Transcriptomics on Synovial Specimen of Early Human (CHECK) and Experimental OA to Identify Pathways and Processes Associated with Cartilage Damage

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Disclosures:

Introduction: The majority of osteoarthritis (OA) patients show synovial inflammation, even relatively early during the disease. How synovitis contributes to the irreversible joint pathology is not known. In the present study we used microarray analysis of synovial tissue of early OA patients and of experimental OA, to identify common pathways that determine cartilage damage in this disease.

Methods: Longitudinal expression analysis was performed on murine synovial tissue at day 7, day 21 and day 42 in collagenase induced OA (CIOA) and the surgically induced DMM model (destabilization of the medial meniscus). CIOA was induced by intra-articular injection of collagenase, which causes joint instability. DMM was induced by transection of the anterior medial meniscotibial ligament. From a subpopulation of patients (n=25) that entered the CHECK Cohort study (Cohort Hip and Cohort Knee) and 7 controls, synovial biopsies were collected at year 0, 2 and 5. CHECK is a prospective 10-year follow-up study on participants with early osteoarthritis-related complaints initiated by the Dutch Arthritis Association. Patients that entered the cohort suffered from knee and/or hip pain and did not see a general practitioner because of these complaints, longer than 6 months before inclusion. Kellgren&Lawrence-score (KL) at inclusion was determined (n=18) and follow up measurements were performed at 2 and 5 years. Affymetrix was used as a platform for for microarray, U133 plus 2.0 for human samples and 430_2a for murine tissue, and analysed using Partek Genomics Suite software. Pathway analysis was done using DAVID.

Results: Among the genes that were strongly upregulated on all 3 time points after induction of CIOA were MMP-3 (6-fold), MMP-13 (16-fold), MMP-14 (6-fold). Wound healing, phagocytosis, chemotaxis and metalloproteases were significantly enriched, as were the complement pathway, the TLR-, TGFβ, BMP and wnt-signaling pathways. Highly similar results were obtained in the DMM model for OA at day 7. However, at day 42 in this model very view genes were still regulated in the synovium compared to other time points or CIOA, indicating that synovial activation differs late between the models (Figure 1.). This was underlined by histological examination, that shows thickened synovial lining mainly in CIOA. All in all, the expression patterns in experimental OA showed compelling similarities with human OA synovium. Gene expression profiles of control synovia were compared to CHECK synovia. Analysis using DAVID indicated enrichment of several biological processes and signaling pathways, including macrophage presence, cell migration, TGFβ-, BMP- and wnt-signaling. This indicates clear activation of the synovium in the CHECK patients compared to controls. Next we compared synovial tissue of CHECK-patients with radiological damage (KL≥1) with CHECK-patients without joint damage (KL=0). In the top 30 genes that were associated with cartilage damage were MMP-1 (18-fold), MMP-3 (10-fold) and S100A8 (6-fold), all of which have been associated with cartilage damage. Functional Annotation Clustering (FAC) analysis further underlined response to wounding, chemotaxis, innate immune response and metalloproteases to be strongly enriched. In particular, complement-activation pathway, TGFβ- and BMP-signaling and TLR-activation were striking.

Discussion: Activation pathways and processes in the two models for OA were highly similar. A major difference lies in the presence of late synovial activation. This may direct the choice for the most optimal model to study certain OA subpopulations, since this difference was obvious in human OA, where roughly 50% shows marked synovitis. The FAC data suggest an active role for the synovium in OA pathology, and identifies pathways likely to be involved. One of the strongest associations was of the complement-pathway with cartilage damage. In addition, synovial MMP expression was associated with cartilage damage, underlining an active role of synovium in OA pathology.

Significance: It is nowadays widely recognized that in a large proportion of OA patients the synovium is inflamed. However, whether and how this activation contributes to pathology is not sure. These results indicate an association of processes in the synovium with cartilage damage, which suggests an active contribution of the synovium in joint pathology. This identifies the synovium as a target tissue for OA treatment. In addition, these results reveal differences in synovial involvement in two murine models for OA. This may guide the choice for a certain model depending on the research question.
Figure 1. Number of differentially expressed genes on day 7, 21, and 42 in the synovium during CIA and DMN compared to control joints. Please note that in CIA many genes are still regulated in the synovium at day 42, whereas in DMN very few genes are differentially expressed, indicating decreased synovial involvement in OA compared to DMN.

References:

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