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Review article

Unfolding the pathogenesis of scleroderma through genomics and epigenomics

Pei-Suen Tsou [a], Amr H. Sawalha [a, b, *]

[a] Division of Rheumatology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA
[b] Center for Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI, USA

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ABSTRACT

With unknown etiology, scleroderma (SSc) is a multifaceted disease characterized by immune activation, vascular complications, and excessive fibrosis in internal organs. Genetic studies, including candidate gene association studies, genome-wide association studies, and whole-exome sequencing have supported the notion that while genetic susceptibility to SSc appears to be modest, SSc patients are genetically predisposed to this disease. The strongest genetic association for SSc lies within the MHC region, with loci in *HLA-DRB1*, *HLA-DQB1*, *HLA-DPB1*, and *HLA-DOA1* being the most replicated. The non-HLA genes associated with SSc are involved in various functions, with the most robust associations including genes for B and T cell activation and innate immunity. Other pathways include genes involved in extracellular matrix deposition, cytokines, and autophagy. Among these genes, *IRF5*, *STAT4*, and *CD247* were replicated most frequently while SNPs rs35677470 in *DNASE1L3*, rs5029939 in *TNFAIP3*, and rs7574685 in *STAT4* have the strongest associations with SSc. In addition to genetic predisposition, it became clear that environmental factors and epigenetic influences also contribute to the development of SSc. Epigenetics, which refers to studies that focus on heritable phenotypes resulting from changes in chromatin structure without affecting the DNA sequence, is one of the most rapidly expanding fields in biomedical research. Indeed extensive epigenetic changes have been described in SSc. Alteration in enzymes and mediators involved in DNA methylation and histone modification, as well as dysregulated non-coding RNA levels all contribute to fibrosis, immune dysregulation, and impaired angiogenesis in this disease. Genes that are affected by epigenetic dysregulation include ones involved in autoimmunity, T cell function and regulation, TGFβ pathway, Wnt pathway, extracellular matrix, and transcription factors governing fibrosis and angiogenesis. In this review, we provide a comprehensive overview of the current findings of SSc genetic susceptibility, followed by an extensive description and a systematic review of epigenetic research that has been carried out to date in SSc. We also summarize the therapeutic potential of drugs that affect epigenetic mechanisms, and outline the future prospective of genomics and epigenomics research in SSc.

Contents

* Corresponding author. Division of Rheumatology, University of Michigan, 1150 W Medical Center Dr., 5520 MSRB1, SPC 5680, Ann Arbor, MI, 48109, USA.
E-mail address: asawalha@umich.edu (A.H. Sawalha).

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1. Introduction

Systemic sclerosis (scleroderma, SSc) is a multisystem disorder with unknown etiology. It is characterized by early vascular injury, immune activation, and consequently fibrosis in the skin and internal organs. Tissue fibrosis often leads to organ dysfunction and is regarded as the major cause of disease-associated morbidity and mortality [1]. Although the overall survival in SSc has improved significantly over the years [2], mostly due to earlier diagnosis and routine evaluation of organ involvement, the therapeutic options for SSc are mainly symptom- and organ-based [3]. The lack of an efficacious treatment for SSc is partly due to the complex nature of the disease and the insufficient knowledge of the cause of this disorder.

Although there is clearly a genetic component in SSc as having a family history of SSc is one of the highest risk factors for the development of this disease [4], there is evidence that subjects with genetic predisposition to SSc also need additional environmental triggers for the disease (Fig. 1). A twin study conducted by Feghali-Bostwick et al. showed that the concordance rate for SSc twins was low compared to other autoimmune diseases and no significant differences were observed between monozygotic and dizygotic twins [5]. Environmental factors, including exposure to silica, organic solvents, welding fumes, viruses, and drugs, have been implicated in the development of SSc [6]. The molecular mechanism of how these external factors trigger an autoimmune response is still not known. However it has been postulated that these factors induce cellular and tissue damage leading to loss of immune tolerance and affecting both innate and adaptive immunity [7]. In addition, these factors can potentially affect gene expression profiles and therefore the behavior of different cell types through epigenetic mechanisms, including DNA methylation, histone modifications, as well as microRNA (miRNA) regulation.

In this review, we will provide a comprehensive overview of recent developments in the involvement of genetics and epigenetics in SSc pathogenesis. The therapeutic implications as well as the recent advances in the tools for epigenomics research will also be discussed.

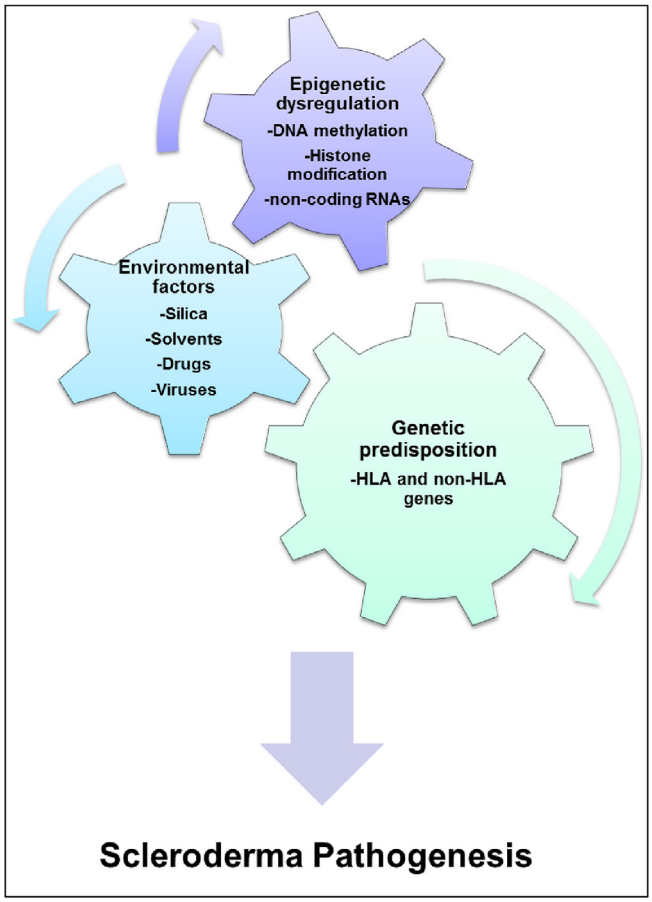

Fig. 1. Key elements pertinent to the development of scleroderma (SSc). In genetically predisposed individuals, environmental challenges, together with dysregulated epigenetic alterations, contribute to the development of SSc.