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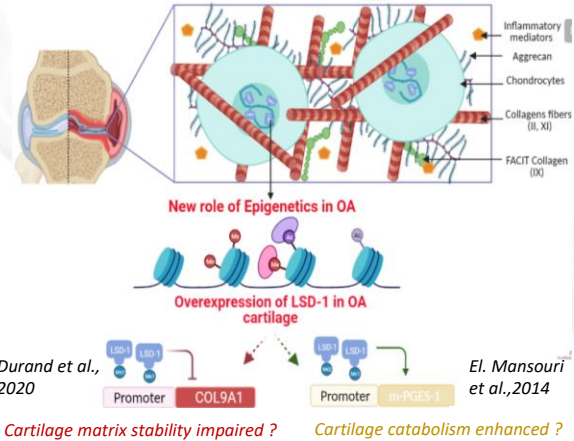
DEVELOPMENT OF A NEW GENETIC MODEL TO INVESTIGATE THE ROLE OF THE CHROMATIN MODIFYING ENZYME LSD-1 DURING OSTEOARTHRITIS

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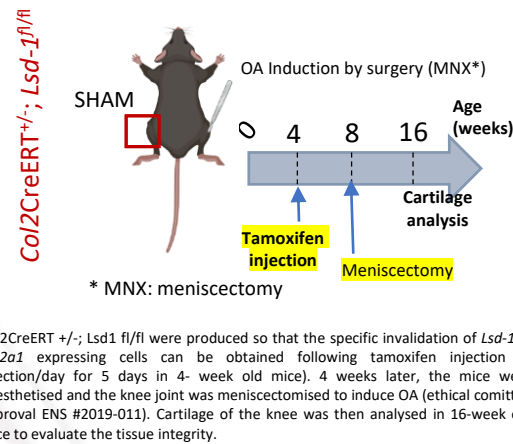
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INTRODUCTION : Osteoarthritis (OA) is a degenerative pathology of the joint involving the articular cartilage. This is the major chronic joint disease worldwide and a major cause of invalidity but there is still no curative treatment. During ageing, that tissue becomes progressively eroded without efficient spontaneous repair. The causes remain unclear but the role of the chondrocytes, where many gene dysregulations occur, is crucial. There are now growing evidences that epigenetic signaling is important to control the gene expression and could alter the homeostasis of articular cartilage. Thus the epigenetic factors have emerged as promising therapeutical targets but they are only scarcely investigated in the context of OA. We investigated the role of the Lysine-Specific Demethylase-1 (*Lsd1*), which is upregulated in human OA cartilage and was shown to alter the expression of important genes for the articular cartilage such as *Col9a1* (Durand et al. 2020) or *mPges-1* (E Mansouri et al. 2014). **METHODS:** we thus developed a new mouse model in which *Lsd-1* was specifically deleted in the articular cartilage, in order to study its role during OA. OA was mechanically-induced in the knee of mice following meniscectomy and cartilage or bone were analysed by histology and histomorphometry. Primary culture of chondrocytes were also used to analyse the interplay of LSD-1 with inflammatory signaling pathways.

LSD-1 regulates matrix and inflammatory genes important for the articular cartilage homeostasis



Hypothesis : LSD-1 promotes the development of osteoarthritis



LSD-1 is more abundant in the articular cartilage of mice in which OA is mechanically induced

