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REVIEW

Epigenetic control of autoimmune diseases: From bench to bedside

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Abstract Genome-wide association studies have revealed several genes predisposing to autoimmunity, however, concordance rates in monozygotic twins are significantly below 50% for several autoimmune diseases. The limited presence of a strong genetic association only in some patients supports that other non-genetic mechanisms are active in these pathologies. Epigenetic modifications such as DNA methylation, histone modification, and microRNA signaling regulate gene expression and are sensitive to external stimuli and they might be as bridging between genetic and environmental factors. Some evidence has highlighted the involvement of epigenetic alterations in the pathogenesis of various autoimmune diseases giving rise to great expectations among clinicians and researchers. The direct role of these alterations in the initiation/progression of autoimmune diseases is still unclear. The knowledge in depth of these pathogenic and epigenetic mechanisms will increase the possibility of the control and/or prevention of autoimmune diseases through the use of drugs that target epigenetic pathways. Moreover, we could use epigenetic-related biomarkers to follow this complicated framework (for example H3K4me3 and miRNA-155 are among those proposed biomarkers). This article reviews current understanding of the epigenetic involvement in the field of

Abbreviations: CREMα, cAMP-responsive element modulator; DMR, differentially methylated region; DNMT, DNA methyltransferase; Gadd45a, growth arrest and DNA damage-inducible 45 alpha; HAT, histone acetyltransferase; HDAC, histone deacetylase; HMGB1, high mobility group box protein 1; HMTs, histone methyltransferases; IGFBP-1, insulin-growth factor binding protein-1; IRF, IFN regulatory factor; MBP, myelin basic protein; miRNAs, microRNAs; MMPs, matrix metalloproteinase; MS, multiple sclerosis; PAD, peptidylarginine deiminase; PBMCs, peripheral blood mononuclear cells; PP2Ac, catalytic subunit of protein phosphatase 2A; RA, rheumatoid arthritis; RFX, regulatory factor for X-Box; SHP-1, Src-homology-2-domain-containing protein tyrosine phosphatase 1; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; TET, ten-eleven translocation.

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autoimmune diseases especially in systemic lupus erythematosus, rheumatoid arthritis, sclerosis multiple and type 1 diabetes.

Contents

1. Introduction

Autoimmune disorders are complex multifactorial diseases characterized by impaired immunological response against healthy cells and tissues due to the lack of recognition and the loss of immunological tolerance versus self. Complex events triggering autoimmunity are still largely unknown for the high heterogeneity of clinical manifestations in autoimmune diseases [1].

Several studies demonstrating high concordance rates among monozygotic compared to dizygotic twins in some disorders are suggestive of a strong involvement of genetic component [2]. The susceptibility or the protection versus autoimmune disease is influenced by multiple genetic variants [3]. Many investigations have evaluated the association between autoimmunity and HLA genes involved in cellular and humoral immune response by analyzing the role of these genes in the susceptibility versus protection from disease [4]. Despite genome-wide association studies have revealed several genes that predispose to autoimmunity, the incomplete concordance rate of the autoimmune disease in monozygotic twins ranging between 12–67% and the presence of a strong genetic association only in some patients strongly supports the involvement of non-genetic mechanisms in these pathologies [5,6].

Increasing evidence shows a role for environmental factors in the development of autoimmunity considering that some of these such as drugs, ultraviolet light and diet, by acting on genetically susceptible subjects, play a causative role in the autoimmune diseases [7,8].

Furthermore, many studies highlight the involvement of epigenetic-related mechanisms in pathogenesis and development of many human diseases including autoimmune disorders [6,9]. Particularly, epigenetic modifications would represent the link between genetic and environmental factors influencing the onset and the evolution of autoimmune diseases [7,9]. Such mechanisms represent modifications in gene expression, stable and heritable, that do not involve changes in DNA sequence [10]. Moreover, epigenetic control is a regulatory mechanism that contributes to physiological processes such as cell growth, development, differentiation and genomic stability. However, epigenetic changes can result in a gene dysregulation causing various pathological conditions such as cancer or autoimmune disease. Specific alterations of epigenetic mechanisms in immune cells such as T helper cells may represent the trigger for self tolerance loss and for cell and/or tissue destruction [11].

This review summarizes recent findings on the main epigenetic mechanisms such as DNA methylation, histone modification and microRNA in the field of some autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), and type 1 diabetes (T1D).

2. Epigenetic modifications

Epigenetic modifications induce alteration of gene expression through chromatin structure change that modulates the access of transcription factors [10]. In a eukaryotic cell the