Lack of Sclerostin Promotes Osteoarthritis by Activating Canonical and Non-Canonical Wnt Pathways


Purpose: Sclerostin is a Wnt inhibitor produced by mineralizing cells such as osteocytes. Sclerostin is also expressed in OA chondrocytes and therefore might regulate the cartilage homeostasis in osteoarthritis through the inhibition of Wnt pathways. We aimed here to assess the role of sclerostin in the chondrocyte metabolism and the development of osteoarthritis in SOST-deficient mice.

Methods: Joint instability was induced by partial transection of the meniscus (MINX) in 10 week-old SOST-KO and wild type (WT) mice. Mice were sacrificed at 4, 6 or 9 weeks after MINX. We analyzed: 1) bone parameters such as bone volume/tissue volume (BV/TV) at the medial femoral condyle, 2) the osteophyte volume by microCT, 3) the cartilage damage using OA score and 4) the expression of matrix proteins. The role of sclerostin in chondrocyte metabolism was investigated in primary murine chondrocytes cultured with Wnt3a and sclerostin (RT-PCR and WB). Functional effect was assessed by the release of proteoglycan content in the culture supernatant and the accumulation of GAGs by Alcian blue staining. We next investigated the role of β-catenin / JNK pathway using SP600125 inhibitor.

Results: Sclerostin expression was restricted to the calcified cartilage and osteocytes in WT mice and was enhanced with the development of OA. In sham-knees, cartilage structure was preserved in SOST-KO mice at all time points with high high BV/TV. MINX resulted in a higher OA score in SOST-KO mice than in WT at Week 4 (6.66 ± 0.57 vs 3.25 ± 0.95, p<0.05) and Week 6 (11 ± 1 vs 7 ± 0.81, p<0.05), along with an increased expression in type X collagen and Adamts-4 that suggested an enhanced catabolism of chondrocytes. However, the osteophyte volume was not affected by the lack of sclerostin at Week 4 (0.033 ± 0.019 vs 0.024 ± 0.01, p; NS) and at Week 6 (0.023 ± 0.01 vs 0.02 ± 0.01, p; NS). In primary murine chondrocytes, Wnt3a increased the proteoglycan release which was rescued by sclerostin. Wnt3a increased the expression of Adamts-4 & -5, MMP-3 & -13 and type X collagen, while this effect was totally abolished by sclerostin through an inhibition of the Wnt canonical pathway. Moreover, Wnt3a promoted the phosphorylation of JNK which was inhibited by sclerostin. We further investigated whether sclerostin-induced inhibition of JNK affects chondrocyte anabolism. In Wnt-induced chondrocytes, sclerostin rescued the accumulation of GAGs and the expression of the anabolic genes when JNK pathway was inhibited. In contrast, sclerostin did not affect the CanK pathway.

Conclusions: Lack of sclerostin results in cartilage damage and disrupts the balance of anabolism/catabolism in OA induced by joint instability. Sclerostin inhibits both Wnt canonical pathway and the non canonical JNK pathway, thereby preserving the chondrocyte metabolism. These data suggest an important role of sclerostin in cartilage integrity in OA.

Cartilage-Specific Deletion of Mtor Upregulates Autophagy and Protects Mice from Osteoarthritis

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Purpose: Recent studies suggest that the process of autophagy, a form of programmed cell survival, is impaired during osteoarthritis (OA) and may contribute towards decreased chondroprotection in the articular cartilage associated with OA pathophysiology. mTOR (a serine/threonine protein kinase) is a major repressor of autophagy. The exact role of mTOR in OA pathophysiology is largely unknown. We determined the expression of mTOR and known autophagy genes in human OA cartilage as well as mouse and dog models of experimental OA. We also created cartilage-specific mTOR knockout (KO) mice to determine the specific role of mTOR in OA pathophysiology and autophagy signalling in vivo.

Methods: Human normal and OA cartilage was subjected to human OA autophagy PCR array, western blotting, qPCR and immunohistochemistry. Inducible cartilage-specific mTOR KO mice were generated and subjected to mouse model of OA. Human OA chondrocytes were treated with rapamycin and ULK1 (most upstream autophagy inducer) SiRNA to determine mTOR signalling pathway.

Results: mTOR is overexpressed in human OA patient cartilage as well as mouse and dog experimental OA. Upregulation of mTOR expression co-relates with increased chondrocyte apoptosis and reduced expression of key autophagy genes during OA. Subsequently, we show for the first time that cartilage-specific ablation of mTOR results in increased autophagy signalling and a significant protection from DMM-induced OA associated with a significant reduction in the articular cartilage degradation, cell death and synovial fibrosis. Furthermore, we show that mTOR is responsible for shutting down ULK1/autophagy signalling pathway resulting in the imbalance in the expression of catabolic and anabolic factors in human OA chondrocytes.

Conclusions: This study for the first time provides a direct evidence of the role of mTOR and its downstream modulation of autophagy in articular cartilage homeostasis. Thus targeting cellular homeostasis mediators, such as mTOR and its downstream signalling by ULK1/autophagy pathway may be a promising therapeutic strategy to achieve chondroprotection and correct the imbalance between catabolic and anabolic processes during OA and related disorders.