Best Practice & Research Clinical Rheumatology 25 (2011) 843–858

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

8

Emerging targeted therapies in scleroderma lung and skin fibrosis

Britta Maurer, Oliver Distler*

Department of Rheumatology and Center of Experimental Rheumatology, University Hospital Zurich, Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland

Keywords:
SSc
Skin fibrosis
Interstitial lung disease
Targeted anti-fibrotic therapies

Systemic sclerosis (SSc) is a multisystemic fibrotic disorder that affects the skin and internal organs. Despite an improved outcome probably reflecting a better management of disease complications, morbidity and mortality remain higher than those of patients with other connective tissue diseases. SSc is still considered incurable; however, during recent years, intensive research activities have deepened the understanding of pathogenic mechanisms and have led to the identification of cellular and molecular anti-fibrotic targets. This review article will discuss potential future targeted therapeutic options based on data from *in vitro* studies, experimental models of fibrosis and first human trials with focus on scleroderma skin and lung fibrosis.

Systemic sclerosis (SSc) is a multisystemic fibrotic disorder that affects the skin and internal organs. Current pathogenic concepts suggest that based on a genetic susceptibility, exogenous stimuli such as infections trigger the onset of the disease. Microvascular injury is supposed to be the initial event which together with inflammatory and autoimmune reactions leads to the activation and transdifferentiation of fibroblasts to myofibroblasts finally resulting in tissue fibrosis [1].

SSc has a worldwide distribution with a prevalence of approximately 0.07% and a female preponderance. The health-related quality of life of scleroderma patients is remarkably decreased compared to the general population. Besides fatigue, which is often among the leading complaints of patients, approximately 80% of patients suffer from gastrointestinal disturbances. Skin fibrosis may lead to joint contractures and impaired mobility, and may affect the facial appearance with hypomimic features and

* Corresponding author. University Hospital Zurich, Gloriastrasse 25, 8091 Zurich, Switzerland. Tel.: +41 44 2552977; fax: +41 44 2554170.
E-mail address: oliver.distler@usz.ch (O. Distler).

1521-6942/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.berh.2011.11.007

microstomia. Physical activity may be further impaired due to lung and cardiac involvement with approximately 50% of patients experiencing dyspnoea. Despite a slightly improved outcome, which probably reflects a better management of disease complications, the mortality remains high with a 10-year survival rate of approximately 55–66%. Whereas in the 1970s scleroderma renal crisis was the main cause of SSc-associated deaths, to date, interstitial lung disease (ILD) and pulmonary arterial hypertension account for >60% of SSc-related mortality [2].

SSc is still considered incurable, but during the last decade basic science and translational studies have provided substantial novel insights into pathogenic mechanisms leading to the identification of numerous cellular and molecular pro-fibrotic key players of which some may qualify as therapeutic targets.

In the present review we will discuss currently available and emerging future therapeutic options with emphasis on molecular or cell-based targeted therapies for skin and lung fibrosis as two of the most devastating complications of the disease. An overview of the discussed targets and currently available drugs will be provided in Table 1. Additionally, challenges for clinical study design and evaluation will be addressed.

Genetic susceptibility

SSc occurs more frequently in families (1.6%) than in the general population (0.026%). These data suggest an approximately 15-fold higher risk for SSc for siblings and an approximately 13-fold higher risk for first-degree relatives [3]. However, another study on familial aggregation reports a lower relative risk for first- and second-degree relatives of approximately 3.0 [4].

SSc is a complex disease that develops in genetically predisposed individuals, and candidate-gene studies have implicated polymorphisms of multiple genetic factors regulating immune, vascular functions, and the synthesis of extracellular matrix to increase the individual risk for SSc. However, it seems that the contribution of individual genes to the genetic risk for SSc may be rather modest and that multiple loci are involved. Therefore, gene–gene interaction studies and especially genome-wide association studies with large sample sizes are more likely to elucidate pathogenic implications of gene variations. Polymorphisms of STAT4, IRF5, TBX21, BANK1, C8orf13-BLK and NLRP1 have been found to additively increase the risk for SSc and SSc-associated lung disease. However, the candidate-gene approach has led to the identification of only few risk loci for SSc, since large sample sizes like those of genome-wide association studies are required to detect novel risk loci. A recent GWAS study (GWAS, genome-wide association study) identified one new locus at CD247 in a US/European cohort and confirmed the role of the MHC, IRF5 and STAT4 gene regions as SSc genetic risk factors [5]. Another genome-wide association study identified two additional risk loci, PSORS1C1 and TNIP1, and a putative one close to the RHOB gene [6]. Recently, three new non-HLA genes (IRF8, GRB10 and SOX5) associated with SSc clinical and auto-antibody subgroups were identified, whereas within the HLA region, HLA-DQB1, HLA-DPA1/B1 and NOTCH4 associations with SSc were suggested to be confined to specific auto-antibodies [7].

One of the most interesting aspects of the identification of genetic susceptibility genes for SSc is the discovery of shared genetic risk factors with a number of different autoimmune diseases. For example, PTPN22, STAT4, IRF5, TNFS4, BANK1, C8orf13-BLK and CD247 are also susceptibility genes for systemic lupus erythematosus (SLE) and/or rheumatoid arthritis (RA) [8,9]. This might indicate a common immunological background or a common immunological repertoire at disease initiation. However, despite the genetic similarities between SSc and, for example, SLE, there must be unique disease-specific factors that contribute to the distinct clinical features. In summary, despite a certain genetic susceptibility in the development of SSc, the influence of single loci seems rather modest but may be enhanced due to gene–gene or gene–environment interactions.

Epigenetic modifications

Sustained activation of fibroblasts with synthesis and accumulation of excessive amounts of extracellular matrix proteins leads to progressive tissue fibrosis in SSc. Epigenetic modifications include all inherited changes in gene expression that are not encoded in the nucleotide sequence of the