Nature Reviews Drug Discovery | Published online 22 Jul 2016; doi:10.1038/nrd.2016.144

INFLAMMATORY DISEASE

T cell-targeted antibody reverses fibrosis

Fibrosis is a pathological feature of most chronic inflammatory diseases, attributed to the accumulation of extracellular matrix components, resulting in progressive tissue damage and eventual organ failure. There are currently no effective therapies that prevent or counteract the fibrotic process. Now, writing in *PNAS,* Allanore *et al.* identify a key role for the tumour necrosis factor superfamily member OX40L in the development of inflammation-driven fibrosis. OX40L blockade prevented fibrosis and induced the regression of established fibrosis in mouse models of the disease.

The glycoprotein OX40–OX40L pair is transiently expressed following antigen recognition and involved in late T cell costimulatory signalling. Interestingly, the gene encoding OX40L, *TNFSF4*, has been identified as a susceptibility gene for the prototypic autoimmune fibrotic disease systemic sclerosis (SSc). In addition, serum OX40 levels have been reported to be significantly higher in patients with SSc than in healthy individuals. Allanore and colleagues therefore set out to further study the role of OX40L in SSc and explore its potential to be therapeutically targeted.

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The authors first analysed biopsy samples taken from the lesional skin of patients with SSc, and found that expression of OX40L was 3.6-fold higher than in skin from healthy individuals. In addition, levels of soluble OX40L were significantly higher in patients with SSc than in healthy controls, with a high serum OX40L level at baseline being predictive of worsening of dermal fibrosis and lung fibrosis, as well as development of pulmonary arterial hypertension (PAH), during the follow-up period of 7 years.

Next, Allanore and colleagues studied OX40L-deficient mice (*Ox40l*$^{-/-}$ mice) and found them to be protected from bleomycin-induced dermal fibrosis — a widely used model of SSc that mimics the early and inflammatory stages of the disease. Levels of T cells, B cells, natural killer cells, macrophages and pro-inflammatory cytokines were significantly reduced in lesional skin of *Ox40l*$^{-/-}$ mice compared to control mice. Gene expression analysis revealed that downregulation of the AP-1 pathway was likely to be involved in mediating these effects.

Blockade of OX40L using a monoclonal antibody (mAb) similarly protected mice against the development of bleomycin-induced fibrosis when treatment was initiated 1 day prior to bleomycin injection. Furthermore, injection of mice exhibiting established fibrosis with the anti-OX40L mAb for 3 weeks induced fibrosis regression, significantly decreasing dermal thickness, collagen content and myofibroblast recruitment.

The OX40L mAb was also effective in a second mouse model of SSc — mice deficient in the FOS-related antigen FRA2 (*Fra2*$^{-/-}$ mice), which exhibit interstitial lung involvement and develop PAH. Treatment of 13-week-old *Fra2*$^{-/-}$ mice with the OX40L mAb for 5 weeks protected against fibrosing alveolitis, reduced perivascular inflammatory infiltrates and prevented the vessel remodelling that leads to PAH.

The authors note that, to their knowledge, this study provides the first evidence that OX40L is involved in the development of inflammation-driven fibrosis and that it may represent a promising disease biomarker. Notably, a human anti-OX40L mAb is currently in clinical development for the treatment of patients with mild allergic asthma.

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ORIGINAL ARTICLE Elhai, M. *et al.* OX40L blockade protects against inflammation-driven fibrosis. *Proc. Natl Acad. Sci. USA* **113**, E3901–E3910 (2016)