

# Epigenetic alterations in autoimmune rheumatic diseases

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**Abstract** | The potential roles of epigenetic alterations in the pathogenesis of autoimmune rheumatic diseases are raising great expectations among clinicians and researchers. Epigenetic mechanisms regulate gene expression and are sensitive to external stimuli, bridging the gap between environmental and genetic factors. Considerable evidence of epigenetic changes, particularly altered patterns of DNA methylation, exists in diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. The importance of such changes in the pathology of rheumatic diseases has been demonstrated by examining the relationship between gene-specific methylation and SLE in monozygotic twins discordant for the disease, in whom genetic variability is excluded as a cause for discordance. Several studies have highlighted the importance of the tissue-specificity of DNA methylation changes, an aspect which—in contrast with genetic analysis—must be considered when designing epigenetic studies. Here I discuss the proposed mechanisms and implications of DNA methylation changes in the pathogenesis of autoimmune rheumatic diseases, the prospects for future epigenetic studies in rheumatology, the relevance of specific DNA methylation markers and the potential use of drugs with an epigenetic effect in the clinical management of these diseases.

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## Introduction

The complex etiopathology of autoimmune rheumatic disorders has been attributed to crosstalk between genetic predisposition and environmental factors. The first genetic studies in autoimmune disease revealed a strong association between genes within the major histocompatibility complex (MHC), particularly human leukocyte antigen (HLA) genes, and several autoimmune diseases.<sup>1</sup> More recently, many other susceptibility genes have been uncovered, some of which, such as *PTPN22*, *IRF5*, and *STAT4*, are also associated with the development of several autoimmune rheumatic diseases,<sup>2</sup> suggesting overlap in their pathogenesis. Complexity arises from the fact that each of these susceptibility genes make small and interlinked contributions to the overall risk of disease. For example, a haplotype of *IRF5* that is associated with risk for systemic lupus erythematosus (SLE) has been linked to increased production of interferon (IFN),<sup>3</sup> and increased sensitivity to IFN- $\alpha$  in patients with SLE is caused by a variant of *STAT4* that is associated with autoimmune disease.<sup>4</sup> Over and above the expression of basic genetic variability, the contribution of genetic factors to disease risk can be modulated by the environment (Figure 1). A number of internal and external environmental factors have been associated with the etiopathology of rheumatic disorders, including viral infection, nutrition, and exposure to chemicals and radiation.<sup>5,6</sup> Such factors influence or modify the profile of epigenetic modifications, which, in turn, have a direct

relationship with the regulation of gene expression, and ultimately the function of the immune system.

Rapid progress in understanding epigenetic alterations in cancer has enabled us to determine the general mechanisms of epigenetic deregulation, identify clinical markers of epigenetic change, and embark on the development of novel therapeutic drugs.<sup>7</sup> By contrast, advances in understanding epigenetic mechanisms in the context of rheumatic diseases, as well as in other disorders, have been much slower, and studies remain confined to a small number of laboratories. Nevertheless, evidence of important roles for these types of alterations in autoimmune diseases is increasing. Furthermore, novel technologies that facilitate gene identification and the systematic search for novel epigenetically deregulated genes support the investment of research in this area. This article summarizes and discusses the evidence for epigenetic mechanisms in autoimmune rheumatic diseases, with a focus on changes in DNA methylation, and outlines the future steps to be taken in the field.

## Epigenetics and gene function

Epigenetic gene regulation has an essential role in determining individual gene function and activity, and, at the genomic level, determines which sets of genes are functional in each specific cell type. Such regulation takes the form of small chemical group additions to DNA or to the protein complex around which DNA is wrapped, particularly core histones. In brief, the two major types of epigenetic modification are DNA methylation and histone post-translational modifications. Both types of

## Competing interests

The author declares no competing interests.

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