Immune Tolerance, Epigenomics, Autoimmune Diseases

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1. Introduction

The immune system's primary function is to attack and destroy the substances that are foreign to the body. Autoimmunity is an increased immune system response to self-antigens as the immune system has trouble differentiating between self and non-self leading to various tissue and organ damage. Symptoms of this type of immune response are termed autoimmune diseases. These diseases are driven by autoantibodies and/or self-reactive T lymphocytes (1)generating mild to life-threatening self-destructive reactions in the body (2). The immune system's capacity not to damage its tissues is expressed as self-tolerance. Immune tolerance can be classified into two types: central and peripheral. The removal of autoreactive cells in the thymus for T cells and the bone marrow for B cells results in mature T and B cells that detect external pathogens while tolerating self-antigens, leading to central tolerance. Complex T cell-intrinsic processes (costimulatory signalling, transcriptional and epigenetic mechanisms) as well as external mechanisms modulate peripheral tolerance (regulatory T cells). Costimulatory signals are also necessary to activate T cells in peripheral tolerance when the TCR–peptide–MHC complex is present. T cells become "anergic" and generate self-tolerance in the absence of these signals (3). The lack of self-tolerance is the root of the majority of autoimmune diseases. Autoimmune diseases can occur when lymphocytes escape from tolerance and become activated. Unfortunately, this escape mechanism is not fully understood. The transcription factor, autoimmune regulator (AIRE,) has been associated with the central tolerance escape of T cells. CTLA 4, an inhibitory receptor, affects autoimmune disorders such as Type1 diabetes, however, its precise function is unknown. The FOXP3 gene has been demonstrated to play a function in the formation of Treg cells in experiments. Induced deletion or spontaneous mutation of the FOXP3 gene in mice results in systemic autoimmune diseases due to the lack of Treg cells. According to these findings, the FOXP3 gene tends to play an essential role in the development of autoimmune diseases (4)

Epigenetics is defined as a change in gene expression that occurs without a change in DNA sequence. Current findings have discovered the significance of epigenetics in autoimmune diseases such as type 1 diabetes (T1D) and systemic lupus erythematosus (SLE), as well as several epigenetic characteristics that can be used as disease biomarkers (5). Demethylation and hydroxymethylation of DNA have been mentioned in the pathogenesis of autoimmune diseases. For example, demethylation of the HOXA9 transcription factor has been found in T1D (6). Besides genetic and epigenetic predisposition, environmental factors such as smoking, viral infections, stress, and nutrition also play role in developing autoimmune diseases. Gender differences have been discovered to play a role in the incidence of autoimmune disorders. Various autoimmune disorders are more prevalent in women than in men (7). The two main types of autoimmune diseases are organ-specific and systemic varieties of autoimmune diseases. T1D is an example of an organ-specific autoimmune disease. In systemic autoimmune diseases, the immune system attacks multiple organs or tissues such as SLE and rheumatoid arthritis (RA) (8)

Immunity and Immunological Tolerance

Non-self molecules are recognized and attacked by the immune system. Innate and adaptive immunity are the two main components of the immune system. The initial line of protection against pathogens is the innate immune system. Skin and mucous, dendritic cells, natural killer cells, neutrophils, and macrophages are all components of the innate system (9). Adaptive immune responses are mainly carried out with their functions with lymphocytes, namely T cells, and B cells. B cells produce antibodies, which are required for long-term immune protection, whereas T cells are divided into several subclasses, each with its own set of tasks, including CD4+T helper cells, CD8+ cytotoxic cells, and regulatory T cells (Tregs) (10).

