ROLE AND EPIGENETIC REGULATION OF P16INK4A-MMP-1 AXIS IN OA-ASSOCIATED SENESCENCE-LIKE PHENOTYPE AND HYPERTROPHY OF CHONDROCYTES

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Background and objectives Osteoarthritis (OA) chondrocyte is characterised by altogether DNA damage accumulation, eroded telomeres, expression of senescence marker such as p16Ink4a and establishment of one specific secretome including IL-1β, IL-8 and MMP-1/-3/-13. Recent data have proposed that tissue specific accumulation of p16Ink4a-positive cells would be deleterious for the tissue function and could be the consequence of the inherent age-associated disorders. Here the authors evaluate the role of p16Ink4a-dependent pathway and its epigenetic regulation by microRNAs in osteoarthritis-associated phenotypes.

Materials and methods The authors performed a genome wide miRNA-array analysis in order to identify microRNAs regulating senescence-associated phenotypes found in OA. The authors used primary OA chondrocytes in 3D culture, IL-1β treatment and gain or loss of function experiments to validate their regulatory effects on senescence-associated targets. Chondrogenic differentiation was induced by culture of mesenchymal stromal cells in micropellets in inductive...
medium for 21 days. Expression of chondrocyte markers was performed by RT-qPCR.

**Results** By miR-array analysis, the authors identified the downregulation of miR-24, one epigenetic known regulator of p16\(^{\text{ink4a}}\). miR-24 expression is repressed upon IL-1\(\beta\) treatment while p16\(^{\text{ink4a}}\) protein accumulates. Based on gain or loss of functions approaches, our results suggest that miR-24 downregulation or p16\(^{\text{ink4a}}\) overexpression, are sufficient to trigger chondrocyte premature ageing characterised by activation of p16\(^{\text{ink4a}}\)-MMP-1 axis as shown by RT-qPCR and ELISA. This reverse correlation is also observed during hypertrophic stage induced by an in vitro chondrogenic differentiation of mesenchymal stromal cells.

**Conclusions** Altogether, our preliminary data show that, in IL-1\(\beta\)-treated chondrocytes, miR-24 expression is downregulated leading to p16\(^{\text{ink4a}}\) accumulation. In turn, p16\(^{\text{ink4a}}\) controls the expression of MMP-1 probably via the transcriptional induction of the transcription factor, ZNF-410. Future experiments are required to validate this last hypothesis and would open new perspectives for putative pharmacological targets to delay OA or other p16\(^{\text{ink4a}}\)-dependent diseases.
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