OSTEOMODULIN IS INVOLVED IN BONE AND CARTILAGE HOMEOSTASIS AND OSTEOARTHRITIS DEVELOPMENT

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BACKGROUND Osteomodulin (**OMD**) is an extracellular matrix protein from the Small Leucine Rich Proteoglycan (SLRP) family. SLRPs are known to perform various functions such as regulating the extracellular matrix assembly, growth and of cell differentiation. Therefore SLRPs have a crucial role in the regulation of bone homeostasis and development. OMD is thought to play the role of a **cytokines reservoir** by binding them in the matrix. It would be involved in the **mineralization** process and its expression and protein level are **downregulated in the subchondral bone of osteoarthritic (OA) patients.**

PURPOSE This study aimed to investigate the function of OMD in **bone** and **cartilage** and in the **remodeling of subchondral bone** associated with **OA**. We used both loss of function (**KO**) and overexpressing **mice** (**UP**) for *Omd* aged 4, 8, and 16 months for *in vivo* characterization as well as a loss of function **mutant** in the **zebrafish**.

1. OMD REGULATES BONE MICROARCHITECTURE

µCT analysis of tibial bone over time – 4/8/16 Months mice

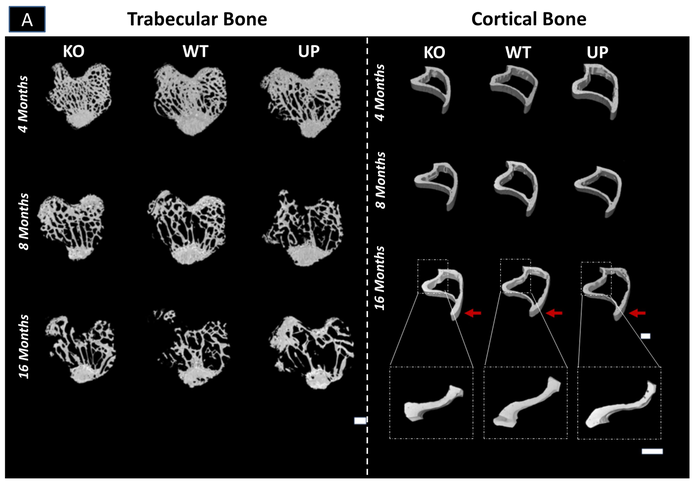
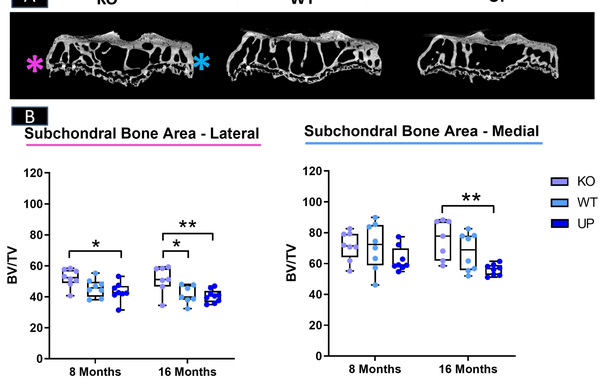


Figure 1.
µCT analysis of the metaphysis of the tibia of the male mice at 4, 8 and 16 months for the mutant loss of function (KO), the WT and the *Omd* overexpressing (UP) mice. The trabecular bone (left) and the cortical bone (right) were analyzed separately. (A) The 3D rendering of each genotype is represented with a scale bar of 500 µm. (B) BV/TV of trabecular and cortical bone were measured and displayed at each time-point. The trabecular number, trabecular porosity, cortical bone thickness, and cortical porosity are represented over time.

