Intrinsic Cartilage Repair by Joint Distraction is Triggered by a Regenerative Transcriptional Response

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INTRODUCTION: Joint distraction provides long-term improvement of pain and function, accompanied by intrinsic cartilage repair evaluated indirectly by imaging and biochemical markers in humans with knee osteoarthritis1. Moreover, joint distraction results in cartilage repair activity in an experimental canine model of osteoarthritis, which corroborates with the structural observations of cartilage repair by surrogate markers in humans2. Despite these promising results little is known about the exact mechanisms that boost them. This study evaluates for the first time the regenerative transcriptional response during joint distraction in an experimental model of osteoarthritis.

METHODS: Knee osteoarthritis was induced in 8 dogs according to the groove model. Ten weeks after osteoarthritis induction, 4 dogs received joint distraction (D) and 4 dogs served as disease controls (OA). After 4 weeks of distraction, the animals were sacrificed and knee tissues including fat pad, synovium, meniscus, bone and cartilage were harvested. qPCR analysis of 64 state-of-the-art regenerative gene markers was performed in the different tissues. The Utrecht University Committee for Experiments on Animals approved the study according to Dutch Law.

RESULTS SECTION: The OA group revealed an upregulation of typical OA markers, like matrix metalloproteinases, and collagen and apoptosis markers, confirming the OA disease cascade in specifically cartilage, bone and synovial tissue. Joint distraction caused downregulation of typical OA markers and the maintenance of some important matrix remodeling genes for regeneration, e.g. aggrecanase. Moreover, genes from several pathways were differentially expressed between the D and OA group, including TGF-β, Wnt- and Notch-signaling pathways. Interestingly, a high number of events occurred in bone, highlighting the importance of this tissue in the regenerative outcome of joint distraction on OA affected cartilage.

DISCUSSION: Distraction is a good candidate for knee osteoarthritis treatment resulting in prolonged clinical and structural changes. This study demonstrates distinctively that joint distraction initiates a transcriptional regulation of several important regenerative genes indicating that a reset of joint homeostasis can lead to cartilage repair in OA.

SIGNIFICANCE: This study demonstrates for the first time that joint distraction initiates a transcriptional regulation of several important regenerative genes indicating that a reset of joint homeostasis can lead to cartilage repair in OA. These data support that joint distraction provides long-term improvement of pain and function, accompanied by intrinsic cartilage repair in humans with knee osteoarthritis.

REFERENCES:

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