2. Low Sirtuin 1 levels in human Osteoarthritis Subchondral Osteoblasts lead to abnormal Sclerostin expression which decreases Wnt/□-catenin activity.

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Background: Wnt/□-catenin (cWnt) signaling plays a key role in osteogenesis by promoting the differentiation and mineralization of osteoblasts, activities altered in human osteoarthritis subchondral osteoblast (OA Ob). Sclerostin (SOST) has been shown to alter cWnt signaling. Sirtuin 1 (Sirt1) acts as a novel bone regulator and represses SOST levels in Ob. However the role of Sirt1 and SOST in OA Ob remains unknown.

Objectives: To explore the role played by Sirt1 and SOST on the abnormal mineralization and cWnt signaling in OA Ob.

Methods: Primary human normal and OA Ob were prepared from tibial plateaus. SOST levels were evaluated by immunohistochemistry, the expression and production of genes by qRT-PCR and WB analysis. Their inhibitions were performed using siRNA. cWnt signaling was measured by the TOPflash TCF/lef luciferase reporter assay. Mineralization was determined by alizarin red staining.

Results: SOST levels were significantly increased in OA Ob compared to normal and were linked with elevated TGF-□1 levels in these cells. Sirt1 expression was significantly reduced in OA Ob compared to normal and not modified by TGF-□1. Specific inhibition of Sirt1 increased TGF-□1 and SOST expressions in OA Ob, while stimulating Sirt1 activity with □-Nicotinamide mononucleotide reduced TGF-□1 expression and increased mineralization in OA Ob. Reduced cWnt signalling, □-catenin levels, and mineralization in OA Ob were all corrected via reducing SOST expression.

Conclusion: These data indicate that SOST is responsible for the reduced cWnt and mineralization of human OA Ob, which in turn is linked with abnormal Sirt1 levels in these pathological cells.