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Review article

The critical role of epigenetics in systemic lupus erythematosus and autoimmunity

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ABSTRACT

One of the major disappointments in human autoimmunity has been the relative failure on genome-wide association studies to provide "smoking genetic guns" that would explain the critical role of genetic susceptibility to loss of tolerance. It is well known that autoimmunity refers to the abnormal state that the dysregulated immune system attacks the healthy cells and tissues due to the loss of immunological tolerance to self-antigens. Its clinical outcomes are generally characterized by the presence of autoreactive immune cells and (or) the development of autoantibodies, leading to various types of autoimmune disorders. The etiology and pathogenesis of autoimmune diseases are highly complex. Both genetic predisposition and environmental factors such as nutrition, infection, and chemicals are implicated in the pathogenic process of autoimmunity, however, how much and by what mechanisms each of these factors contribute to the development of autoimmunity remain unclear. Epigenetics, which refers to potentially heritable changes in gene expression and function that do not involve alterations of the DNA sequence, has provided us with a brand new key to answer these questions. In the recent decades, increasing evidence have demonstrated the roles of epigenetic dysregulation, including DNA methylation, histone modification, and noncoding RNA, in the pathogenesis of autoimmune diseases, especially systemic lupus erythematosus (SLE), which have shed light on a new era for autoimmunity research. Notably, DNA hypomethylation and reactivation of the inactive X chromosome are two epigenetic hallmarks of SLE. We will herein discuss briefly how genetic studies fail to completely elucidate the pathogenesis of autoimmune diseases and present a comprehensive review on landmark epigenetic findings in autoimmune diseases, taking SLE as an extensively studied example. The epigenetics of other autoimmune diseases such as rheumatic arthritis, systemic sclerosis and primary biliary cirrhosis will also be summarized. Importantly we emphasize that the stochastic processes that lead to DNA modification may be the lynch pins that drive the initial break in tolerance.

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1. Introduction

Autoimmunity refers to the abnormal state that the dysregulated immune system attacks the healthy cells and tissues due to the loss of immunological tolerance to self-antigens. This aberrant state present clinically in the form of a wide spectrum of autoimmune disorders characterized by the presence of autoreactive immune cells and (or) the development of autoantibodies. These autoimmune responses can be widespread and involve multiple organs and systems, resulting in systemic autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatic arthritis, systemic sclerosis and primary Sjögren's syndrome, a group of disorders also commonly referred to as connective tissue diseases. The pathological damage of autoimmunity can also be limited to specific organs, causing organ-specific autoimmune diseases such as primary biliary cirrhosis, type 1 diabetes mellitus, multiple sclerosis, Hashimoto's thyroiditis, Graves' disease, and skin disorders including vitiligo and alopecia areata.

The origins of the loss of immunological tolerance to self-antigens and the mechanisms underlying autoimmunity onset and development are highly complex and remain largely unknown. Both genetic predisposition and environmental factors such as nutrition, infection, chemicals and ultraviolet exposure are considered to participate in the pathogenic process of autoimmunity [1]. However, how each of these genetic or environmental factors causes autoimmunity is still a challenging question. The emergence of epigenetic studies, arising along with the progressing of human genome project since the end of the last century, has provided us with a brand new perspective to understand these complex mechanisms and has shed light on a new era for research of autoimmunity.

Epigenetics refers to the study of potentially heritable changes in gene expression and function that do not involve alterations of the original nucleotide sequence of the DNA. The major epigenetic mechanisms, i.e. DNA methylation, histone modification, and noncoding RNA, play crucial roles in various life processes such as cellular differentiation, growth, development, ageing, and immune response [2]. These epigenetic mechanisms are implicated in the pathogenesis of in a variety of complex diseases, including autoimmune diseases. As an important complement to the genetic studies, epigenetics provides a better understanding of how environmental triggers cause changes to gene expression and disturbance to immune homeostasis. In addition, compared to the multiple mutant genes or chromosome anomalies, the reversible nature of epigenetic abnormalities provides an easier approach to being "corrected" and holds much greater potential for treatment of autoimmune diseases. Indeed, the exponentially increased number of publications on epigenetic research of autoimmune diseases is an example of how attractive and active this field has become [3–5].

To better explain the significance of epigenetics in autoimmunity, we will herein start with a brief interpretation of how genetic studies fail to completely elucidate the pathogenesis of autoimmune diseases. Taking SLE as a typical and extensively studied example, we will then present a comprehensive review of the epigenetic mechanisms implicated in pathogenesis of autoimmunity, and how these different epigenetic mechanisms interplay with each other and with genetic variants and environmental factors. We will also briefly review the significant epigenetic findings of other autoimmune disorders such as rheumatic arthritis, systemic sclerosis, and primary biliary cirrhosis to further elucidate the diverse roles of epigenetics in autoimmunity.