2. OMD IS ASSOCIATED WITH THE SUBCHONDRAL BONE SCLEROSIS

Spontaneous subchondral bone sclerosis – 16 Months mice



Subchondral bone sclerosis – DMM model

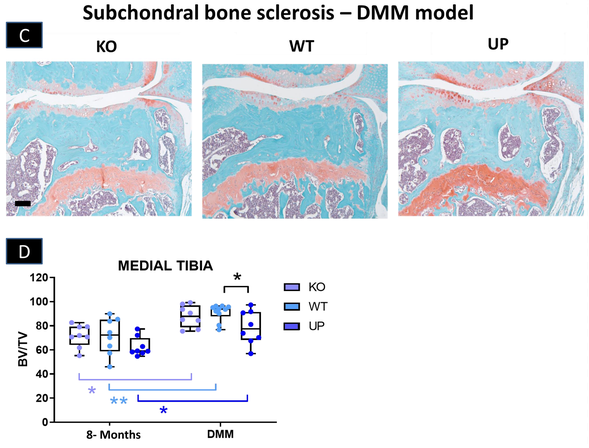
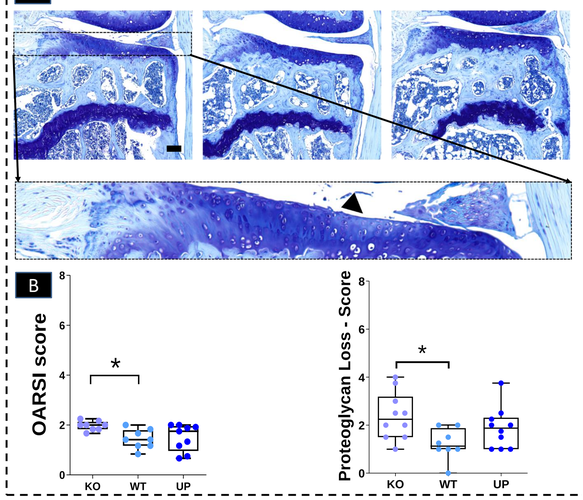


Figure 2.
(A) µCT of the subchondral bone of the tibia of the mice at 16 months. The pink asterisk indicates the lateral plateau and the blue asterisk indicates the medial plateau. (B) BV/TV of the subchondral bone area at 8 and 16 months for the lateral and medial tibial plateaus. (C) Illustrations of medial plateau stained with Safranin-O Fast Green of the mouse DMM model. Scale bar = 100 µm. (D) BV/TV of the subchondral bone area of the DMM model in comparison to 8 months mice (similar age).

3. OMD IS ASSOCIATED WITH SPONTANEOUS OA LESIONS

Spontaneous OA lesions of the medial tibial plate – 16 Months mice



Spontaneous OA lesions of the jaw joint – 1-year-old Zebrafish

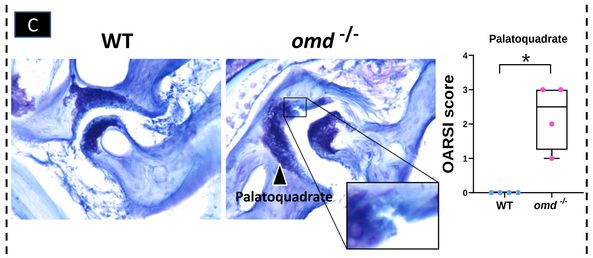
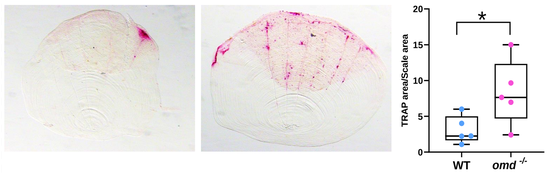


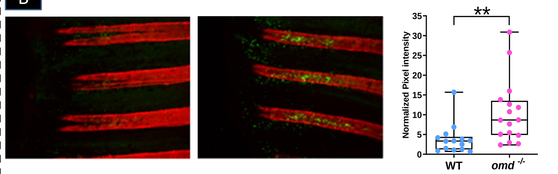
Figure 3.
(A) Analysis of the development of spontaneous OA lesions in 16 months mice. Illustrations of medial plateau stained with Toluidine Blue. Scale bar = 100 µm. (B) Associated OARSI score and score of the proteoglycan loss. (C) Analysis of the development of spontaneous OA lesions in the jaw joint of 1-year-old zebrafish. Illustrations of the articular cartilage of the WT and mutant loss of function zebrafish stained with Toluidine Blue and the associated OARSI score for the palatoquadrate cartilage.

4. OMD REGULATES THE OSTEOCLASTOGENESIS

TRAP staining on zebrafish scale



Osteoclast count from zebrafish regenerating caudal fin



Direct binding assay between OMD and RANKL

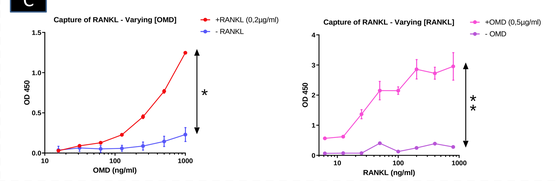


Figure 4.
(A) TRAP staining on the zebrafish elasmoid scales and quantification of the stained area. (B) Osteoclast count from WT and mutant lines crossed with the *Tg(ctsk:Citrine)*, marking osteoclasts in yellow, during the caudal fin regeneration. The regenerated fin was stained with Alizarin red to observe bone in red. (C) Direct binding assay between OMD and RANKL *in vitro*. RANKL was coated on a plate followed by OMD addition and their binding was assessed through anti-OMD antibody signal quantification

CONCLUSIONS

OMD preserves bone and cartilage integrity and a local decrease of its production leads to the development of OA mainly by increasing subchondral bone sclerosis via impaired osteoclastogenesis.

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