AUTOIMMUNE DISEASE

New route to targeting TNF

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The pro-inflammatory cytokine tumour necrosis factor (TNF) is a major target in the treatment of inflammatory autoimmune diseases, such as rheumatoid arthritis (RA). However, currently marketed TNF-targeted agents are not effective in all patients with RA and have been associated with serious adverse effects. Now, reporting in *Science*, Liu and colleagues identify a novel TNF receptor ligand that exhibits potent anti-inflammatory activity in mouse models of arthritis, and may therefore lead to novel therapies.

Although the autocrine growth factor progranulin (PGRN) is implicated in a variety of disease processes, including tumorigenesis and inflammation, its receptors have remained unidentified, thus hampering any potential therapeutic exploitation of this molecule. Given this, Liu and colleagues sought to better understand the mechanism of action and functions of PGRN.

First, by screening a yeast cDNA library, they identified TNF receptor 2 (TNFR2) as a PGRN-associated protein. Additional *in vitro* studies revealed that PGRN bound with equal affinity to both TNFR isoforms. Furthermore, PGRN prevented TNF binding, which resulted in blockade of downstream inflammatory signalling pathways. Consequently, PGRN exhibited potent anti-inflammatory effects *in vivo* — *Pgrn* knockout mice were highly susceptible to collagen-induced arthritis (CIA), whereas treatment with intraperitoneal recombinant human PGRN (rhPGRN) completely blocked disease progression and prevented inflammation.

Next, to explore the therapeutic potential of PGRN as an anti-inflammatory agent, the authors identified the exact domains of this molecule that are required for its interaction with TNFRs. Using this information, they generated a mutant peptide that exhibited greater selectivity for TNFRs than PGRN, which they termed Atsttrin ('antagonist of TNF–TNFR signalling via targeting to TNF receptors').

This novel peptide comprised half-units of the PGRN domains A, C and F plus the linker regions P3, P4 and P5. Like PGRN, Atsttrin inhibited TNF–TNFR signalling pathways, prevented inflammation and suppressed disease progression in several mouse models of arthritis. Strikingly, Atsttrin exhibited greater efficacy than both rhPGRN and etanercept (a TNF inhibitor that is currently used for treating autoimmune diseases such as RA), and a single intraperitoneal dose of Atsttrin (10 mg per kg) delayed the onset of inflammation for 3 weeks in mice that were subjected to CIA. Atsttrin was also effective at treating mice with established CIA. Importantly, both rhPGRN and Atsttrin were well tolerated.

These findings may lead to novel therapies with potential applications in an array of TNF-associated disorders. Liu has co-founded a company, ATreaon, to further develop Atsttrin.

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ORIGINAL RESEARCH PAPER Tang, W. *et al.* The growth factor progranulin binds to TNF receptors and is therapeutic against inflammatory arthritis in mice. *Science* 10 Mar 2011 (doi:10.1126/science.1199214)