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EP3 Integrative scRNA-seq and spatial transcriptomics uncovers distinct macrophage-fibroblast cross-talk in human hip synovium between patients with femoroacetabular impingement and osteoarthritis

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Introduction: Hip osteoarthritis (OA) affects one in four people by the age of 85, and it has been linked to synovitis and abnormal hip morphology including Cam-type femoroacetabular impingement (FAI). Nevertheless, little is known about altered synovial cellular compositions, their associated transcriptomic profiles, and cell-cell interactions between FAI and hip OA. In this study, we hypothesize that synovial tissues from FAI and hip OA patients exhibit distinct transcriptomics and cell-cell interactions.
Methods: De-identified synovium from sex-matched cohort of FAI and hip OA patients (n = 6/condition) (STUDY0001802) were analyzed using integrative single-cell RNA sequencing and spatial transcriptomics. Distinct cell populations were annotated by Gene Ontology (GO) based on unbiased clustering and expression of differentially expressed genes (DEGs). Identified cells were then mapped to Spatial-seq datasets to pinpoint their spatial locations within the synovium. Differentiation trajectory analysis was performed using Monocle and iRegulon algorithm. Cell-cell crosstalk and downstream-activated genes were determined by MultiNicheNet package.
Results: Compared to FAI, epiregulin (EREG)-enriched lining synovial fibroblast-like synoviocytes (FLS) were significantly increased in the hip OA. These EREG+ FLS are pro-inflammatory due to elevated expression of CXCL1, IL8, and MMPs. Pseudotime analysis predicts that EREG+ FLS are derived from DPP4+PI16+ sublining FLS, likely regulated by NIFX and REL as well as ELK3 and ETV6 TFs under FAI and OA conditions, respectively. Importantly, cell-cell interaction analysis indicates that fibroblast growth factor 2 (FGF2) secreted from COL1A1+IGFBP5+ fibrotic macrophages signal through syndecan 4 (SDC4) expressed by EREG+ lining FLS, inducing expression of IL6, IL8, MMP1, and PTGS2. The GO analysis of activated genes downstream of FGF2-SDC4 signaling revealed that biological processes associated with inflammation and angiogenesis were upregulated in hip OA, while mechanical stimulus was dominant in FAI. Moreover, we also found that EREG+CCL20+MMP3hi lining FLS as well as most macrophage and monocyte populations are unique to hip OA patients when compared to knee OA and RA patients.
Conclusion: Our results suggest that targeting distinct signaling molecules at different disease stages may be required to prevent hip OA progression from FAI, offering a groundwork in tailoring novel targets and therapies for FAI and hip OA patients.