Distinct stromal and immune cell interactions shape the pathogenesis of Rheumatoid and Psoriatic arthritis.

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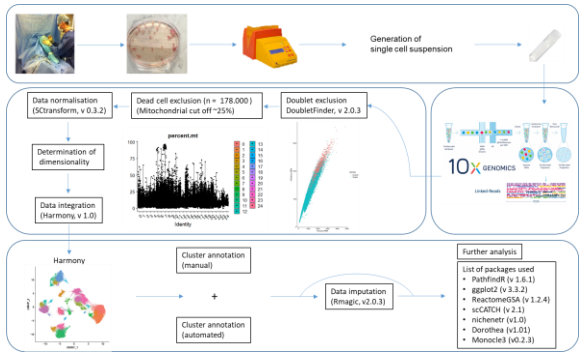
Introduction

Rheumatoid (RA) and psoriatic arthritis (PsA) are common autoimmune diseases of unknown aetiology characterised by complex synovial pathology. While recent studies have identified unique synovial cell clusters in RA, no studies to date have examined the synovial landscape of PsA, in addition to characterising the differential and complex immune-stromal cell cross talk that may define the distinct synovial pathotypes observed in RA and PsA

Methods



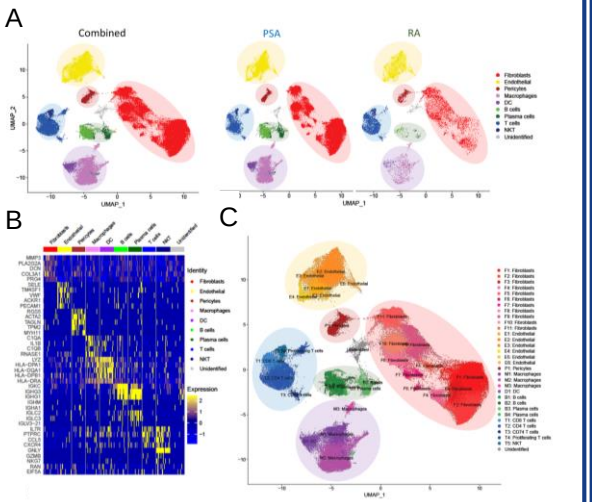
Highlights

1. Generation of the first cell-atlas of the RA and PsA synovial tissue.
2. Only a fraction of synovial T cells are actively proliferating.
3. Synovial plasma cells may not be derived from synovial tissue memory B cell populations.
4. Immune-stromal cell interactions shape the transcriptome of pathogenic synovial fibroblast clusters.

Conclusions

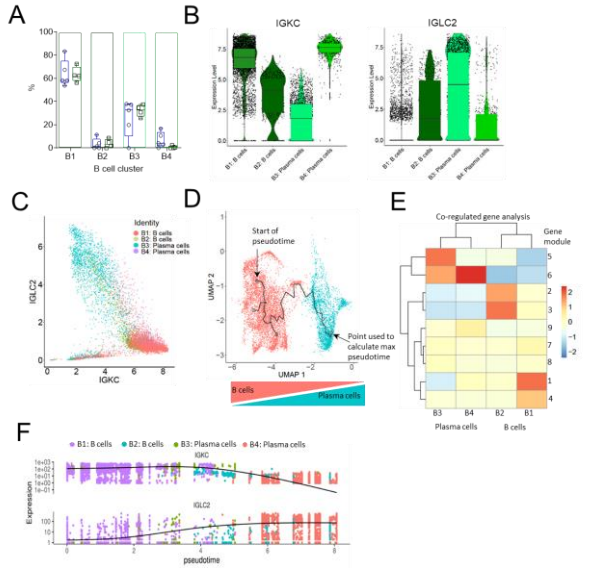
Deciphering the crosstalk between immune and stromal cells can reveal opportunities for targeted therapeutic intervention. The cellular landscape of RA and PsA reveals points of convergence and distinct underlying mechanisms of synovial inflammation with utilisation of receptor ligand interaction networks providing evidence of T cell and macrophage synergy in shaping the transcriptome of invasive fibroblasts in RA.

