EXPERIMENTAL RHEUMATOLOGY

Title

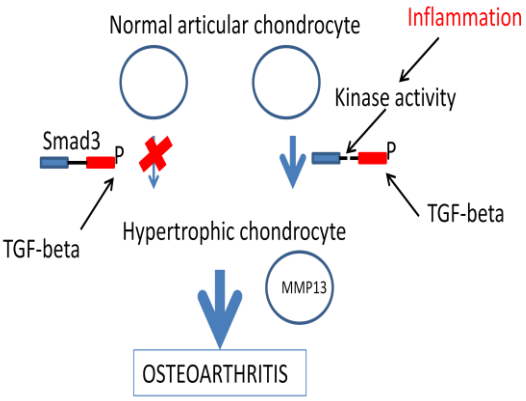
The Smad3 linker as the missing link between inflammation and chondrocyte hypertrophy in osteoarthritis

Clinical Relevance

Osteoarthritis (OA) is the most common joint disease that affects millions of people worldwide. Healthy cartilage provides smooth movement of the joints and acts as a cushion between the bones. During OA the articular cartilage breaks down, causing pain, swelling and problems moving the joint. It was previously thought that osteoarthritis is caused by aging. However, it is increasingly common that joint inflammation plays an important role in the development of osteoarthritis. What the mechanistic connection is between inflammation and cartilage damage is not yet clear.

Background

Chondrocyte hypertrophy is thought to play a central role in OA development, resulting in expression of proteolytic enzymes (e.g. MMP13) and cartilage damage. In healthy cartilage hypertrophic differentiation is prevented by the TGF-beta signaling protein Smad3. The Smad3 protein consist of a N-terminal MH1 domain, a linker domain and a C-terminal MH2 domain. TGF-beta activates Smad3 by C-terminal phosphorylation. Recently it has been shown that the function of Smad3 is also greatly dependent on phosphorylation of the linker region. Inflammatory mediators are able to activate intracellular kinases, which can induce Smad3 linker modifications.



Goals

In this project we want to investigate how different inflammatory factors modulate the intracellular signaling of TGF-beta and SMAD3 function. Bovine cartilage explants and isolated chondrocytes will be used as reliable source of healthy articular cartilage. These chondrocytes will be exposed with different inflammatory stimuli or OA-conditioned medium. Expression of hypertrophic markers will be analyzed by quantitative RT-qPCR and Western blot analysis. Function of SMAD3 will be monitored using the CAGA-luc reporter assay.

We Offer

We are working in a state of the art laboratory that is internationally renowned for its research on rheumatic diseases. You will work in a motivating environment in which you will be able to improve your laboratory skills, further develop your scientific thinking and expand your knowledge on molecular processes and immunology. Want to know more? Don't hesitate and contact us.

Contact

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