

Novel signalling pathway(s) for the LRP5/6 antagonist sclerostin (SOST), mediate cartilage catabolic gene expression

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Description of Project:

Activation of Wnt signalling is initiated by binding of Wnt proteins to frizzled receptors and co-receptors, the low density lipoprotein receptor (LRP)5 or 6. Binding of Wnt to the co-receptor complex leads to inhibition of b-catenin phosphorylation and proteasome-mediated degradation; stabilized b-catenin then translocates to the nucleus, where it interacts with resident lymphoid enhancer factor/T-cell transcription factor (LEF/TCF) elements to activate Wnt target genes. The functional activities of Wnt-b-catenin signalling is modulated by endogenous antagonists in the extracellular milieu, which include sclerostin (SOST), dickkopf 1 (DKK1) and secreted frizzled-related protein. Binding of SOST to LRP5/6 can prevent b-catenin translocation to the nucleus, and activate ERK1/2 MAPK signalling pathway. SOST was previously thought to be an osteocyte-specific protein and to play a major role in regulating new bone production by osteoblasts. Recent data from our laboratory demonstrates that SOST is also expressed by chondrocytes in arthritic cartilage, and enhances catabolic gene expression by these cells, but seems to do this by an LRP5/6-independent pathway.

This study will investigate the novel signalling mechanisms involved in SOST-mediated cartilage catabolic gene expression. The effect of siRNA silencing of LRP5/6 and inhibitors of ERK/MEK and JNK/p38 inhibitor on SOST-mediated effects in three different cell types (C-28/I2 cells, HEK293 and primary sheep chondrocyte) will be examined. Outcome measures include gene expression analysis by real-time PCR and protein phosphorylation by Western blot analysis.

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