Ann Rheum Dis: first published as 10.1136/annrheumdis-2011-201237.14 on 22 February 2012. Downloaded from http://ard.bmj.com/ on September 18, 2024 by guest. Protected by copyright.

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

D Philipot,[1,2] D Guerit,[1,2] E Olivotto,[3] D Platano,[3] P Chuchana,[1,2] J Piette,[4] C Jorgensen,[1,2,5] R M Borzi,[3] D Noel,[1,2] J-M Brondello[1,2] *[1]INSERM U844, CHU St Eloi, Bat INM, montpellier, France; [2]Université de Montpellier-1, France; [3]Laboratorio di immunoreumatologia e rigenerazione tissutale, Istituto di ricerca Codivilla Putti, Bologna, Italy; [4]UMR5535, CNRS, CRBM, Montpellier, France; [5]Unité clinique, thérapeutiques des maladies des os et articulations, CHU Lapeyronie, Montpellier, France*

CJ, RMB, DN and JMB have equally contributed.

10.1136/annrheumdis-2011-201237.14

Background and objectives Osteoarthritic (OA) chondrocyte is characterised by altogether DNA damage accumulation, eroded telomeres, expression of senescence marker such as $p16^{Ink4a}$ and establishment of one specific secretome including IL-1b, IL-8 and MMP-1/-3/-13. Recent data have proposed that tissue specific accumulation of $p16^{Ink4a}$-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 $p16^{Ink4a}$-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^{Ink4a}. miR-24 expression is repressed upon IL-1 β treatment while p16^{Ink4a} protein accumulates. Based on gain or loss of functions approaches, our results suggest that miR-24 downregulation or p16^{Ink4A} overexpression, are sufficient to trigger chondrocyte premature ageing characterised by activation of p16^{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 β -treated chondrocytes, miR-24 expression is downregulated leading to p16^{ink4A} accumulation. In turn, p16^{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^{ink4a}-dependent diseases.

Ann Rheum Dis: first published as 10.1136/annrheumdis-2011-201237.14 on 22 February 2012. Downloaded from http://ard.bmj.com/ on September 18, 2024 by guest. Protected by copyright.