Human Immunology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Human Immunology

journal homepage: www.elsevier.com/locate/humimm

Review

Epigenetics and pathogenesis of systemic sclerosis; the ins and outs

Saeed Aslani, Soheila Sobhani, Farhad Gharibdoost, Ahmadreza Jamshidi, Mahdi Mahmoudi*

Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
SSc
Epigenetics
Fibrosis
Immune abnormality
Vascular injury

ABSTRACT

The pathogenesis of many diseases is influenced by environmental factors which can affect human genome and be inherited from generation to generation. Adverse environmental stimuli are recognized through the epigenetic regulatory complex, leading to gene expression alteration, which in turn culminates in disease outcomes. Three epigenetic regulatory mechanisms modulate the manifestation of a gene, namely DNA methylation, histone changes, and microRNAs. Both epigenetics and genetics have been implicated in the pathogenesis of systemic sclerosis (SSc) disease. Genetic inheritance rate of SSc is low and the concordance rate in both monozygotic (MZ) and dizygotic (DZ) twins is little, implying other possible pathways in SSc pathogenesis scenario. Here, we provide an extensive overview of the studies regarding different epigenetic events which may offer insights into the pathology of SSc. Furthermore, epigenetic-based interventions to treat SSc patients were discussed.

1. Introduction

Systemic sclerosis (Scleroderma, SSc) is a heterogeneous multisystem autoimmune and connective tissue disorder of unknown etiology characterized by skin fibrosis, excessive deposition of extra cellular matrix (ECM), vascular impairment, immune system abnormalities, and various organ dysfunctions such as heart, kidney, etc. [1–3]. Difficulties regarding pulmonary hypertension, intestinal perforation, Scleroderma Renal Crisis (SRC), and abnormalities in cardiac microcirculation are life-limiting complications of SSc [4–6].

By the progression of human genome project, it was shown that the pure analysis of DNA sequencing itself will not uncover the distinct mechanisms of the heterogeneity in SSc [7–8]. In other words, genetic factors have been unable to be completely responsible for the development of SSc, especially when there is little concordance rates of SSc observed in monozygotic twins [9]. Moreover, lower bound for SSc heritability in a narrow sense has been identified. Even though powerful studies of large cohorts exerting cutting-edge genotyping profiles have recognized novel loci involved in autophagy, apoptosis, and fibrosis in SSc pathogenesis, the genetic contributing factors for SSc predisposition belong predominantly to immune response loci [10].

On the other side, there is consensus that environmental factors such as viruses, pesticides, drugs, organic solvents, etc. lay an important role in the etiology of SSc as confirmed by many geographical clustering studies [11–13]. This claim is supported by the fact that the low concordance of SSc was similar in MZ and DZ twins, regarding the 4.7% concordance rate [14]. A new trend of investigations has reported epigenetic aberrant modifications in genes related to the pathogenesis of SSc. Consequently, epigenetic regulatory mechanisms orchestrate the scenario of interactions between genome and exposome and, thereby, contribute to SSc development.

Epigenetics refers to the stable and mitotically heritable modifications in both gene expression and function in a form that the DNA sequence does not change [15]. The various epigenetic alterations occurred in genes such as DNA methylation, histone modification, long non-coding RNAs (lncRNA), and miRNAs can influence the susceptibility of human beings to variety of disorders [16].

Estimations show that about 10% of common single nucleotide polymorphisms (SNPs) are linked to diversities found in methylation levels of immediate CpG sites between the two alleles. It has been proposed that methylation is a quantitative feature that is genetically modulated through methylation quantitative trait loci (methQTLs), which oftentimes seem to be cell type or tissue specific [17–18].

In this review, we provide a comprehensive overview of recent progresses with respect to the different epigenetic events which may offer insights into the pathology of SSc. In each part of this paper, according to the most important clinical specifications of SSc disease, we will discuss every proposed pathway of SSc pathogenesis by defining its mechanism and epigenetic implications.