Immune tolerance refers to the ability of the immune system to prevent itself from attacking its molecules, cells, or tissues. All adaptive immune responses, whether in normal immunity or autoimmunity, begin with innate immune responses. Innate immunity has been found to have a crucial role in the protection of self-tolerance. DCs are components of innate immunity as mentioned above, key participants in establishing unbalanced active immune responses, which can contribute to the development of autoimmune disorders in those with genetic predispositions. DCs, on the other hand, are in charge of modulating inhibitory responses to self-antigens and maintaining self-tolerance. T-cell activation and other immune-mediated inflammatory responses are induced when DCs fail to acquire their tolerogenic qualities due to an elevated ratio of activating/inhibitory receptors on their surfaces (11). In order to better understand immune tolerance, several key concepts, such as central tolerance, peripheral anergy, and T regulatory cells (Tregs) and their receptors should be understood. Immune system homeostasis depends on tolerance in bone marrow and thymus. If immature T-cells are potentially reactive to self-peptides, they are negatively selected and deleted in healthy hosts. After mature T cells exit the thymus, peripheral tolerance is performed by deleting or rendering anergic most of the self-reactive T cells. For immature B cells, surface IgM that recognizes ubiquitous self-surface antigens is eliminated by a process known as clonal deletion. In a process known as receptor editing, autoreactive B cells can avoid deletion. Mature B cells also undergo peripheral tolerance. Even as there is strict tolerance control, potentially self-reactive T and/or B lymphocytes that produce autoantibodies may cause autoimmunity. (12)

Autoimmune Disorders

An autoimmune disorder is characterized by an inflammatory response to specific organs or systemic inflammation that damages tissues. These may occur, when tissue undergoes a rapid transformation due to the result of a cell-killing illness or a localized injury and this tissue damage sends out signals that cause the immune system to attack itself. It may also occur when tissue antigens and infection antigens are highly similar, and the host possesses a TCR that recognizes both. When a T-cell becomes activated, it loses its ability to distinguish between infection and tissue, and normal tissue antigens trigger a continuing immune response. However, it is seldom known which of these routes disease has evolved in humans (13). It should be noted that this may not always lead to pathology. Nevertheless, the first tolerance loss to self that sustained by both central and peripheral tolerance systems, is the first stage in autoimmune pathogenesis (14).

There is a significant impact of autoimmune disorders on mortality and morbidity. Incidence and prevalence change with distinctions in age, gender and ethnicity. However, it occurs higher in monozygotic twins and first-degree relatives. Studies have shown that genetic predisposition and environmental factors play key roles in the loss of immunologic tolerance (12) .

Epigenetic Modifications

DNA methylation, histone modifications, and miRNAs are epigenetic modifications and these modifications don't change the DNA sequence; however, they can alter the gene expression. DNA methylation is catalyzed by DNA methyltransferases (DNMTs), which attach a substituent to the 5′ end of cytosine on CpG dinucleotides. DNA methylation occurs mostly in CpG islands, which provide important regulatory functions and are located in the promoter regions of approximately half of all genes. Altered CpG island methylation can change chromatin structure and gene expression level (15). Histones comprise a globular core domain with unstructured N- and C-terminal tails. Posttranslational modifications to the N-terminal tail, including acetylation, phosphorylation, ubiquitination, and methylation, can cause significant changes in the local chromatin structure (16). These changes affect gene transcription by influencing the interaction between histones, DNA, and nuclear proteins. For example, lysine acetylation is one of the most well-

studied histone modifications, deacetylation of the terminal lysine residues contributes to gene silencing. Histone acetylation is controlled by histone acetyltransferases (HATs), which add an acetyl group to the histone tails, and histone deacetylases (HDACs), which remove the acetyl group. Histone methylation is another common histone modification. Gene expression is enhanced by methylation of histone H3 at H3K4, H3K36, and H3K79 (H3K4me2, H3K36me2/3, and H3K79me2), whereas gene expression is suppressed by methylation at H3K9me2/3, H3K27me3, and H4K20me2. Non-coding RNAs can also influence gene expression. An example of a non-coding RNA is a short miRNA, which is a genome-encoded 21 to 23 base pair RNA involved in post-translational gene regulation (17). Relationships between epigenetic modifications and autoimmune disorders have been demonstrated by several studies. As a result of these studies, specific epigenetic alterations are linked to autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and type 1 diabetes (TD1). Rheumatoid arthritis synovial fibroblasts (RASFs) play a key role in the pathophysiology of Rheumatoid arthritis (RA) through epigenetic modifications, which can activate them intrinsically and drive them to produce inflammatory cytokines. Reduced DNMT1 and LINE1 gene expression in RASFs has been shown in RA, leading to increased activity of these cells and disease progression (18).