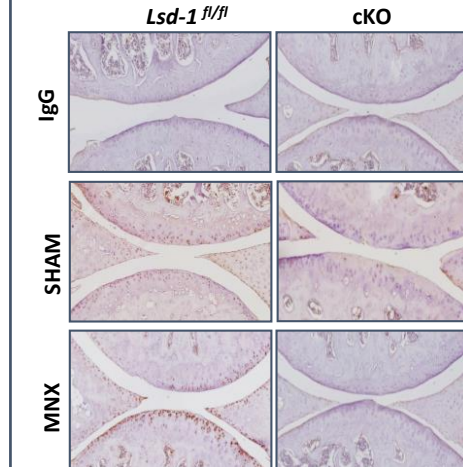
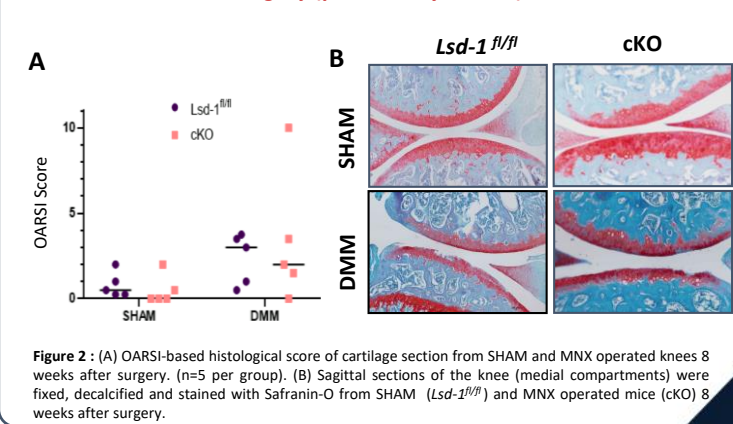


Figure 1 : Immunohistochemistry against LSD-1 was performed on histological sections of the articular cartilage from the left /SHAM and right/ MNX knees 8 weeks after surgery in vehicle injected (*Lsd-1*^{fl/fl}) and Tamoxifen injected mice (cKO). (IgG: technical control where primary antibody was omitted)

Deletion of *Lsd-1* reduces OA development 8 weeks after MNX surgery (preliminary results)



The inactivation of *Lsd-1* reduces the ectopic bone formation in the knee of mice in which OA was mechanically induced

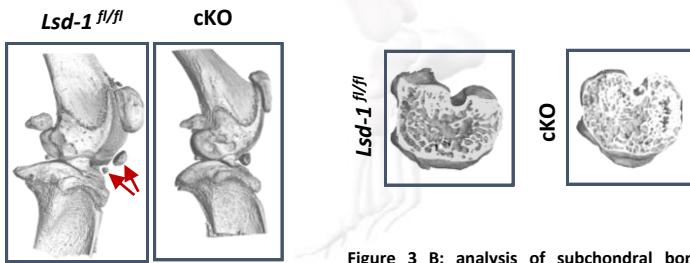


Figure 3 A: analysis of bone formation. 8 weeks after MNX, microCT scan of the knee joint was analysed and three-dimensional reconstruction was performed. SHAM and operated mice in *Lsd-1*^{fl/fl} (vehicle) and cKO (tamoxifen injected) were compared. (n=1)

Figure 3 B: analysis of subchondral bone architecture. Transaxial view of 3D reconstructed pictures of tibial medial compartment from vehicle (*Lsd-1*^{fl/fl}) and Tamoxifen injected mice (cKO) 8 weeks after MNX. (n=1)

Pharmacological inhibition of LSD-1 reduces *Mmp-13* expression in mouse articular chondrocytes

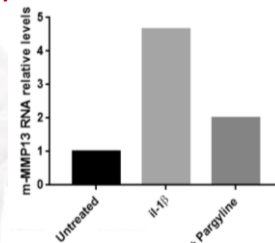


Figure 4 : m-MMP13 RNA relative level was analysed by q-PCR in primary chondrocytes treated or not for 5 hours with IL-1β with or without a pharmacological inhibitor of LSD-1 (Pargyline) n=1.

CONCLUSIONS : we generated a new mouse model in which *Lsd-1* demethylase is deleted. It provides a new tool to study the role of a chromatin modifying enzyme in the development of osteoarthritis. Following the meniscectomy, we were able to mechanically induce a phenotype of OA in the mice (cartilage damage and ectopic bone formation), and observed LSD-1 is more abundant in the cartilage, which is similar to what was previously observed in humans. Preliminary results show that the inducible deletion of *Lsd-1* in the articular cartilage reduces the development of OA in mice. We want to confirm these results with more mice and various time after MNX, and want to better characterise the molecular changes mediated by LSD-1.