New pathways in the pathogenesis of SSc

The new frontier in systemic sclerosis: from epigenetics to new treatments

Review series on pathways in the pathogenesis of systemic sclerosis

SSc is a heterogeneous autoimmune CTD characterized by widespread vasculopathy, formation of autoantibodies and varying degrees of skin and major organ fibrosis [1, 2]. The life-threatening nature of this disease is well depicted by a 5-year mortality of 30-50% in a subset of patients with dcSSc and internal organ involvement. Despite the substantial research over the past decade, the aetiology of SSc remains poorly understood; hence treatment is often organ based and does not result in a cure. Nonetheless, the emerging role of epigenetics and the identification of new potentially disease-modifying therapies along with stem cell-based approaches to treating certain aspects of the disease are opening new windows towards personalized medicine, raising hope among researchers and clinicians.

In this issue and subsequent issues of this Journal, three SSc expert panels present a comprehensive update on epigenetics as a key pathogenic machinery worth targeting, old medications and new targeted therapies, and haematopoietic stem cell transplantation (HSCT) in the management of this condition [3-5].

In recent years, genome-wide association studies have revealed several genes that may predispose a person to develop SSc. However, the low concordance rate in monozygotic twins and the presence, only in some patients, of a strong genetic association may support the involvement of non-genetic mechanisms as well [6]. The comprehensive review by Altorok et al. [3] focuses on the pivotal role of epigenetic modifications in SSc, but leaves many questions unanswered about heterogeneous pathogenetic aspects of the disease. In particular, epigenetic modifications could represent the missing link between genetic and environmental factors influencing disease onset and evolution, hence helping to better define individual susceptibility. Such mechanisms represent stable and heritable modifications in gene expression. These mechanisms do not involve changes in DNA sequence, but include modifications in chromatin structure that modulate the access of transcription factors (i.e. DNA methylation and histone code modifications) and changes in the expression levels of miRNAs, which are small non-coding RNAs acting through negative regulation of post-transcriptional events, transcript degradation or translational suppression [6]. In SSc, specific alterations of different epigenetic mechanisms in key cellular players, such as immune cells, endothelial cells and fibroblasts, may represent the trigger for loss of self-tolerance, vascular injury and fibrosis, respectively [3]. Although the causal nature of epigenetic alterations in SSc remains elusive, oxidative stress and hypoxia are among the best candidates. Notably, epigenetic variation appears to target landmark pathways involved in SSc pathogenesis, such as TGF-β and downstream signalling cascades [3]. Furthermore, it is very important to underline that epigenetic alterations are potentially reversible. Thus, inherited epigenetic modifications can vanish after a variable number of cell divisions, and epigenetic risk factors could be counteracted by treatment with currently available epigenetic modifier molecules, such as histone deacetylase inhibitors and DNA methyltransferase inhibitors, and even synthetic miRNAs [3, 6]. However, the use of these non-specific compounds is likely limited by unwanted side effects. Whether epigenetic modifications are the cause of abnormal immune response, endothelial cell injury and fibroblast activation, or the result of disease progression, or both, still remains unknown. However, an in-depth characterization of the specific epigenome in various cell types involved in SSc pathogenesis may lead to more efficient and tailored therapeutic or even preventive strategies, or both.

In the meantime, a better understanding of other key SSc pathogenic pathways and the development of novel therapeutic agents are paving the way for new treatments of a range of disease manifestations, including skin and pulmonary fibrosis, pulmonary arterial hypertension and digital ulcers [4, 7]. As thoroughly reviewed by Nagaraja et al. [4], current treatment of SSc is mainly organ based and employs compounds that are used in clinical practice for a variety of autoimmune, cardiovascular and fibrotic conditions, independent of pathogenic mechanisms. Currently, there is no efficient regulatory body-approved treatment for skin fibrosis. Data from treatment trials in SSc support the use of immunosuppressive therapy (i.e. CYC), with the treatment benefit largely relating to the prevention of progression of interstitial lung disease. Recently, the use of targeted therapies and the intensity of the treatment have been considered as pivotal issues for SSc management. Today, the only targeted therapies in SSc are the oral endothelin receptor antagonists and PDE-5 inhibitors that have been associated with
substantial haemodynamic improvements in pulmonary arterial hypertension [4] and the reduction of the occurrence of new digital ulcers in SSc patients with multiple ulcers [8]. However, in the past decade the most significant progress in this field has been the discovery of a large number of cellular and molecular key players in the pathogenesis of fibrotic disease manifestations. This has led to the identification of novel possible candidates as molecular targets for the treatment of SSc-related fibrosis [4, 9]. On the basis of their level of evidence, from preclinical studies and first clinical results, the most promising targets are the inhibitors of B cells, TGF-β and connective tissue growth factor pathways, tyrosine kinases, serotonin receptors, IL-6 receptor and Wnt, Hedgehog and Notch morphogen pathways [4, 9]. In particular, several inhibitors of Wnt, Hedgehog and Notch have recently been developed, and some have already been approved for clinical trials [9]. Finally, besides novel potential molecular-based therapeutic approaches, van Laar et al. [5] provide an overview on the use of high-intensity treatment such as HSCT for SSc patients with a poor prognosis. Of note, a recent randomized clinical trial showed that in selected patients with early dcSSc, autologous HSCT using high-dose CYC and reinfusion of mobilized CD34+ cells was more effective than conventional monthly i.v. pulse CYC and, despite an early treatment-related mortality rate of 10.1% and an increase in serious adverse events, had a long-term survival benefit [10]. In some patients, HSCT even sustained complete normalization of skin changes and reversal of positive autantibody status, allowing withdrawal of immunosuppressive medication [10].

The present series of articles, devoted to cutting edge novel understanding of and therapies for SSc, may partly disclose the impressive increase in knowledge of the mechanisms of the disease pathogenesis and may also help in understanding some therapeutic burning issues. In the near future, the new wave of clinical trials exploring the efficacy of new drugs targeting cytokines and costimulatory molecules may shed light on relevant pathways to be pursued for an efficient disease-modifying strategy for SSc.

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