

**A11** Cytokine synergy, collagenases and cartilage collagen breakdown

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My studies have focused on mechanisms of collagen turnover.

When cartilage is resorbed collagen is released after proteoglycans, both the tissue often loses the ability to replace collagen and irreversible connective tissue destruction occurs.

The collagenolytic MMPs (MMP-1, -8 and -13) all specifically cleave collagen and are present in the rheumatoid joint. Structural studies of high specific activity forms of pig synovial collagenase (MMP-1) reveal a four bladed beta-propeller attached to an ellipsoidal domain which contains the catalytic zinc ion at the bottom of the active site cleft.

We have shown that oncostatin M (OSM), a member of the IL-6 family of cytokines, synergises with the proinflammatory cytokines interleukin-1 and tumour necrosis factor alpha to promote the up regulation of these collagenolytic MMPs followed by the release of collagen when cartilage is treated *in vitro*. Co-expression of OSM and proinflammatory cytokines in model systems reveal a profound synergistic interaction in terms of joint destruction and MMP production. The mechanism of synergy involves the overlap of different signalling pathways that lead to high levels of transcription of MMP genes.

These studies are relevant to human joint diseases in that OSM is made by macrophages within the RA joint and treatment with antibodies to OSM prevents joint destruction in models of disease.