CONNECTIVE TISSUE DISEASES
NOTCH INHIBITION
PREVENTS FIBROSIS

New results show that the Notch signaling pathway is activated in patients with systemic sclerosis (SSc), and that inhibition of this pathway in several mouse models of SSc not only prevents skin fibrosis, but also induces regression of established dermal thickening. Such fibrosis, resulting from the activation of fibroblasts, is a characteristic feature of SSc.

Notch signaling is essential for the regulation of cell differentiation, and aberrant activation of this pathway is implicated in the pathogenesis of several malignancies. Cleavage of the Notch receptor by γ -secretase leads to release of the Notch intracellular domain (NICD), which translocates to the nucleus and activates Notch target genes.

The accumulation of NICD was detected by immunohistochemistry in skin biopsy samples from 11 patients with SSc, but not in those from 8 healthy controls. The patients also had increased messenger RNA levels of the Notch target gene *HES1*. Blocking the Notch pathway with DAPT, a γ -secretase inhibitor, reduced dermal thickening in the bleomycin-induced and *Fbn1*^{Tsk} mouse models of skin fibrosis (representative of the early and late stages of SSc, respectively). The researchers also demonstrated that inhibition of Notch signaling led to regression of established thickening in a modified model of bleomycin-induced fibrosis. Dermal fibrosis markedly decreased in mice challenged with bleomycin for 6 weeks and treated with DAPT for the last 3 weeks, compared with animals that did not receive the antifibrotic agent.

The researchers conclude that inhibition of Notch signaling could be a potential molecular target for antifibrotic therapies, and that their findings might lead to clinical trials of Notch pathway inhibitors in patients with SSc.

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