

A62 **INHIBITION OF P38 SIGNALING NEGATIVELY AFFECTS CHONDROGENESIS BY PROGENITOR CELLS IN VITRO, BUT DOES NOT INHIBIT ANKYLOSIS IN A MODEL OF ANKYLOSING SPONDYLITIS**

Kirsten Braem, Inge Derese, Frank P Luyten, Rik J Lories *Laboratory for Skeletal Development and Joint Disorders, Division of Rheumatology, KU Leuven, Belgium*

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Background Ankylosing spondylitis (AS) is characterised by chronic inflammation of the spine and joints as well as progressive ankylosis leading to loss of function and disability. In spite of increasingly successful control of inflammation with tumour necrosis factor α inhibitory agents, structural progression of disease appears not to be affected by these drugs. Bone morphogenetic proteins (BMP) have been identified as key

players in onset and progression of ankylosis. BMP associated intracellular signaling cascades (SMAD and p38 mitogen activated kinase (MAPK) signaling) play a role during chondrogenesis and osteogenesis in vitro and in vivo. p38 MAPK is not only a downstream molecule in tissue differentiation, but also in inflammation. Here, we studied the inhibition of p38 on chondrogenesis and ankylosis in vitro and in vivo and the effect of BMP signaling on chemokine induction.

Materials and methods Male DBA/1 mice from different litters were caged together at the age of 8 weeks. From week 10 onwards, mice were injected daily with SB203580 (50 µg/g body weight) or DMSO and studied for prospective signs of arthritis. Mice were killed at the age of 17 weeks and toe joints were analysed by histology to assess disease severity. For in vitro experiments, human periosteal progenitor cells were cultured in pellets and stimulated with BMP2 or TGFβ1 in the presence or absence of SB203580, interleukin-1 (IL-1) and TNF. Chondrogenic differentiation was evaluated at day 7, 11 and 14 using quantitative PCR marker analysis. Mesenchymal cell types (periosteal and bone marrow stromal cells) in monolayer were treated with BMP2 in presence or absence of dexamethasone and studied for chemokine expression by quantitative real-time PCR.

Results p38 inhibition by SB203580 downregulated chondrogenic markers (Sox9, Col2, Col10) in periosteal progenitor cell pellet cultures stimulated by TGFβ1 or BMP2. This inhibition was also found with proinflammatory cytokines IL-1 and TNF. In contrast, the in vivo experiments resulted in an increased clinical incidence of peripheral arthritis and pathology severity score in mice receiving SB203580. In vitro, BMP2 stimulation upregulated neutrophil chemokines in different mesenchymal joint associated cell types, which was inhibited by dexamethasone.

Conclusions p38 activation occurs both downstream of proinflammatory cytokines and TGFβ superfamily members. In vitro inhibition of p38 negatively affects chondrogenesis. In a mouse model of ankylosing spondylitis, p38 inhibition however appeared to stimulate ankylosis. These contrasting features could be explained by dominant inhibition of the negative effects downstream of proinflammatory cytokines on ankylosis. Furthermore, BMP signaling induces neutrophil chemokine expression, suggesting that activation of progenitor cells can contribute to inflammation