associated with disease. Recently, extracellular vesicles (EVs) have emerged as mediators of intercellular communication. There is however very little known about the pathophysiological role of EVs in musculoskeletal diseases. In this study, we investigate whether plasma EVs from OA patients can drive chondrocyte terminal differentiation, a pathophysiological process observed in affected joints and a hallmark of OA.

Objectives Study the effect of plasma-derived EVs from OA patients during chondrogenic differentiation of mesenchymal stem cells.

Methods Plasma-derived extracellular vesicles (pEVs) were isolated from plasma of OA patients and age-matched healthy controls using size-exclusion chromatography. EV containing fractions were characterised according to ISEV guidelines.¹ Pelleted MSCs were stimulated with TGF- β and BMP-2 to induce chondrogenic differentiation, either in the presence of pEVs isolated from OA patients or healthy controls. After 8 days, RNA was isolated and RT-qPCR was performed to determine the gene expression profiles.

Results No significant difference was observed in particle concentration, size or protein concentration between OA patients and age-matched controls. In the presence of pEVs from OA patients MSC-derived chondrocytes showed a significant increase in the expression of *MMP13* (6.1-fold), *RUNX2* (1.9-fold) and *RANKL* (2.3-fold), compared to pEVs from healthy controls. A trend towards higher *ADAMTS5* expression (2.5-fold, $p=0.0685$) with OA pEVs was also observed. Additionally, we found significantly higher expression of *WISP1* (24-fold), suggesting activation of Wnt signalling. All other proinflammatory genes tested were not significantly different between the two groups.

Conclusions Here, we show direct evidence that circulating pEVs from OA patients can enhance OA-related genes, like *MMP13*, in MSC-derived chondrocytes. The expression profile found suggest the presence of Wnt-proteins on pEVs from OA patients, which are known to be involved in cartilage development and can induce chondrocyte hypertrophy, and we previously have shown that *WISP-1* expression is a feature of experimental and human OA.² We showed that pEVs can transfer disease-related phenotypic changes and this might implicate them in the pathophysiological process of OA.

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EPIGENETIC CONTROL OF DISTALLY EXPRESSED HOXD GENES IN SYNOVIAL FIBROBLASTS

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Introduction Synovial fibroblasts (SF) from different joint localizations exhibit profound differences in their expression profiles

that might predispose specific joints for certain forms of arthritis.¹ Homeobox (*HOX*) genes were shown to play important roles in limb development and might influence the site-specific development of various diseases.

Objectives To analyse the expression of distally expressed *HOXD* genes in SF from hands and to investigate their epigenetic regulation.

Methods The expression of *HOXD10*, *HOXD11* and *HOXD13* was analysed by quantitative Real-time PCR. The histone marks H3K4me1 (enhancers), H3K4me3 (transcriptional starts of transcribed genes), H3K27me3 (inactive gene promoters) and H3K27ac (active enhancers) in SF from one RA (finger) and one osteoarthritis (OA; thumb) patient were analysed by ChIP DNA sequencing (ChIPseq). Hand SF ($n=7$) were treated for 24 hour with the bromodomain inhibitor I-BET151 (1 μ M), targeting the bromodomain and extra-terminal domain (BET) proteins. The expression of the histone-acetyltransferases CREBBP-binding protein (CBP) and p300 was silenced by transfection of antisense LNA gapmeRs in hand SF ($n=4$).

Results *HOXD10*, *HOXD11* and *HOXD13* transcripts were significantly increased in SF from RA and OA patients in digits II-IV and wrists compared to SF from digit I (thumb). Accordingly, ChIPseq showed an increase of H3K27ac and H3K4me3 marks in the genomic region between *HOXD9* and *HOXD13* in SF from a RA finger compared to SF from an OA thumb, paralleled by a loss of the repressive histone marks H3K27me3 between *HOXD12* and *MIR10B*. Treatment of SF with I-BET151 reduced the expression of *HOXD10*, *HOXD11* and *HOXD13* by 50% (± 23 ; $p<0.001$), 29% (± 29 ; $p<0.05$), and 27% (± 27 ; $p<0.05$) respectively. Silencing of CBP reduced the expression of *HOXD10* by 47% (± 10 ; $p<0.01$) and *HOXD11* by 22% (± 19 ; $p=0.1$) but not *HOXD13*. Also silencing of p300 reduced the expression of *HOXD10* by 47% (± 24 ; $p=0.06$) and *HOXD11* by 55% (± 10 ; $p<0.01$) but not *HOXD13*.

Conclusions Distally expressed *HOXD* genes exhibit site-specific expression between digits II-IV and the thumb. The site-specific expression is maintained by a specific set of histone modifications and regulated by epigenetic writer (CBP, p300) and reader proteins (BET proteins). This epigenetically regulated expression of *HOXD* genes might influence the different occurrence of RA and OA in the small joints of the digits II-IV and the thumb.

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