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Fra-1 regulates inflammatory and degenerative arthritis

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Introduction

Rheumatoid arthritis (RA) and osteoarthritis (OA) are chronic joint diseases that target synovial membrane, cartilage and bone. Cartilage and bone damage is a hallmark of both diseases and often necessitates joint replacement surgery during the disease course.

Aim

To evaluate the impact of chronic Fra-1 over-expression on experimental models of inflammatory and degenerative arthritis.

Methods

Fra-1tg mice were crossed with hTNF-transgenic (hTNFtg) mice. Clinical and histological signs of arthritis, synovitis and cartilage damage were established. *In situ* hybridization (ISH) for osteocalcin and osteopontin were performed. Structural and dynamic parameters of systemic bone were evaluated by bone histomorphometry and calcein labelling. *In vitro* studies with wt and *fra-1tg* chondrocytes were performed for gene expression.

Further, an established OA model (collagenase-induced OA) was performed in wildtype and *fra-1tg* mice. Cartilage degeneration and osteophyte formation were evaluated.

Results

Mice overexpressing Fra-1 and hTNF showed increased clinical arthritis scores as compared to hTNFtg mice. Histological analysis showed an increase of synovial inflammation in Fra-1tgxhTNFtg mice. These mice had virtually no synovial bone erosions and showed enhanced osteoblast function and matrix deposition compared to hTNFtg mice. Interestingly, cartilage integrity was also preserved in Fra-1tgxhTNFtg mice. *In vitro* TNF-stimulated *fra-1tg* chondrocytes showed reduced expression of matrix metalloproteinases as compared to wildtype chondrocytes challenged with TNF. Further, *fra-1tg* chondrocytes showed higher proliferative rates and expression of cyclin genes compared to wildtype chondrocytes.

Finally, preliminary results suggest a cartilage-protective effect of Fra-1 in the collagenase-model of OA.

Discussion

This study shows that increased osteoblastic function is able to prevent local and systemic bone loss in arthritis despite active signs of local and systemic inflammation. Further, overexpression of the transcription factor Fra-1 seems to reduce cartilage destruction in hTNFtg mice and an experimental OA model. Strategies to build up bone and protect cartilage might therefore be considered as key tools to preserve joint architecture.

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