Wnt-1 Induced Secreted Protein 1 is Expressed in OA and Induces Cartilage Degradation Independent of Interleukin-1

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ABSTRACT INTRODUCTION:
Matrix metalloproteases (MMPs) are thought to be important factors that mediate cartilage degradation in osteoarthritis (OA). Interleukin-1 (IL-1) is a strong inducer of chondrocyte MMP expression however, a role for IL-1 in OA has never been clearly demonstrated; therefore other factors may play a roll in regulating MMP expression and cartilage remodeling. Polymorphisms identified in genes from the wnt/β-catenin pathway have been associated with OA and recently, we found that wnt1-inducible secreted protein-1 (WISP1) was expressed at high levels during experimental OA. The aim of the present study was to examine WISP1 expression in human OA tissue and to determine the potential of WISP1 to cause cartilage degradation independently of IL-1.

METHODS:
Expression of WISP1, both in human OA synovium and cartilage was determined at the RNA-level by Q-PCR. Immunohistochemistry was used to demonstrate protein expression of WISP1. To study the effect of WISP1 on cells we stimulated macrophages and chondrocytes with recombinant WISP1 and assayed the effect on the induction of cartilage degrading enzymes. An adenoviral vector for WISP1 overexpression was generated, and injected in the murine knee joint of either control mice or IL-1β-/- mice. Subsequently, at day 4 markers for cartilage degradation were determined.

RESULTS SECTION:
At the RNA level, WISP1 expression in human tissue was 3 times higher in OA synovium and over 2 times higher in cartilage, compared to control tissue. In cartilage of OA patients there was clear expression of WISP1 at the protein level in chondrocytes and also located pericellularly in the adjacent extracellular matrix. WISP1 was not detected in control (post-mortem) cartilage (Figure 1). Stimulation of macrophages with WISP1 for 24 hours resulted in the induction of MMP-3, MMP-9 and MMP-13, 8-5- and 3-fold respectively. Remarkably, no IL-1β was induced by WISP1.

In chondrocytes and fibroblasts, only MMP-3 was significantly induced by WISP1. Synovial overexpression of WISP1 following WISP1 adenovirus injection into murine knee joints resulted in strong induction of MMP-3, MMP-9, MMP-13, ADAMTS4 and ADAMTS5 in the synovium (12-, 8-, 2-, 10- and 2-fold), and of MMP-3, MMP-13 and ADAMTS4 in the cartilage (100-, 12, and 3-fold). Neo-epitope markers for enzymatic cartilage damage, VDIPEN (MMPs) and NITEGE (aggrecanases) were significantly induced in knee joints, 4 days after WISP1 overexpression. Control virus did not induce any markers for cartilage degradation. Interestingly, cartilage damage and expression of catabolic enzymes were identical in IL-1β-/- and wild type mice after WISP1 overexpression, indicating that WISP1 induces cartilage damage independently of IL-1 (Figure 3).

DISCUSSION:
WISP1 is expressed in human OA synovium and cartilage, and levels are strongly increased compared to controls. WISP1 is a potent inducer of several MMPs and overexpression causes cartilage degradation. This effect on cartilage damage is independent of IL-1. We have identified a novel mechanism that may contribute to cartilage loss in OA that works independently of IL-1. Further research using blocking studies is needed to prove involvement of WISP1 in OA pathology.