Synovial tissue homing properties of novel monocyte subpopulations in active treatment naïve psoriatic arthritis.

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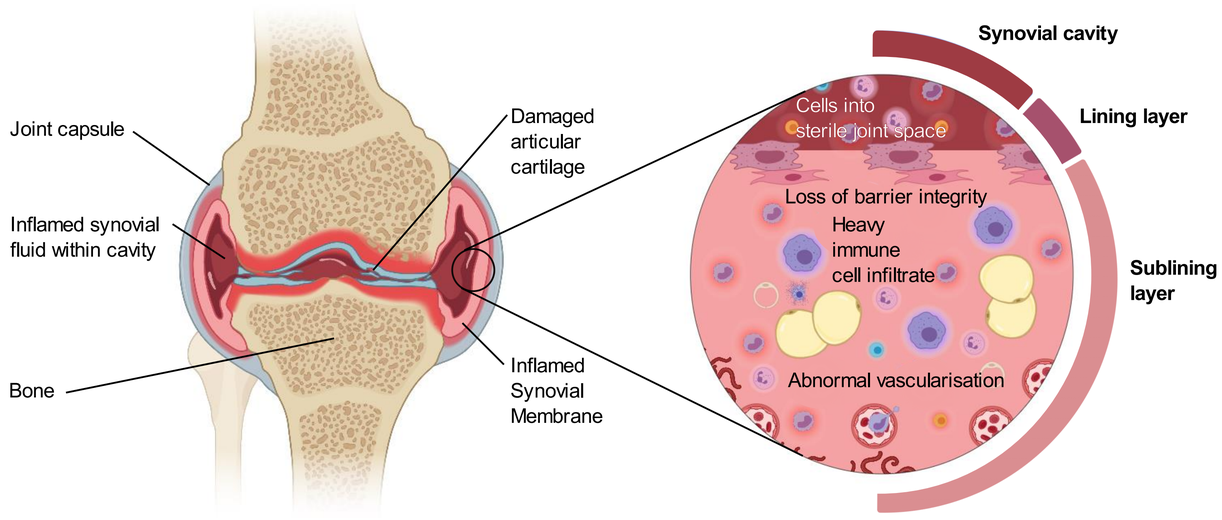
Background

Psoriatic arthritis (PsA) is a common immune-mediated inflammatory arthritis and is associated with permanent joint damage and significant sequelae. A key feature is abnormal recruitment of leukocytes into joint tissues and increased vascularisation. The mechanisms underlying this infiltration across different affected tissues and disease states are poorly understood.

A common cell type recruited to inflamed joints are mononuclear phagocytes (MPS). These are a heterogenous population of cells consisting of monocytes, tissue macrophages, and multiple dendritic cell (DC) subsets. MPS sit at the interface between innate and adaptive immunity and are critical for normal tissue functioning via mediating homeostasis, vascularisation, defence against infection, and initiation and resolution of inflammation. These processes are abnormal in PsA, and MPS have also been linked to the development of key adaptive effector cells enriched in PsA joints. This makes them prime candidates for a significant role in the initiation and perpetuation of PsA.



Therefore, we aim to understand:

- What are the role of MPS in both the blood and joint in PsA?
- What are the key interactions that permit inflammation-causing cells to migrate into the joint?

Results

Figure 1 Altered circulating MPS populations in the circulation of patients with active treatment naïve PsA. **(A)** Workflow for measuring absolute counts of blood MPS from healthy controls, and active treatment naïve PsA, and for high-sequencing depth bulk RNA-sequencing of sorted populations using SmartSeq2. **(B)** Representative example of absolute MPS count on treatment naïve PsA blood with coloured gates highlighting final subsets. **(C)** Absolute counts of blood MPS subsets in health (blue) and PsA (red). Significantly differentially expressed cells between disease states via Students T-test with Welch's correction indicated with *. Significantly altered DC1s (p=0.0076) and DC3s (CD14+ CD163+, p=0.0152).

