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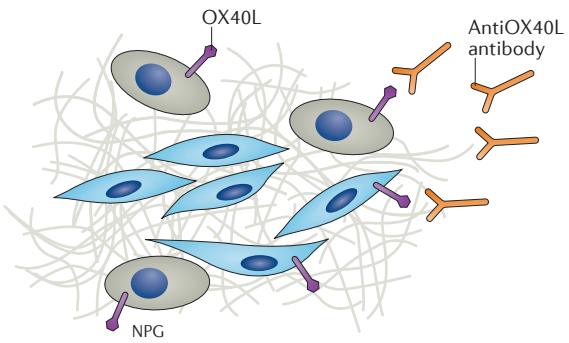
CONNECTIVE TISSUE DISEASES

OX40L inhibition blocks tissue fibrosis

> "…lesion sites had reduced numbers of infiltrating inflammatory cells…"

Blockade of the glycoprotein OX40 and its ligand OX40L (which are involved in late co-stimulatory signalling in T cells) might be effective in treating fibrotic disease, according to the results of a new study. Although previous work in animal models had shown that blocking OX40 and OX40L can prevent the development of several inflammatory and autoimmune diseases, this new study provides evidence that the same approach can both prevent the development of inflammation-driven fibrosis and ameliorate established fibrosis in mouse models of systemic sclerosis (SSc).

"Genetic studies have suggested that *TNFSF4*, which encodes OX40L, is an SSc susceptibility gene, suggesting a potential role of this pathway in SSc," explains Muriel Elhai, lead author of the study.



In fibrotic skin samples from patients with SSc, Elhai and colleagues found that OX40L is expressed in T cells, B cells and endothelial cells as expected. However, the researchers also found high levels of expression (3.6-fold greater than in the skin of healthy controls) in fibroblasts and myofibroblasts from these patients.

To determine whether the presence of OX40L had any functional relevance in fibrosis, the researchers used a model of bleomycin-induced dermal fibrosis in *Tnfsf4*$^{-/-}$ mice. Not only were these mice protected from developing bleomycin-induced fibrosis, but lesion sites in these mice had reduced numbers of infiltrating inflammatory cells and reduced levels of proinflammatory cytokines compared with lesion sites in wild-type mice.

Elhai and colleagues then blocked OX40L with a monoclonal antibody in mice with bleomycin-induced fibrosis. Anti-OX40L both prevented the development of dermal fibrosis and induced regression of established fibrosis. "These very promising results led us to investigate the effect of our antibody on prevention of severe involvement in SSc using the FRA2 transgenic mouse model," says Elhai. These mice spontaneously develop remodelling of pulmonary arteries and interstitial lung disease, resembling human SSc-associated pulmonary arterial hypertension.

Treatment with anti-OX40L was protective against both fibrosing alveolitis and pulmonary arterial hypertension in FRA2 transgenic mice, suggesting that OX40L blockade could be a promising therapeutic approach for SSc. To this end, the research team are planning a proof-of-concept study to see whether an existing human OX40L monoclonal antibody (which was well tolerated in phase II trials for mild allergic asthma) could be repurposed for use in the treatment of SSc.

Joanna Collison

ORIGINAL ARTICLE Elhai, M. *et al.* OX40L blockade protects against inflammation-driven fibrosis. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1523512113 (2016)