ALTERED SCLEROSTIN SYNTHESIS IN CARTILAGE AND BONE CONTRIBUTE TO OA PATHOLOGY

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Introduction: Canonical Wnt signalling and increased β-catenin activity have been implicated in the process of cartilage degradation in osteoarthri-
tis (OA). Increased Wnt-induced signalling protein 1 (WISP1) in OA cartilage induces cartilage degradation by upregulating matrix metalloproteinases (MMPs) and aggrecanases (ADAMTS-4 and ADAMTS-5). Wnt signalling is inhibited by endogenous antagonists dickkopf-1 (DKK1), secreted frizzled-related proteins (sFRP) and sclerostin (SOST). Despite increased chondrocyte β-catenin promoting cartilage degradation, insufficiency of sFRPfn (TNF) altered OA cartilage damage in mice, and inhibition of DKK1 reduced rather than increased cartilage damage in a surgical model of OA in rats. These conflicting results demonstrate the complexity of Wnt-β-catenin regula-
tion. SOST is a potent Wnt-β-catenin antagonist and a key regulator of bone metabolism but no previous studies have investigated its role in OA pathology.

Methods: SOST, WISP-1 and β-catenin were immuno-localised in osteo-
articular sections of surgically-induced OA in sheep and mice, as well as human tibial plateaus obtained at arthroplasty for OA. Expression of Sost, Wisp-1, β-catenin, Lrp-5/6, Dkk1, Mmp-1 & -13, Adams-4 & -5, Timp-1 & -3, aggrecan and collagen II by chondrocytes in OA, and with stimulation by 10ng/ml interleukin-1α (IL-1) or 10ng/ml tumour necrosis factor α (TNF) in culture, was quantified by real-time RT-PCR. The effect of 25-500ng/ml rhSOST on cartilage degradation and chondrocyte gene expression was examined in explant culture.

Results: Contrary to being osteocyte-specific, Sost mRNA was expressed by articular chondrocytes in all species, and was upregulated in OA mice and by IL-1 but not TNF in culture. Chondrocyte Sost protein was significantly increased only in the focal area of cartilage damage in surgically-induced OA in sheep and mice, as well as end-stage human OA. In contrast, osteocyte SOST was focally decreased in the subchondral bone in OA in association with increased bone sclerosis. SOST was biologically active in chondrocytes, increasing expression of Mmp-13 from as early as 4 hours and maintained to 24 hours. At 48 hours, exogenous SOST decreased mRNA levels of aggrecan and type II collagen, inhibited Wnt-β-catenin signalling and down-regulated Mmp-13, Adams-5 and Timp-1 and Timp-3 expres-
sion. SOST augmented IL-1α’s stimulatory effects on chondrocyte Mmp-1, Adams-4 and Adams-5, and its inhibition of aggrecan and collagen II expression.

Conclusions: Taken together, this data suggests that SOST may actively participate in the pathological progression of OA by affecting both cartilage and subchondral bone. The differential change in SOST in cartilage and subchondral bone highlight the potential tissue/cell specific regulation of Sost, and the opposing effects of altering Wnt-β-catenin activity in bone and cartilage. Overall the effects of SOST in cartilage are pro-catabolic, with inhibition of aggrecan, collagen II and Timp expression, and acute upregulation of Mmp-13. In bone, SOST increases osteoblast activity and bone formation, and inhibition of SOST and DKK1 have potential in treating osteoporosis. In light of this and the multiple potential mechanisms of action of SOST, it will be important to determine what effect its inhibition may have on progression of both bone and cartilage changes in OA in vivo.