2. Plausible connection between epigenetic abnormalities and SSc etiopathogenesis

It is a remarkable fact that different cells in the human carry the

* Corresponding author at: Rheumatology Research Center, Shariati Hospital, Kargar Ave., Tehran, Iran.
E-mail address: mahmoudim@tums.ac.ir (M. Mahmoudi).

https://doi.org/10.1016/j.humimm.2018.01.003
Received 28 September 2017; Received in revised form 25 December 2017; Accepted 8 January 2018

same genome while representing different cell types and various functions. Cells differ because they have sets of genes that can be switched on or expressed while other sets can be switched off or inhibited by factors rather than DNA chain. Epigenetics involves factors other than DNA sequence in order to control the expression of gene, leading to the monitoring of normal cellular process [19]. The human genome consists of more than three billion base pairs of DNA particles in a condition that their complete assembly makes the whole human genome which can be affected by other chemical modifications harboring DNA or DNA-associated proteins called epigenome [20]. The reason for the different distribution of autoimmunity between individuals is mainly based on the interaction between genetic factors and environmental stimuli in the progression of the disease [21]. Even though the genetic loci which seemed to have effect on the susceptibility of SSc disease have been identified, the exact mechanism of correlation between environment and genetic is not completely known [22–23]. It is nowadays a matter of consensus that SSc pathogenesis dose not rely on genetic variations only, as the identified genetic loci in SSc risk have had modest size effect. On the other hand, the concordance rate of SSc among MZ twins has not been remarkable, with the same occurrence rate observed in dizygotic twins, implying on the involvement of other mechanisms in disease etiopathogenesis [14]. Previous articles have discussed the three mechanisms for the role of epigenetic regulation in the activation of immune system, fibrosis progression and vascular injury in SSc patients [24]. Therefore, another choice, epigenetics viewpoint, is sensed to deter our mindset and look at SSc pathogenesis differently. In this part, we aim to go through the details of each epigenetic mechanism and its exact contribution to different pathogenesis perspectives of SSc.

3. The role of epigenetics in fibrosis

The three hallmarks of SSc pathogenesis include extensive fibrosis, dysregulation of both innate and adaptive immune system and vascular injury. Fibrosis is the major contributor to the high prevalence of morbidity and mortality between the three mentioned hallmarks of SSc. The most discussed feature in the pathology of SSc is cutaneous fibrosis; however, the fibrosis of visceral organs results in various clinical outcomes [25]. Whether the exact mechanisms underlying the fibrosis in SSc is not clear, the main consensus is that the endothelial cell injury triggers the release of cytokines which stimulate the production of profibrotic cytokines such as transforming growth factor-β (TGF-β), connective tissue growth factor (CTGF) and platelet-derived growth factor (PDGF) from fibroblasts [26–28].

4. DNA methylation in fibrosis

DNA methylation as well other epigenetic regulatory mechanisms have been developed to regulate various cellular mechanisms during normal physiological process. Nonetheless, dysregulations in this pathway result in aberrant gene expression settings, leading to a pathological state occurring in cancer and autoimmunity.

DNA methylation refers to covalent binding of a CH_3 methyl group to cytosines in the DNA strand. For occurrence of gene transcription process, the gene promoter is exposed to transcription factors and other regulatory proteins. DNA methylation develops a condensed DNA configuration (heterochromatin) and, therefore, prevents transcription factors from accessing to the DNA strand [29]. The CpGs determining the sites of DNA methylation are those which a cytosine nucleotide followed by a guanine (G) nucleotide, which are highly methylated in the human genome. Promoter regions of many genes also include the unmethylated CpG-rich regions, called CpG islands (CGIs). The most CGIs are known as sites with distinct chromatin conformation for the initiation of transcription process [30]. The CpGs are substrates for the DNA methyl transferases in order to provide tension for the facilitation of chromatin switching between active and inactive structures (Fig. 1) [31].

