OSTEOARTHRITIS

Targeting cathepsin K to prevent cartilage loss: evidence from a dog model of OA

New research suggests that blocking the activity of cathepsin K could prevent the structural damage associated with osteoarthritis (OA), a condition for which no disease-modifying therapies are currently available. The mild-to-moderate beneficial effects of treatment observed in the canine partial medial meniscectomy model of the disease suggest that "inhibition of cathepsin K may represent a valid therapeutic strategy for treatment of OA," say the study's lead investigators, Janice Connor and Sanjay Kumar.

Cathepsin K was first identified as a molecular target for bone diseases, owing to its established role in bone turnover and capacity to digest bone matrix proteins such as type I collagen. In addition, this cysteine protease breaks down type II collagen and aggrecan, the two main structural components of articular cartilage. Evidence of synovitis and cartilage degeneration in transgenic mice overexpressing cathepsin K provided further justification for investigating cathepsin K as a potential disease-modifying therapy for OA. "The availability of potent small-molecule inhibitors of cathepsin K developed for osteoporosis provided us with an opportunity to test a cathepsin K inhibitor in a dog model of experimental OA," says Kumar.

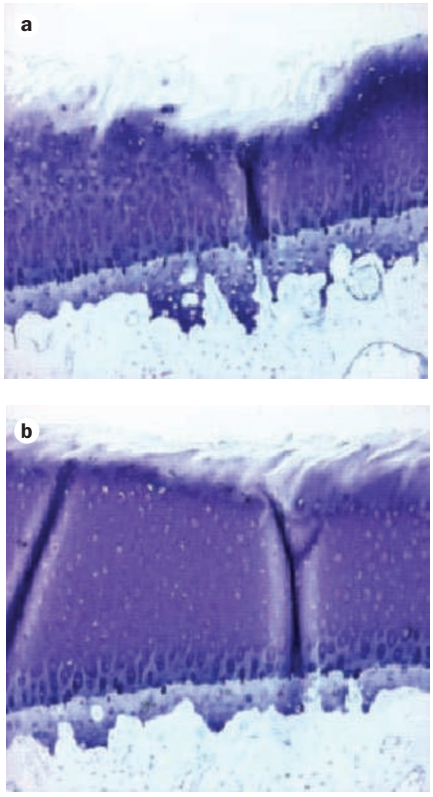

Figure 1 | Proteoglycan loss in dogs treated with **a** | placebo and **b** | SB-553484.

In contrast to other models of OA, the partial medial meniscectomy-induced OA canine model produces rapidly progressive, focal cartilage degeneration; in addition, a high degree of joint stability minimizes hypertrophy, which can otherwise complicate the interpretation of potential therapeutic effects. "In this model, although a major component of the lesion pathogenesis is mechanically driven, there is significant biochemical change related to matrix degrading enzymes," adds Connor. "In addition, the lesion that develops in this model is histologically comparable to the human OA lesion." To evaluate the effects of cathepsin K inhibition on the structural damage associated with this OA model, the investigators randomly allocated 40 adult female beagle dogs to receive oral treatment with either SB-553484 or vehicle for 28 days beginning 1 day before surgical transection of the medial meniscus.

After 28 days, visual assessment of tibial plateau cartilage lesions showed that, on average, subjective and calculated gross scores of degeneration, respectively, were 29% and 46% lower in dogs treated with SB-553484 than in controls. Histopathological analysis of the disarticulated joints also demonstrated that treatment significantly reduced cartilage degeneration: the overall degeneration score for the anterior, middle and posterior tibial compartments was 21% lower in treated dogs than in controls. Proteoglycan loss occurred to a lesser extent in SB-553484-treated than in vehicle-treated dogs, as illustrated in a representative mid-level section of the most severely affected tibial areas (Figure 1). Finally, urinary biomarkers of collagen type I and type II degradation were reduced by 80% and 70%, respectively, in the treatment group when compared with controls at day 21. The significant reductions in these markers suggest that SB-553484 has a direct effect on bone and cartilage turnover. "These data," says Kumar, "provide us with sufficient rationale to progress further with this mechanism."

Although the study is the first to demonstrate the beneficial effects of SB-553484 treatment on joint degradation in this canine model of OA, several questions remain regarding the mechanism of the protection. The investigators established that SB-553484 inhibits cathepsin K much more potently than it does cathepsins L, S, and B; however, "it is not clear whether the efficacy [of SB-553484] in the dog model is solely due to inhibition of cathepsin K, another cathepsin or some combination thereof," Kumar suggests. "Furthermore, it is not clear if the efficacy in this model is because of the action of the inhibitor in cartilage or in bone or both." Future research will attempt to clarify these possibilities, as well as evaluate the clinical potential of this therapeutic approach to not only alleviate the symptoms of but also modify the underlying disease processes of OA.

Sarah Price

Original article Connor, J. R. *et al.* Protective effects of a cathepsin K inhibitor, SB-553484, in the canine partial medial meniscectomy model of osteoarthritis. *Osteoarthritis Cartilage* doi:10.1016/j.joca.2009.03.015