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Review

# Epigenetic mechanisms: An emerging role in pathogenesis and its therapeutic potential in systemic sclerosis☆

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ABSTRACT

Systemic sclerosis (SSc) is a heterogeneous and life-threatening autoimmune disease characterized by damage to small blood vessels, interruption of immune homeostasis and ultimately, fibrosis. Currently, the mechanisms involved in SSc pathogenesis remain unknown. An increasing amount of data shows that, *via* certain signaling pathways, epigenetic mechanisms, including DNA methylation, histone modification, and miRNAs, are closely related to the three primary processes that characterize SSc: vascular abnormalities, activation of immune system, and excessive extracellular matrix deposition. In the clinical setting, identification of molecules and biomarkers for determining disease severity, predicting disease progression and assessing response to treatment remains challenging. In this review, we aim to summarize the key epigenetic mechanisms involved in the pathogenesis of SSc. Certain cytokines or molecules, such as CD40, CD70, and Fli-1, are expressed at varying rates in SSc due to epigenetic modification and play important roles in SSc. It is therefore likely that these molecules may be biomarkers for SSc. In addition, epigenetic changes of certain genes, including Fli-1, BMPRII, CD11a, Foxp3, and eNOS, influence the expression of these genes to ultimately result in an anti-fibrotic effect. The influence that epigenetics has on SSc pathogenesis suggests that epigenetics-targeting drugs may have potential therapeutic effects against SSc. This article is part of a Directed Issue entitled: Epigenetics dynamics in development and disease.



**Contents**



*Abbreviations:* SSc, systemic sclerosis; SRC, scleroderma renal crisis; PAH, pulmonary arterial hypertension; SMR, standardized mortality ratio; DNMTs, DNA methyltransferases; SAM, S-adenosyl-methionine; 5mC, 5-methylcytosine; MBD, methyl-CpG-binding domain; Tet, ten–eleven translocation; HATs, histone acetyltransferases; HDACs, histone deacetylases; MiRNAs, microRNAs; MZ, monozygotic; DZ, dizygotic; MVECs, microvascular endothelial cells; FBs, fibroblasts; JAMs, junctional adhesion molecules; CTGF, connective tissue growth facto; TGF-β, transforming growth factor beta; CCN2, connective tissue growth factor; Fli1, Friend leukemia integration-1; TF, transcription factor; PECAM, platelet/endothelial cell adhesion molecule; PDGF, platelet derived growth factor; S1P1, sphingosin 1 phosphate; CXCL5, CXC chemokine ligand-5; BMPs, bone morphogenetic proteins; BMPRII, bone morphogenetic protein type II receptor; ET-1, endotheline-1; uPA, urokinase-type plasminogen activator; MBD, methyl-CpG-binding domain protein; ICAM, intercellular adhesion molecule; KLF5, Kruppel-like factor 5; Tregs, regulatory T cells; Runx1, Runt-related transcription factor 1; FOXP3, forkhead box protein 3 gene; ECM, extra cellular matrix; PDGF, platelet-derived growth factor; dSSc, diffuse systemic sclerosis; lSSc, limited systemic sclerosis; PCAF, protein-associated factor; Egr-1, early growth response 1; DDR2, discoidin domain receptor 2; TAB1, TGF-β activated kinase 1 binding protein 1; BAFF, B cell-activating factor; TSP-2, thrombospondin-2; MRTSS, Modified Rodnan total skin score; SDAI, Valentini scleroderma disease activity index; HC, healthy controls; SLE, systemic lupus erythematosus; SSD, scleroderma spectrum disorder; MTX, methylaminopterin; CYC, cyclophosphamide; MMF, mycophenolate mofetil; ACE, angiotensin converting enzyme; NO, nitric oxide.

