BONE-CARTILAGE CROSSTALK MODEL

IL-6 mediates subchondral osteoblasts-induced cartilage degradation

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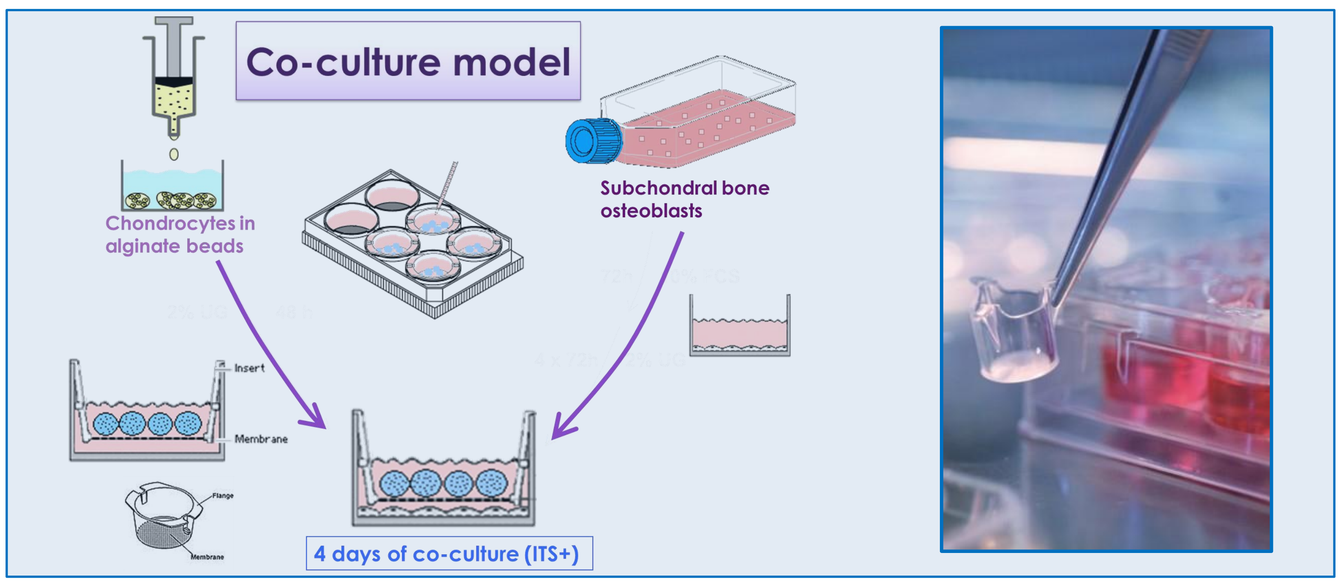
PURPOSE. Previously, we have demonstrated that osteoblasts from the sclerotic subchondral bone express a particular phenotype characterized by an overproduction of interleukin (IL)-6, transforming growth factor (TGF)-β1, alkaline phosphatase and osteocalcin but similar amount of IL-1β than non sclerotic osteoblasts. Further, we have observed in a co-culture model that osteoblasts from the sclerotic zone of osteoarthritic (OA) subchondral bone dysregulated the metabolism of chondrocytes. This work was designed to identify the mediators involved in these osteoblasts-induced effects.

METHODS. Human chondrocytes were isolated from OA cartilage and cultured in alginate beads for 4 days in the absence or in the presence of non sclerotic or sclerotic OA subchondral osteoblasts in monolayer (co-culture system). During co-culture, monoclonal antibodies (Mab) neutralizing IL-6 were added. Chondrocytes in monoculture were conducted in parallel as controls. Aggrecan, sox9 and matrix metalloproteases (MMP) -3 and -13 mRNA levels in chondrocytes were quantified by real time PCR. Aggrecan and MMP-3 production was assayed by ELISA.



