CONNECTIVE TISSUE DISEASES

Integrins crucial for the onset of fibrosis in systemic sclerosis—a new therapeutic target?

Insights into the role of integrins and the potential for integrin-modulating therapies for the prevention of fibrosis in systemic sclerosis (SSc) have been revealed by a new study published in *Nature*. The study

Skin from wild-type (top) and mutant mice with SSc (bottom). Trichrome stain (blue) shows expanded zone of dense dermal collagen and complete replacement of subcutaneous fat by 3 months in mutant mice. Courtesy of E. E. Gerber.

findings demonstrate that alterations in cell–matrix interactions initiate inflammation and profibrotic pathways that could prove useful as future therapeutic targets for treatment of SSc.

In Hal Dietz's laboratory, Elizabeth Gerber and colleagues developed two different mouse models of stiff skin syndrome (SSS) to gain insights into the onset of fibrosis in SSc. "One model had a mutation in the fibrillin-1 gene, which regulates TGF- β that we had seen in a SSS family," explains Gerber, whilst "the other, we changed the RGD sequence to RGE," which led to a loss of integrin binding.

Both types of mutant mice developed skin fibrosis that mimicked human disease, including increased collagen deposition and disorganized microfibrillar aggregates in the dermis. Crucially, skin fibrosis in mutant mice could be prevented by modulating integrins (by use of β 1 integrin-activating

antibody or targeted deficiency in β 3 integrin), and reversed by antagonism of TGF- β . Proinflammatory immune cells (such as plasmacytoid dendritic cells and helper T cells) and autoantibody production were observed in skin samples from mutant mice, features that were not observed in mutant mice treated with integrin-modulating therapies or TGF- β neutralizing antibody.

"These data suggest many potential therapeutic strategies for SSc, including β 1 integrin agonists and antagonists to β 3 integrin, TGF- β and ERK," says Gerber, who plans further testing of these therapies in experimental models and hopes for future progress to clinical trials in humans.

Katrina Ray

Original article Gerber, E. E. *et al.* Integrin modulating therapies prevent fibrosis and autoimmunity in mouse models of scleroderma. *Nature* doi:10.1038/12614