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## 1. Introduction

Systemic sclerosis (SSc) is a life-threatening and complex connective tissue disease characterized by vasculopathy, autoimmune dysfunction, excessive extracellular matrix (ECM) deposition, and ultimately, fibrosis in the skin and/or other organs. The life-limiting complications of SSc include scleroderma renal crisis (SRC), pulmonary arterial hypertension (PAH), interstitial lung disease, heart failure, and gastrointestinal failure (Muangchan et al., 2013). Because of the severe and often multiple organ involvement, SSc patients have a standardized mortality ratio (SMR) of 3.24 (95% confidence interval) compared with national population (Kuo et al., 2011). The 3-year survival rate of patients with SSc-associated pulmonary hypertension is only 52% (Lefevre et al., 2013). While SSc is life-threatening and severely impacts quality-of-life, there are still no specific therapies targeting this disease. Current disease management strategies include general immunosuppression and immunomodulation, and organ-based and/or complication-specific therapies (Nagaraja et al., 2014). The identification of more sensitive and specific biomarkers of SSc presents an opportunity to develop optimal therapeutic approaches. While various studies have investigated the pathogenesis of SSc, the exact etiology underlying the development of these conditions remains for the most part unknown. However, there is consensus that environmental exposure to factors such as silica, organic solvents, bacteria, viruses, drugs, pesticides and silicones, can influence genetically susceptible individuals through epigenetic mechanisms and result in autoimmune abnormalities and fibrosis (Luo et al., 2013). Recent studies have focused on a seemingly pivotal role that epigenetics plays in the development of SSc. In this review, we focus on the recent developments in understanding epigenetics in the pathogenesis, prognostic biomarkers, and their potential therapeutic effect in SSc.

## 2. Epigenetics

Epigenetics is the study of heritable traits not caused by the changes in DNA sequence. Epigenetics mechanisms involve DNA methylation, histone modification, and non-coding RNA transcripts (Lu, 2013). In DNA methylation, DNA methyltransferases (DNMTs) transfer a methyl group to the C5 position of cytosines with S-adenosyl-methionine (SAM) as the methyl donor to form 5-methylcytosine (5mC). This programming is located mainly in the gene promoter region and the methylated state of the DNA sequence increases the binding of methyl-CpG-binding domain (MBD) proteins, decreases the binding of transcription factors, and alters the chromatin structure to form a co-repressor complex, thereby repressing gene transcription. Otherwise, the demethylation of DNA activates gene transcription (Fan and Zhang, 2009). These two different states of DNA sequences are mostly regulated by DNMTs, which consists of the following five members: maintenance DNMTs (DNMT1, DNMT2), and *de novo* DNMTs (DNMT3A, DNMT3B, DNMT3L). DNA methylation can be negatively regulated by the following two pathways: 5-hydroxymethylation through ten–eleven translocation (Tet) family of proteins and the APOBEC-mediated deamination of 5mC. While 5-hydroxymethylation leads to 5mC being hydroxylated into 5hmC by Tets (Tet1, Tet2, Tet3) (Lo and Weksberg, 2014).

Histone modification, as another epigenetic mechanism, includes acetylation, methylation, phosphorylation, deamination, β-N-acetylglucosamine, ADP ribosylation, ubiquitination, and sumoylation. This epigenetic phenomenon can change the charge of histones and affect the structure of chromatin to up-regulate or down-regulate gene expression (Yun et al., 2011). For example, histone acetylation, the most common alteration of histone, is catalyzed by histone acetyltransferases (HATs) and histone deacetylases (HDACs). While HATs transfer an acetyl group from acetyl CoA to the ε-amino group of lysine side chains, HDACs remove an acetyl group from the lysine tail. The acetylated state of histone neutralizes its positive charge which may weaken the interaction between histone and the DNA strands. Thereby acetylation results in the N-terminus of histones, due to its negatively charged phosphate backbone, to move away from the DNA strands. These changes lead to a more open chromatin structure thus upregulating gene expression (Budden et al., 2014).

MicroRNAs (MiRNAs) are a group of endogenous, non-coding RNAs that are approximately 18–25 nucleotides in length. MiRNAs are important post-transcriptional regulators of gene expression (DP); MiRNAs regulate gene expression by inducing transcript degradation or preventing translation based on the degree of complementarity between miRNA strand and 3′untranslated region (3′UTR) of the target gene mRNA and modulating DNA methylation of promoter sites and histone modifications (Bartel, 2004; Luo et al., 2013).

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