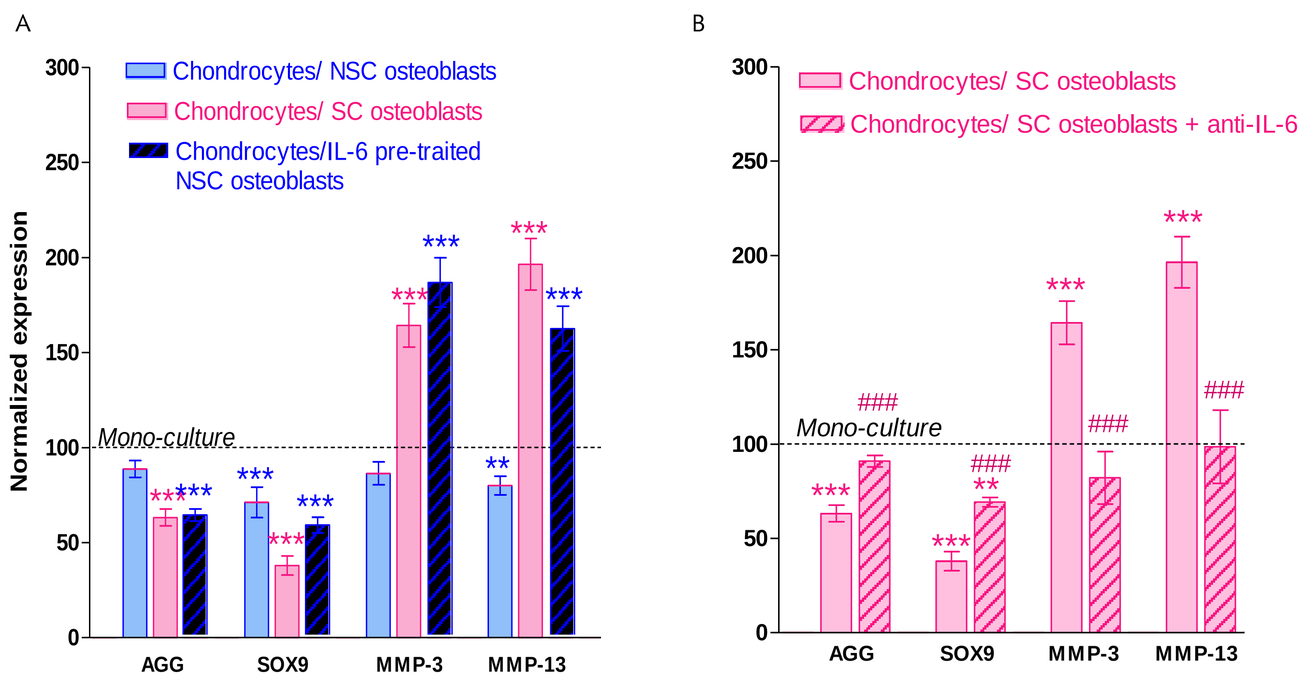


Fig. 1
AGG, SOX9, MMP-3 and MMP-13 genes expression by chondrocytes after 4 days of co-culture with non sclerotic (NSC) or sclerotic (SC) osteoblasts.
(A) NSC osteoblasts were or not pre-incubated during 72h with IL-6 (100 ng/ml + 50 ng/ml d'IL-6sR).
(B) Co-cultures were performed in the presence or not of monoclonal antibodies neutralizing IL-6 biological activity.
Results are expressed in mono-culture percentage. Genes expressions are GADPH normalized and are represented by the mean of 3 independent cultures ± SEM. Each experimental condition was performed in triplicate (n=9). Significant statistical differences are represented by ** = p<0,01 and *** = p<0,001 between co-culture and mono-culture, and ###=p<0,001 between co-culture with or without anti-IL-6 antibodies.

References
Sanchez C et al Osteoarthritis Cart 2005, 13 : 979-987
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RESULTS AND VALORIZATION

In co-culture, sclerotic, but not non sclerotic, osteoblasts significantly decreased (- 27 %, p<0.001) aggrecan production and aggrecan gene expression by human chondrocytes. In parallel, sox9 expression was decreased (- 52 %, p < 0.001) whereas MMP-3 and MMP-13 gene expression were increased (+ 44 and + 76%, respectively, p < 0.001). Anti-IL-6 Mab, prevents all these osteoblasts-induced effects. This model is unique to investigate the effect of drugs or nutraceuticals on OA subchondral bone/cartilage crosstalk. It could also be helpful to better understand the mechanism of action of new treatments.

CONCLUSION

OA subchondral osteoblasts could contribute to cartilage degradation by stimulating chondrocytes to produce more matrix metalloproteases and by inhibiting aggrecan synthesis. Herein, we have identified IL-6 as a key mediator of the osteochondral pathophysiological axis. This model is helpful to find new active pathways for anti-rheumatic drugs.