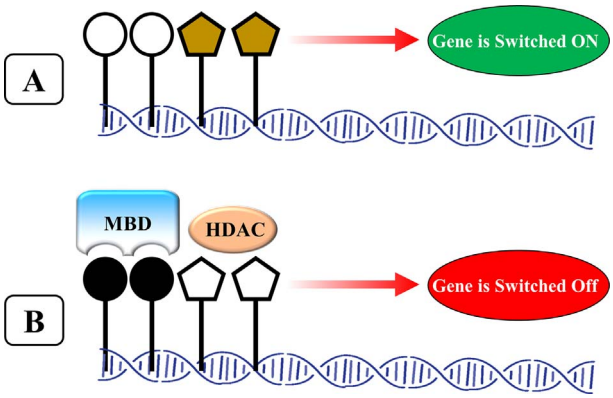

Fig. 1. Scheme illustration of DNA methylation and histone acetylation involvement in regulation of gene expression. A; Unmethylated cytosines of CpG sites and acetylated histone proteins result in euchromatin/open conformation, which allows transcription factors to bind to promoter of gene, leading to transcription initiation (green color). B; Binding of Methyl-CpG-binding domain proteins (MBD) to CpG sites alongside with deacetylation of histone proteins via histone deacetylase (HDAC) enzymes, recruited by MBD, construct heterochromatin/close conformation, which inhibit binding of transcription machinery to promoter of gene, leading to transcription suppression (red color).

The CGI DNA may impose activation or inactivation of transcriptional pathways. The interaction between different biochemical factors exaggerate the pure effect of CGIs. For example, the histone H3 trimethylated at lysine 4 (H3K4me3) tends to form a complex with inhibitor of growth 4 (ING4) PHD finger, which results in human acetylase binding to ORC1 (HBO1) acetylation on H3 tails at ING4 target promoter and thus augments the active configuration of chromatin [32]. Otherwise, the H3K4me3 will inhibit the DNA methyltransferases (DNMTs) which subsequently induce inhibitory modifications, leading to transcriptional repression [33]. The crosstalk between different molecular pathways will affect the pure tendency of CGIs on transcriptional alterations.

The skin biopsies of SSc patients demonstrated a hypermethylation of CGIs in *Friend leukemia integration-1* (*FLI1*) gene promoter region which is a main factor in suppressing the collagen transcription via sp-1-dependent pathway [34–35]. Therefore, the function of FLI1 as a negative regulator of extracellular matrix has been approved by epigenetic modification of CpG islands in SSc fibroblasts [35].

DNA methylation is the most prevalent epigenetic process which monitors the expression of developmental genes and will guide the correct marking of imprinting genes [36]. DNMTs accelerate the methylation of CpG sites in genomic DNA [37]. DNMT1 itself might be regulated by DNA methylation of promoter [38]. The elevated level of DNMT enzymes will cause the growing accumulation of collagen in dermal fibroblasts and also the fibroblasts isolated from keloid scars of SSc patients [39].

Previous studies have indicated the role of 3 biologically active DNMTs, including Dnmt1, Dnmt3a, and Dnmt3b, which are involved in the pathological process of fibrosis in various disorders like liver, heart, kidney, and SSc. The long term exposure of kidney fibroblasts to the pro-fibrotic factor TGF-β1 resulted in the activation of Dnmt1, leading to pathologic hypermethylation of *Rasal1* promoter region [40]. The Dnmt3a is a crucial factor in silencing pathways of regulatory genes. By harboring siRNAs which knockdown the Dnmt3a, the Ras association domain family 1 isoform A (RASSF1A) expression will be inhibited, resulting in activation of ERK1/2 signal pathway, which is a decisive intracellular pathway for regulating fibroblast formation in SSc patients [41].

5. Histone modifications in fibrosis

Histones are highly conserved proteins, forming dimer and tetramer complexes participating in the fundamental building blocks of