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Review

Epigenetic modifications and epigenetic based medication implementations of autoimmune diseases

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ABSTRACT

Recent genome-wide association studies have documented a number of genetic variants to explain mechanisms underlying autoimmune diseases. However, the precise etiology of autoimmune diseases remains largely unknown. Epigenetic mechanisms like alterations in the post-translational modification of histones and DNA methylation may potentially cause a breakdown of immune tolerance and the perpetuation of autoreactive responses. Recently, several studies both in experimental models and clinical settings proposed that the epigenome may hold the key to a better understanding of autoimmunity initiation and perpetuation. More specifically, data support the impact of epigenetic changes in autoimmune diseases, in some cases based on mechanistical observations. Epigenetic therapy already being employed in hematopoietic malignancies may also be associated with beneficial effects in autoimmune diseases. In this review, we will discuss on what we know and expect about the treatment of autoimmune disease based on epigenetic aberrations.

Contents

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1. Introduction

Autoimmune diseases are usually complex and multifactorial. Human genetics determines one's susceptibility or resistance to autoimmune diseases. However, genetic is not causal nor adequate factor for such diseases [1] and the exact mechanisms underlying of autoimmune responses are not well determined yet. Recent studies have shown a strong genetic basis behind autoimmune diseases, however, such studies have not found a particular causal gene taking part in failure of immune tolerance [2]. Studies based on epigenetic dimensions of diseases are coming along and, concurrently, their relation with clinical signs of disease is assessed. Epigenetic changes have been shown in increasing number of human diseases such as many types of cancers and autoimmune diseases (AIDs).

In the setting of autoimmunity, there is an abnormal state in which the immune system attacks against self-compartments. Nowadays, it has been accepted that AIDs are the ramification of complex and simultaneous interaction between genetic and environmental factors [3–5]. On the other hand, the significant incomplete concordance rates of autoimmune diseases in monozygotic twins strongly suggest other alternative mechanisms to participate in gene expression modulation, which eventually culminate in a disease state.

Farh et al. [6] report integrated genetic and epigenetic fine-mapping to classify causal variants in AID-associated loci and explore their functions. According to dense genotyping data [7], they established an innovative algorithm to predict for each individual variant associated with 21 AIDs, the probability that it represents a causal variant. Separately, they generated cis-regulatory element maps for a range of immune cell types. Remarkably, ~60% of likely causal variants map to enhancer-like elements, with preferential correspondence to stimulus-dependent CD4+ T-cell enhancers that respond to immune activation by increasing histone acetylation and transcribing noncoding RNAs. Although these enhancers frequently reside within extended clusters, their distinct regulatory patterns and phenotypic associations suggest that they represent independent functional units. The latter provides an exclusive resource for the study of autoimmunity, links causal disease variants with high probability to context-specific immune enhancers, and proposes that most non-coding causal variants doing by changing non-canonical regulatory sequence instead of recognizable consensus transcription factor motifs [6].

Considering the fact that many human diseases rely partially on an epigenetic dysregulation, several investigations have been focused on development of a new epigenetic based therapeutic approach, which is known as epigenetic therapy. Numerous agents that modulate DNA methylation patterns or the acetylation/methylation settings of histones have been recently explored in clinical trials for epigenetic therapy [8].

Disease onset, perpetuation and outcome of AIDs appear to be influenced by environmental triggers, which are capable of altering the epigenetic patterns [9]. Taking the drugs that can reverse aberrant epigenetic patterns into consideration, the identification and manipulation of epigenetic markers in disease, might hopefully provide novel therapeutic tools for autoimmune disorders. In this review, the circumstances in which epigenetic mechanisms might explain some of the remaining uncertainties in AID etiopathogenesis are outlined. Moreover, treatments considering the manipulation of epigenetic dysregulations will be discussed.

2. Can epigenetics explain etiopathogenesis of autoimmune diseases?

Numerous surveys attempted to disclose the etiopathology of AID and provide an understanding that environmental factors take part in the initiation and perpetuation of AIDs [10]. Nevertheless, animal model studies have confirmed that environmental factors can either initiate AID or exacerbate the disease manifestations [11]. It is well-documented nowadays that environmental factors can break immune tolerance by post-translational modifications [11,12]. Regarding these observations, it is strongly believed that epigenetics takes an important part in the etiology of AID and explains these conundrums.

3. Epigenetics and environment

Some studies have suggested a possible role for epigenetics in interaction between environment and genetics trough which environmental changes can affect gene expression (Fig. 1). First of all, investigations done on fetus have demonstrated such an attribution, using special diets for assessing probable alterations in gene expression. A study showed that pregnant rodents, Agouties, fed a diet rich of methyl donator elements, got offspring different from offspring fed a normal diet. Such an observation can be explained by DNA methylation, a well-known epigenetic mechanism [13]. Methylation deactivates "intra-cisternal A particle (IAP)", a retroviral insertional element, and eventually suppresses expression of Agouti allele. Another instance is about people from Netherland, whose fetal and infancy stage was concurrent with second world war and suffered famine resulted from war. Study of DNA methylation in regulatory regions of Insulin like Growth Factor-2 (*IGF2*) gene among aforementioned people has revealed hypo-methylation of these regions compared to other people [13]. Recent studies have found an association between DNA methylation and some environmental factors such as air pollution [14,15], using alcohol [16] and smoking [17] in prenatal period. Consequently, epigenetic mechanisms should be considered as a novel intersection between environmental and genetical interactions. It has been documented in animal studies that environmental factors (such as physical, chemical, and biological agents) can either induce AID or exacerbate the disease circumstance [18]. It is believed nowadays that environmental factors can break tolerance through posttranslational modifications as well as molecular mimicry to induce self-antigen modulation and then trigger a range of immune responses [5,19] (Fig. 1). Fraga et al. showed how epigenetics may explain discordance/concordance in autoimmune diseases among monozygotic twins [13], who show significant epigenetic and phenotype changes as they grow up. These changes are due to "epigenetic drift" and are in a relationship with different environmental pressures during life time [20].

4. An overview of epigenetic mechanisms

Epigenetics is typically known as stable but heritable alterations in gene expression without aberration in DNA nucleotides.