Nature Reviews Drug Discovery | AOP, published online 21 September 2015; doi:10.1038/nrd4745

BONE DISEASES

Targeting myostatin for direct joint defence

> MSTN enhances RANKL-induced formation of osteoclasts and thus contributes to the degradation of bone in inflammatory arthritis

Rheumatoid arthritis (RA) is an autoimmune disease characterized by inflammatory joint erosion resulting from increased bone degradation by osteoclasts and diminished bone repair by osteoblasts. Now, Pap and colleagues show that blocking myostatin (MSTN; also known as growth and differentiation factor 8) attenuates receptor activator of nuclear factor-κB ligand (RANKL)-induced formation of osteoclasts and can ameliorate joint destruction in a mouse model of RA.

Although RA can be treated with anti-inflammatory agents, long-term use of such therapies may be associated with adverse events such as infections. Thus, there are increasing efforts to directly prevent joint destruction independently of inflammation. In this study, the authors found higher expression of MSTN in the synovial membranes of people with RA than in those of individuals with osteoarthritis. Furthermore, inflammatory mediators such as tumour necrosis factor (TNF) increased MSTN expression in synovial fibroblasts taken from people with RA, suggesting that synovial inflammation may trigger upregulation of MSTN.

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To determine the effects of MSTN on bone erosion in RA, the authors stimulated murine bone marrow-derived macrophages (BMMs) with RANKL and macrophage colony-stimulating factor (M-CSF) — to mimic the inflammatory conditions in RA joints — with or without MSTN. MSTN increased the RANKL- and M-CSF-induced osteoclast differentiation. Moreover, co-cultures of BMMs and osteoblasts in which one cell type was MSTN-deficient led to reduced RANKL-induced differentiation into osteoclasts, implying that MSTN has both autocrine and paracrine effects on this process.

Regarding the mechanism, MSTN- and RANKL-stimulated BMMs showed increased levels of the transcription factors phosphorylated SMAD2 (pSMAD2) and nuclear factor of activated T cells cytoplasmic 1 (NFATC1). Compared with stimulation with RANKL alone, additional stimulation with MSTN increased levels of complexes containing both pSMAD2 and NFATC1 in the nucleus of BMMs. Thus, MSTN may exert its effects by increasing pSMAD2-dependent nuclear translocation of NFATC1, which upregulates transcription of osteoclast genes.

To investigate the effects on bone erosion, the authors performed an *in vitro* bone resorption assay in which wild-type osteoclasts co-stimulated with RANKL and MSTN resorbed a larger total area of calcium phosphate 'bone' than did osteoclasts stimulated with RANKL alone. Mice carrying a transgene encoding human TNF (hTNFtg mice; a model of RA) develop joint-destructive inflammatory arthritis similar to RA; however, compared with these mice, hTNFtg mice that lacked MSTN exhibited less-severe disease: they had greater paw grip strength and less paw swelling, joint inflammation and bone erosion. Interestingly, in the acute K/BxN serum-transfer model of arthritis, MSTN deficiency protected against joint erosion but not synovial inflammation, indicating that the protection of bone seen in MSTN-deficient mice is not secondary to anti-inflammatory effects.

An MSTN-specific antibody, RK35, was administered either intraperitoneally or subcutaneously into the hind paws of 5-week-old hTNFtg mice. 7 weeks later, the tarsal joints of these mice exhibited less inflammation, fewer osteoclasts and 58% less bone erosion than did the joints of vehicle-treated hTNFtg mice.

Together, these findings demonstrate that MSTN enhances RANKL-induced formation of osteoclasts and thus contributes to the degradation of bone in inflammatory arthritis. MSTN inhibition may therefore directly prevent joint erosion and could be useful in conjunction with anti-inflammatories.

Natasha Bray

ORIGINAL RESEARCH PAPER Dankbar, B. *et al.* Myostatin is a direct regulator of osteoclast differentiation and its inhibition reduces inflammatory joint destruction in mice. *Nat. Med.* **21**, 1085–1090 (2015)