Development of a rat model of early osteoarthritis based on Wnt hyperactivation

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INTRODUCTION: Osteoarthritis (OA) is the most common chronic joint disease characterized by articular cartilage degeneration, with associated changes in other joint tissues. Current therapy for OA patients is limited to symptom relief and joint replacement surgery in advanced stages of the disease. Intervention at early stages may prevent structural cartilage changes that would otherwise progress to end-stage OA. Nevertheless, the lack of animal models for research on early-stage OA still constitutes a significant challenge. Current models that involved trauma to the internal ligaments (ACL) or joint structures (DMM) mainly reflect post-traumatic OA conditions and be less representative for early primary OA events. In this respect, Dysregulation of Wingless-related integration site (Wnt) signaling is known, to contribute to the development of OA. In particular, excessive Wnt signaling has been shown to be already present in early stages of the OA disease1,2. In this study, we aimed to establish an early OA rat model based on Wnt signaling upregulation in order to study the early events of the OA disease process in a physiological environment.

METHODS: To develop the rat model of early OA, two studies were conducted testing different dosages of on intra-articular administration of the Wnt agonist CHIR99021. In the first pilot study, six 12-week-old male Sprague-Dawley rats were subjected to three intra-articular knee injections per week, during two weeks. The injected solution had a concentration of 10mg/ml and a volume of 30 microliters. As a control, an equivalent volume of a vehicle solution was injected into the contralateral knee of each rat. . In the second pilot study, the same injection frequency was followed and four 12-week-old male Sprague-Dawley rats were injected with a concentration of 20mg/ml and a volume of 50 microliters. For both studies, histological analysis was conducted. Knee joints were harvested four weeks after the final injection and histological analysis was performed to evaluate cartilage damage in accordance with OARSI guidelines. Osteophyte formation and synovial inflammation were assessed by pathology scores. Three rats in the first pilot were used for molecular analysis to assess the expression of the cartilage anabolic markers ACAN and COL2A1, the catabolic marker MMP13, and the Wnt target gene TCF1.

RESULTS SECTION: In the first study (low CHIR dose) (Figure 1), changes in the molecular expression levels of the studied genes were observed between treated and control knees in one of the three rats. Specifically, upregulation of TCF1 concomitant with downregulation of the anabolic markers COL2A1 and ACAN was observed. Histological analysis in the remaining three rats showed no substantial disparities in cartilage, calcified cartilage, or subchondral bone impairment. Nevertheless, an increase in synovial inflammation was observed ($p < 0.0167$).

In the subsequent study involving a higher dosage of CHIR99021 (high CHIR dose) (Figure 1), differences ($p < 0.001$) were observed for cartilage damage, evident by the differences in OARSI scores of the control (0.21) and the treated knees (0.77). Likewise, significant alterations in synovial inflammation ($p < 0.001$) were observed, along with minor shifts in calcified cartilage and subchondral bone impairment ($p < 0.04$) (n=4).

DISCUSSION AND CONLUSION: The second injection model more effectively induced early OA state as evidenced by the OARSI score being around 1, hence characterizing an early OA condition. This model's enhanced ability to induce cartilage damage, trigger synovial inflammation, and induce minor subchondral bone alterations underscores its potential utility as an instrumental tool for exploring the intricacies of OA's initial phases. These preliminary findings collectively highlight the promise and significance of this rat model as a valuable means for in-depth investigations into the early manifestations of OA disease.

SIGNIFICANCE/CLINICAL RELEVANCE: Animal models of OA hold significant importance in elucidating the fundamental tissue biology and pathophysiology underlying the disease. They enable the examination of isolated risk factors and grant access different time points of the disease progression, in this case, the early disease state.

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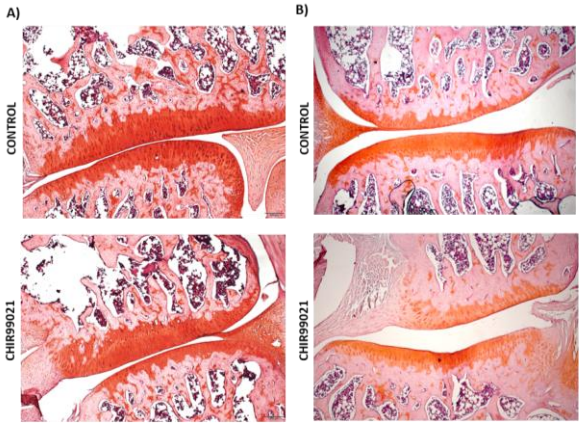

Figure 1. A) Histology for the quantifications of the first study (low CHIR dose).
B) Histology for the quantifications of the second study (high CHIR dose).