1. The cell atlas of the inflamed joint



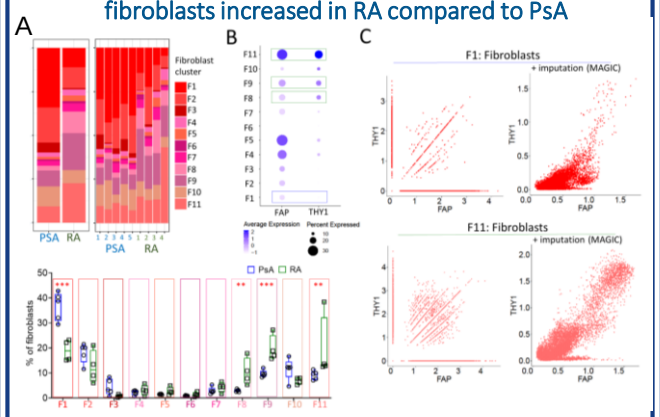
A. UMAP representation of 9 "mega"-clusters based on 178,170 cells across all cell types and synovial tissue biopsies (n=4 and 5 for RA and PsA patient biopsies respectively). B. Differential gene expression analysis identifies upregulated or downregulated marker genes of the identified mega-clusters. C. Division of the 9 identified mega-clusters into a total of 33 sub-clusters.

2. κ and λ chain usage by synovial B cells



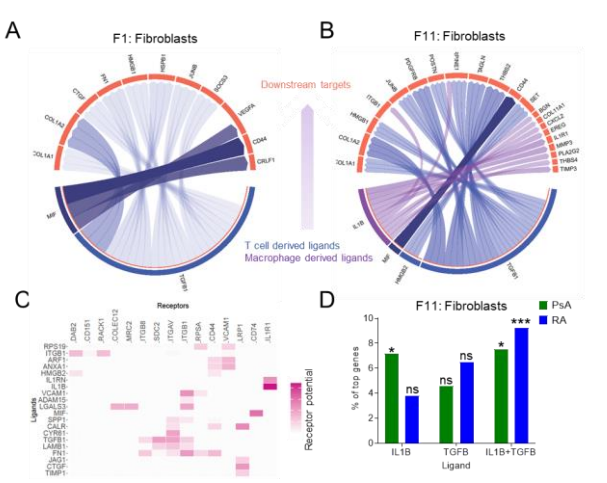
A. Abundance of B cell clusters in RA and PsA patient synovial biopsies. B. Violin plot for IGKC (κ chain) and IGLC2 (λ chain) by B cell clusters. C. Scatter plot of IGKC and IGLC2 following data imputation. D. Trajectory analysis. E. Heatmap of co-regulated genes as a function of pseudotime. F. Expression of IGKC and IGLC2 as a function of pseudotime.

3. Inflammatory FAP⁺THY1⁺ synovial fibroblasts increased in RA compared to PsA



A. Abundance of fibroblast clusters in RA and PsA patient synovial biopsies. B. Expression and percentage of positive cells per fibroblast cluster for FAP and THY1. C. Scatterplots for showing the relation between THY1 and FAP expressing cells before and after data imputation. D. Fibroblast clusters with significantly different abundances between RA and PsA are indicated by green (higher in RA) and blue (higher in PsA) boxes. D. Frequency of fibroblast clusters in PsA and RA patient synovial biopsies (n=4-5), data are presented as Box and whiskers plots (min to max), symbols represent individual samples.

4. Immune – stromal cell interactions



A. Circo plot depicting the top ligand and downstream target interaction for enriched in PsA synovial fibroblast cluster F1. B. Circo plot depicting the top ligand and downstream target interaction for enriched in RA, invasive synovial fibroblast cluster F11. C. Heatmap of ligand receptor interactions for synovial fibroblast cluster F11. D. Percentage of gene targets downstream of IL1B, TGFB1 or IL1B+TGFB as part of the top targets regulated by F11 fibroblast cluster receptors..