were significantly higher in HDF (0.2 ± 0.16, n=7) compared to ND (5.2 ± 0.98, n=8). No difference was found in Cia-severity between HDF and ND. However, Cia induction increased the number of CLS in HDF (2.77 ± 1.07, n=6) and importantly in ND (1.4 ± 0.23, n=5) compared to healthy ND (0.45 ± 0.03, n=4) and healthy HDF mice (2.57 ± 0.53, n=4) without Cia. As expected, HDF led to a significant increase in systemic leptin in healthy animals in both models. Interestingly, Cia and DMN induction decreased systemic leptin levels significantly in ND and HDF, which was more prominent in Cia. The systemic effect was not reflected by local leptin distribution in the joints (Cia) which were not altered by ND or by DMN. However, ND led to a reduction in both local adipose tissue expression as well as by the reduced expression of clinogetic phenotype of our cartilage tissue component by HE and Alcian Blue staining as well as by the reduced expression of clinogetic phenotype of our cartilage tissue component by HE and Alcian Blue

Conclusion: The data show that HDF deteriorates OA, which is similar to observations in humans. In contrast, HDF induction showed no significant difference in Cia severity compared to ND. Furthermore, Cia reduced local adipokine expression under HDF at later time points but not under ND. According to high numbers of CLS in ND/Cia animals and the strong reduction of leptin in Cia with HDF, Cia onset and severity seems to be obesity independent and more dependent on inflammation while OA appears to be directly influenced by obesity. However, HDF-induced obesity seems to alter local and systemic adipokine expression also in Cia. Interestingly, local adipokine distribution in affected joints was independent from systemic adipokine levels.

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DEFINING SYNOVIAL SIGNATURES IN THE RAT CIA MODEL: WHAT CAN WE LEARN ABOUT RA PROGRESSION?

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Background: Patients showing inadequate or no response to current therapies represent a key unmet need in rheumatoid arthritis (RA). To address this, novel or combination therapies are of high clinical interest. Identification of novel therapeutic targets requires a greater understanding of the pathogenic molecular drivers in the RA synovium. However, our current knowledge of human molecular patterns that emerge as a result of disease progression is complicated by patient-to-patient heterogeneity and access to synovial tissue.

Objectives: Here we use the current knowledge of human synovial heterogeneity to conduct a longitudinal study of global molecular responses in the rat collagen-induced arthritis (CIA) model to better understand synovial biology, improve the preclinical modeling of human disease, and discover novel targets for RA.

Methods: A rat CIA model was performed as previously described.1 RNA-Seq was performed on 56 knee synovial tissues collected at multiple time points throughout the course of disease. Differential gene expression was determined at each individual time point and longitudinally with disease progression. Published human synovial datasets were used to categorize these genes into myeloid, lymphoid, fibroid, and low inflammatory signatures.2 Differentially expressed genes (DEGs) at each time point were compared to human synovial datasets of RA patients before and after treatment. In addition, we compared disease-driven genes in CIA to genes in RA patients that are unchanged following therapy to identify possible combination therapies.

Results: Disease pathology in the rat CIA natural history study progressed as expected: significant decreases were seen in body weight, as well as increases in ankle diameter, paw weight, and histopathology scores of joints in collagen-injected vs non-injected rats. There were 1900 DEGs identified between diseased and naive rats over the course of disease, representing disease-induced gene signatures (Fig. 1). Comparing these DEGs to reported human RA synovial signatures, both the lymphoid and myeloid signatures were found to be highly upregulated. Interestingly, there were no significant DEGs representing the human fibroid and low inflammatory signatures identified in the CIA rat model. This suggests that the rat CIA model most closely models RA patients with an immune synovial phenotype. In addition, we examined the overlap between disease-driven genes in CIA and genes in RA patients that are unchanged following therapy to identify signaling pathways that may be of utility in combination therapy. Of genes that were upregulated in CIA, 94% of genes that mapped to extracellular matrix-receptor pathways remained unchanged in the synovial tissue of RA patients following tocilizumab treatment.

Conclusion: Previous studies have shown that nearly 30% of treatment-naïve early RA patients exhibit a strong fibroid phenotype that correlates with less severe disease and a relatively poor response to disease-modifying anti-rheumatic drugs.3 These data indicate that the synovial biology associated with such patients (fibroid or pauci-immune) is not well captured in CIA, the most common preclinical RA model. To assess potential new therapies targeting these patients, it will be necessary to develop alternative animal models with more intact fibroid signatures. In addition to these findings, we also characterized the global molecular changes that occur with disease progression in the CIA rat and made a comparison to RA patients on treatment, providing an overall understanding of


Disclosures:

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