EGR-LEY AWAITING A “PERSONALIZED MEDICINE” APPROACH TO TREAT SCLERODERMA

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ABSTRACT

Scleroderma, an autoimmune disorder characterized by skin and organ fibrosis, has no treatment. Although over the past decade valuable insights into the molecular mechanisms underlying scleroderma have been generated, results in clinical trials have been disappointing. This issue is likely to arise due to the heterogeneity of scleroderma. Molecular insights into the heterogeneity of this disease have been provided by genome-wide expression profiling. In a recent paper, Bhattacharyya and colleagues (PLOS One, 2011; 6: e23082) to show that the overexpression of a range of “fibroproliferative” genes in diffuse cutaneous scleroderma patients are likely to be caused by the overexpression of transcription factor Early growth response (Egr)-1. Only a minority of Egr-1-regulated genes were also found to be regulated by TGF-β. Moreover, Greenblatt and colleagues (Am J Pathol., epub) have shown that the overexpression of “inflammatory” genes overexpressed in “localized” scleroderma and a small subset of limited and diffuse scleroderma patients is likely to be due to the activity of interleukin-13 (IL-13). Intriguingly, at a gene expression level, murine sclerodermatous graft-versus-host disease (sclGVHD) approximates this subset of scleroderma. These data suggest that targeting Egr-1 expression/activity might be a novel therapeutic strategy to control fibrosis in a subset of diffuse scleroderma patients, and further emphasize that notion that elevated TGFβ signaling is insufficient to explain the fibrosis observed in scleroderma. Moreover, targeting IL-13 expression/activity might be a novel therapeutic strategy to target the inflammation leading to “localized” scleroderma.
Scleroderma is a multisystem autoimmune disease that is characterized by the presence of auto-antibodies, vascular damage, and fibrosis (Abraham et al., 2009). A two-disease subset model of the systemic form of scleroderma (systemic sclerosis, SSc), consisting of limited and diffuse scleroderma (ISSc and dSSc, respectively) based on the extent of cutaneous involvement, is commonly used today (LeRoy and Medsger, 2001). Localized scleroderma (LS) (also called morphea) affects mainly children and is restricted to a specific area. Unlike SSc, LS appears has histopathologic similarities to chronic graft-vs-host disease (cGVHD) (Fleming et al., 2009; Zulian, 2008).

Research conducted in the past decade has led to a much better appreciation of the pathogenic mechanisms underlying scleroderma. For example, both non-canonical transforming growth factor (TGF)β and endothelin-1 signaling is important for the activated fibrotic phenotype of the myofibroblasts found in the lesional areas of diffuse SSc patients (Leask, 2008). However, in spite of this rapid progress, results in clinical trials have been disappointing. The literature is filled with observations that certain antifibrotic compounds in individuals, but data often conflicts among treatment groups, and the results of randomly controlled clinical trials have been disappointing (Denton et al., 2007; Giordano et al., 2010; Seibold et al., 2010; Simms and Lafyatis, 2010). A possibility for why large clinical trials have not yielded positive results may be due to the fact that SSc is a heterogeneous disease; clinical manifestations of SSc vary from patient to patient. This heterogeneity is masked by grouping these patients into the same clinical trial. That is, definitive conclusions regarding the efficacy of particular drugs cannot be made unless patient heterogeneity is considered.

An ideal method that allows the heterogeneity of scleroderma to be captured is genome-wide expression profiling, which allows the examination of tens of thousands of genes at one time. This technique has been used by Whitfield and collaborators to show that the skin of SSc patients possess a gene expression profile that is reproducibly different than that of the skin of healthy individuals. Given that SSc is by definition systemic, it was not surprising that lesional and non-lesional skin possesses essentially identical gene expression profiles (Whitfield et al., 2003).
Whitfield and collaborators went on to use functional cluster analysis to further subcategorize the gene expression profile of SSc patients’ skin. Healthy control skin (and some dSSc and lSSc patients) possessed a “normal” gene expression profile. LS and a small subset of lSSc and dSSc patients possessed an “inflammatory” signature. Finally, dSSc patients possessed a “diffuse-proliferation” (fibroproliferative) gene expression profile. As might be expected, given the notion that TGFβ signaling and its downstream mediator endothelin-1 contribute to the fibrosis observed in dSSc (Leask, 2008), a subset of genes in the “diffuse-proliferation” corresponded to a gene expression signature that was found in normal fibroblasts treated with TGFβ (“TGFβ-responsive” signature) (Sargent et al., 2010; Greenblatt et al., in press).

In a recent study, the expression profile of dSSc patients was characterized further. The transcription factor early growth response (Egr)-1 appears to be important for fibrosis. Egr-1 is upregulated in fibrotic conditions including SSc and is required for bleomycin-induced fibrosis (Bhattacharyya et al., 2011a). When overexpressed in human dermal fibroblasts, Egr-1 elicited the overexpression of a set of genes that this ‘Egr-responsive’ signature corresponded with a group of genes also found in the “diffuse-proliferation” group of dSSc patients (Bhattacharyya et al., 2011b). Intriguingly, this profile was distinct from the ‘TGFβ-responsive’ signature that was revealed by microarray analysis (Bhattacharyya et al., 2011b). These data provide yet another illustration that canonical TGFβ signaling is insufficient to explain the SSc phenotype (Holmes et al., 2001; Ishida et al., 2006).

Greenblatt and colleagues (in press) also used genome-wide expression profiling to show that murine sclerodermatous graft-versus-host disease (sclGVHD) approximates the “inflammatory” expression signature that is especially important in LS. These two subsets showed IL-13 cytokine pathway activation. Of the genes coordinately upregulated in sclGVHD, the human inflammatory subset, and IL-13-treated fibroblasts, the chemokine CCL2 emerged. Finally, anti-CCL2 antibodies prevented sclGVHD. Collectively these data suggest that an inflammatory subset of scleroderma (most notably LS patients) is driven by IL-13.
These observations illustrate the heterogeneity of SSc at a molecular level and suggest that targeting Egr-1 expression or activity might be a novel therapeutic strategy to control fibrosis in specific SSc subsets. Blockade of IL-13/CCL2 may be important especially in LS. These results point to the potential validity ‘personalized medicine’ to treat SSc.

REFERENCES


