FIBROTIC DISEASE

Fixing a feedback loop in fibrosis

> NR4A1 deficiency exacerbates TGFβ-associated fibrosis

Transient signalling by transforming growth factor-β (TGFβ) is crucial in tissue repair, but in fibrotic diseases, TGFβ signalling is chronically upregulated, leading to overproduction of collagen and extracellular matrix by activated fibroblasts. Now, Palumbo-Zerr and colleagues in the Distler group show that this may be due to a broken regulatory loop involving the nuclear receptor NR4A1, and that cytosporone B (Csn-B; a known selective NR4A1 transcriptional agonist) can ameliorate several mouse models of fibrosis.

First, the authors found that levels of *NR4A1* mRNA were higher in fibrotic skin of patients with systemic sclerosis than with healthy skin, and showed that TGFβ signalling induces NR4A1 expression in dermal fibroblasts.

In mice overexpressing a constitutively active TGFβ receptor type I (TBRI mice; a model of fibrosis), as well as in two other mouse models of skin fibrosis and a model of lung fibrosis, genetic deficiency of NR4A1 exacerbated fibrotic symptoms, including increased TGFβ signalling and numbers of fibroblasts. The authors demonstrated that NR4A1 recruits complexes that contain SP1 and histone deacetylase 1 to epigenetically silence TGFβ target genes, such as those encoding collagen. Together, these data indicate that NR4A1 usually downregulates TGFβ signalling, and NR4A1 deficiency exacerbates TGFβ-associated fibrosis.

Interestingly, fibroblasts chronically or repeatedly exposed to TGFβ showed an initial increase followed by a reduction in levels of NR4A1. By contrast, levels of phosphorylated NR4A1 (pNR4A1) — which cannot bind SP1 — rose steadily in fibroblasts stimulated with TGFβ, and were elevated in TBRI mice and in fibrotic tissues of animals in other models of fibrosis. These findings suggest that long-term exposure to TGFβ — as in fibrosis — may induce NR4A1 phosphorylation and thus impair NR4A1-mediated repression of TGFβ target genes.

Finally, the authors investigated whether activating NR4A1 with Csn-B could reduce fibrosis. In TBRI mice, but not in *Nr4a1*$^{-/-}$ TBRI mice, Csn-B (injected intraperitoneally) lowered TGFβ-target-gene expression, collagen production, dermal thickening and myoblast differentiation. Csn-B ameliorated fibrosis in models of skin, pulmonary, hepatic and renal fibrosis, even when the drug was administered after fibrosis had been established.

Substantial efforts have been made to target TGFβ signalling in disease — particularly in cancer — but have often been limited by the challenges of achieving a viable therapeutic window, given the complex, 'double-edged' nature of TGFβ signalling. Overall, this study indicates that NR4A1 agonists could provide a new way to therapeutically intervene in a TGFβ regulatory loop that is impaired in fibrosis, but potential side effects will need careful consideration.

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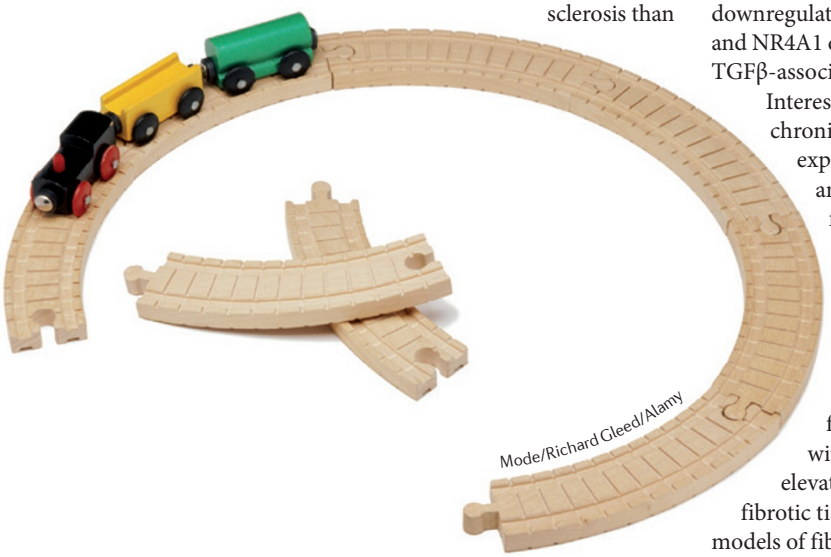

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