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REVIEW

Epigenetics in the treatment of systemic lupus erythematosus: Potential clinical application

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Abstract The current treatments of systemic lupus erythematosus (SLE) have been based on the use of immunosuppressive drugs which are linked to serious side effects. The more effective therapeutic approaches with minimal or no side effects for SLE patients are hard to develop, mainly due to the complexity of the disease. The discovery of pharmacoepigenetics provides a new way to solve this problem. Epigenetic modifications can influence drug efficacy by altering gene expression via changing chromatin structure. Although still in early development, epigenetic studies in SLE are expected to reveal novel therapeutic targets and disease biomarkers in autoimmunity. For example, miRNAs, which have been identified to govern many genes including drug targets, are altered in disease development and after drug administration. This review aims to present an overview of current epigenetic mechanisms involved in the pathogenesis of SLE, and discuss their potential roles in clinical and pharmacological applications.

Contents

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease characterized by T cell overactivation and B cell hyper-stimulation, with various clinical features such as skin rashes, constitutional symptoms, hair loss, arthritis, serositis, kidney and CNS involvement, among others. The incidence and prevalence of SLE are higher among non-white racial groups [1]. The etiology of SLE is multifactorial including genetic factors, sex hormones, and environmental and immunological mechanisms.

SLE therapy should be individualized and based on the patients' clinical presentations. Nowadays, SLE is primarily treated with anti-malarials, corticosteroids, high-dose immunoglobulins and immunosuppressants such as azathioprine, cyclophosphamide (CTX), methotrexate (MTX) and mycophenolic acid [2]. However, the existing drugs are far from satisfactory owing to the frequent side-effects and drug inefficiency. The heterogeneity of the disease, the unpredictable clinical course of SLE and the choice of outcome measures all confound the design of a clinical trial to show drug efficacy [3]. Although several new drugs targeting specific pathways of SLE, such as monoclonal antibodies (mAbs), especially belimumab, have entered the market, and may be an alternative to the conventional therapy of SLE in a selected group of patients [4], most of the currently used medications have frequent adverse drug reactions and serious side effects, and are of limited efficacy in different populations [5].

Epigenetics refers to alterations in gene expression without changes in DNA sequences, involving DNA methylation, histone modifications and small RNA dysfunctions. Epigenetic mechanisms play important roles both in normal growth and development, and may lead to gene dysregulation and thus a variety of pathological processes including SLE [6]. Advances in epigenetics and epigenomics provide insights into the pathogenesis of various diseases and developments of new drugs. With a great influence of epigenomic studies on pharmacology, pharmacoepigenetics, a brand new specialty, has surfaced as the study of the epigenetic basis for variations in drug responses. This review aims to summarize the epigenetic roles in the development of lupus and focus on the current and potential treatments of lupus therapies.

2. Epigenetics is involved in the pathogenesis of SLE

SLE is a complex and poorly understood autoimmune disease. The exact underlying mechanisms that lead to the breakdown of tolerance in SLE remain largely unknown. Genetic factors alone are insufficient to explain the mechanisms of the disease [7]. A growing number of reports have indicated that epigenetic mechanisms such as DNA methylation, histone modifications and RNA-based modifications may also be involved in the pathogenesis of SLE [8].

2.1. DNA methylation and SLE

DNA methylation is one of the most studied epigenetic mechanisms. It is catalyzed by DNA methyl transferases (DNMT), including DNMT3A and DNMT3B, both establish DNA methylation patterns in utero, and DNMT1, which maintains DNA methylation patterns ex utero. DNA methylation suppresses gene expression by methylating the deoxycytosine base at the 5 position to form deoxymethylcytosine [9]. Genome-wide DNA methylation studies in $CD4^+$ T cells revealed that DNA methylation plays a vital role in the pathogenesis of SLE [10,11]. $CD4^+$ T cells from idiopathic SLE patients are significantly hypomethylated compared to healthy control $CD4^+$ T cells [12]. Decreased global methylation in SLE $CD4^+$ T cells is negatively correlated with increased expression of immune related genes, such as CD11a, CD70, CD40 ligand (CD40L) and perforin (PRF1) [13–15].The X chromosome is demethylated, which can explain the predominance of SLE in women [16,17]. Procainamide and hydralazine can cause drug-induced lupus by inhibiting DNA methylation levels [18].The expression levels and enzymatic activity of DNMT1 are reduced in $CD4^+$ T cells of SLE patients [19]. Subsequent studies suggested that defective ERK signaling due to impaired phosphorylation of PKC-delta is at least in part responsible for reduced DNMT1 levels in lupus T cells [20].

Protein phosphatase 2A (PP2A) is a heterotrimeric serine/threonine phosphatase involved in essential cellular functions. In T cells from SLE patients, overexpression of the catalytic subunit of protein phosphatase 2A (PP2Ac) resulted in decreased MEK/ERK phosphorylation, decreased DNMT1