In systemic lupus erythematosus (SLE), DNA hypomethylation play a crucial role in the pathogenesis of the disease and decreased global DNA methylation levels in T cells of individuals with active lupus were observed (19). DNA hypomethylation may change the expression of genes that cause autoreactivity (20). In lupus patients, CD4+ T cells have hypomethylation of ITGAL (21), CD11a and TNFSF7 (CD70) (22) was observed in patients. Evidence in SLE confirmed hypomethylation in CD40+ T cells, which contributes to the overexpression of SLE-related genes such as CD11a, CD70, and CD154/CD40 ligand (CD40L) (20). Furthermore, hypomethylation of the CD40L promoter was linked to clinical disease in female SLE patients (23).

Studies have shown that the DNA methylation status of RAB22A, STX1B2, and LGALS3BP are positively and DNASE1L1 and PREX1 are negatively correlated with disease activity in SLE (24). The SLE disease activity index (SLEDAI) is adversely linked with histone H3 acetylation levels (19). Histone H3 and H4 global acetylations and H3K9 global methylation have been identified in CD4+ T cells from SLE patients. In SLE, modifications of histones appear to play an important role (25). In cytokine genes, histone code changes have been extensively studied (26). JMJD3, a histone demethylase, can induce T-cell proliferation in SLE patients. In vitro studies showed that JMJD3 could regulate B-cell differentiation by promoting naive B-cell differentiation into CD27+ B cells and that Blimp-1 and Bcl-6 levels were also reduced after inhibitor treatment. These findings point in a new direction for the pathogenesis of SLE and may inspire future drug development (27).

Type 1 diabetes mellitus (T1D) is an autoimmune disease in which the pancreas insulin-producing ß-cells are destroyed, resulting in a continuous reliance on insulin therapy (28). The abnormal activation of T-helper cells and impaired functionality of Treg cells may lead to the production of autoantibodies against β-cells and contribute to the development of T1D (29). DNA methylation has a pivotal role in several biological processes, like transcriptional regulation, reversible promoter suppression, and chromosomal destabilization. The methylation status of GPX7, GSTT1, and SNX19 has been shown to directly affect the proliferation and apoptosis of pancreatic cells. Hypermethylation of FOXP3 in CD4+ cells was observed in T1D (30). Hypomethylation of CpG-19, -135, and -234 in the insulin promoter region proximal to the TSS might be associated with T1D disease progression (31). Based on methylation data and genome-wide association study (GWAS) data, they discovered that HLA-E, HLA-DOB, HLA-DQ2A, INS, IL-2RB, and CD226 were among

the differentially methylated sites (32). According to a growing body of research, histone alterations may be significant for various autoimmune diseases, including T1D. T1D patients have greater acetylated histone H4 or H3K9 acetylation versus controls in case-control studies. In addition, lymphocytes from T1D patients have higher levels of H3K9me2 in T1D-related genes, such as CTLA4, when compared to the control group (33). In T1D, miRNAs are related to β cell dysfunction. T1D is prevented by miR-21, which targets PDCD4 and prevents β cell death. Moreover, miR-25 is found to be adversely related to β cell function (29).

Rheumatoid arthritis (RA) is a complex autoimmune disease characterized by chronic inflammation of multiple joints' synovial tissues (34). Many pathogenic cell types in RA have abnormal changes in specific and global miRNA levels (35). The Wnt, NF-B, Janus kinase/signal transducer and activator of transcription (JAK/STAT), and TLR pathways are the most significantly implicated intracellular pathways in the altered expression of miRNAs (36). Elevated level expression of miR-21, miR-26a-5p, miR-203, miR-221, miR-222, miR-323-3p, and miR-346 has also been observed in RA (37). Studies showed that S100A8, S1000A11, and S1000A12 protein levels were found to be elevated in RA monocytes, mirroring their increased production in serum in RA patients (38).

2. Discussion and Conclusion

The pathophysiology of autoimmune diseases is influenced by epigenetic alterations, environmental factors, and genetic background. Greater knowledge of epigenetic mechanisms is essential to discover important target epigenetic pathways. Identifying novel biomarkers for disease prevention, diagnosis, prognosis, and individualized treatment can be aided by understanding epigenetic changes in T1D. In light of this information, by understanding the genetic history of autoimmune diseases, we can say that stem cell therapy, which will be used as a future treatment, is promising when epigenetic changes are used as a biomarker and combined with early diagnosis of diseases.

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