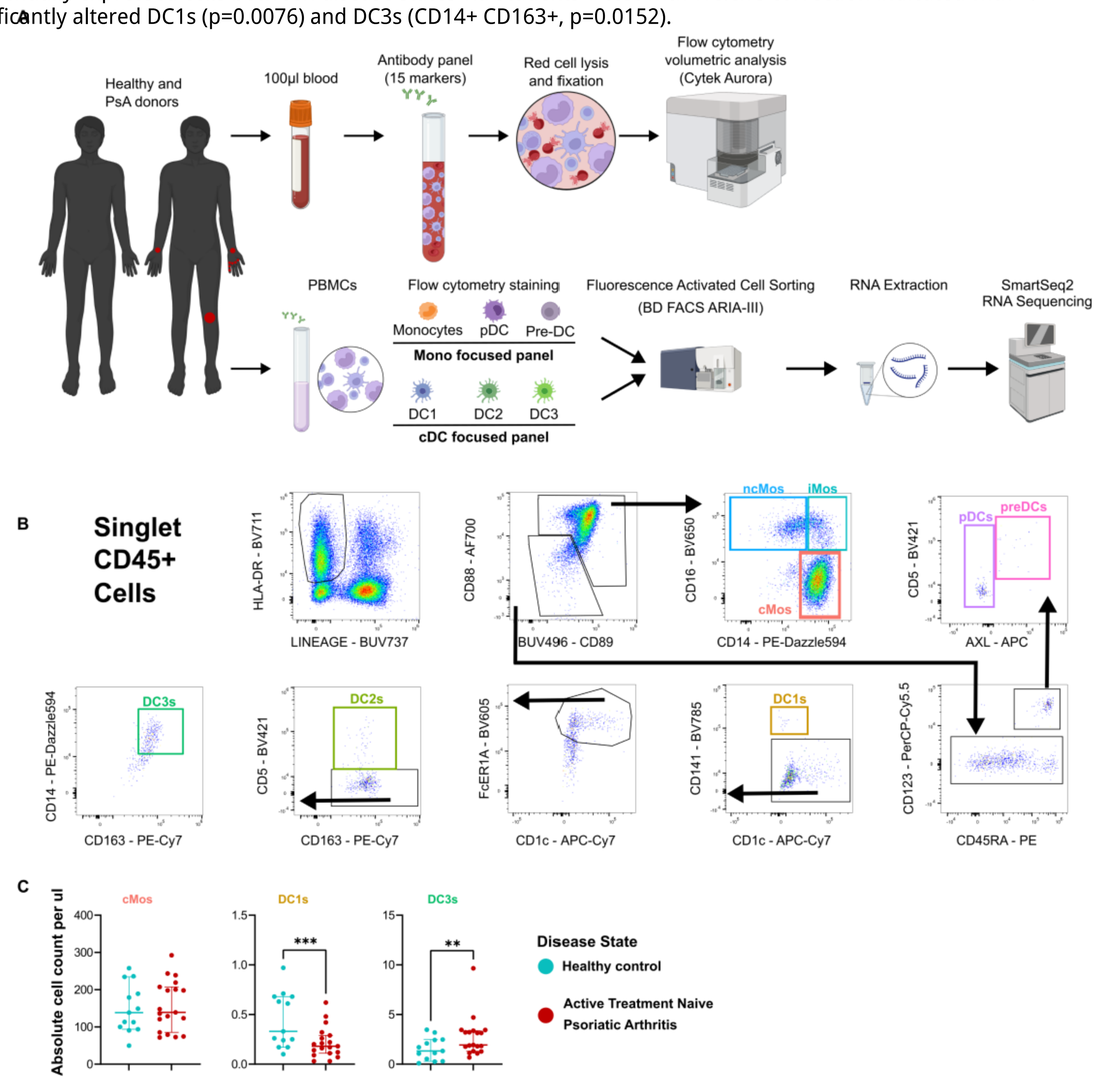


Figure 2 High-depth bulk RNA-sequencing and mass cytometry of blood MPS identifies osteoclast precursor population that is expanded in PsA. **(A)** Gene-set enrichment analysis plots of key pathways enriched in PsA cMos (N=5) compared to healthy controls (N=4)) using high sequencing depth bulk RNA-seq using the SMART-Seq2 platform. **(B)** Uniform manifold approximation and projection (UMAP) plot of 200,000 antigen presenting cells from the peripheral blood of N=10 healthy and N=10 donors with active treatment naïve PsA, putative osteoclast precursor (OCP) population highlighted in purple. **(C)** UMAP plot of 4,442 synovial tissue myeloid cells from N=5 donors with psoriatic arthritis, enrichment for lineage-defining markers for blood OCP population highlighted using Nebulosa. **(D)** Box and whisker plot showing proportion of CD45+ cells that are OCPs in N=10 healthy vs. N=10 donors with active treatment naïve PsA as enumerated by mass cytometry, Mann-Whitney-U p=0.0041.

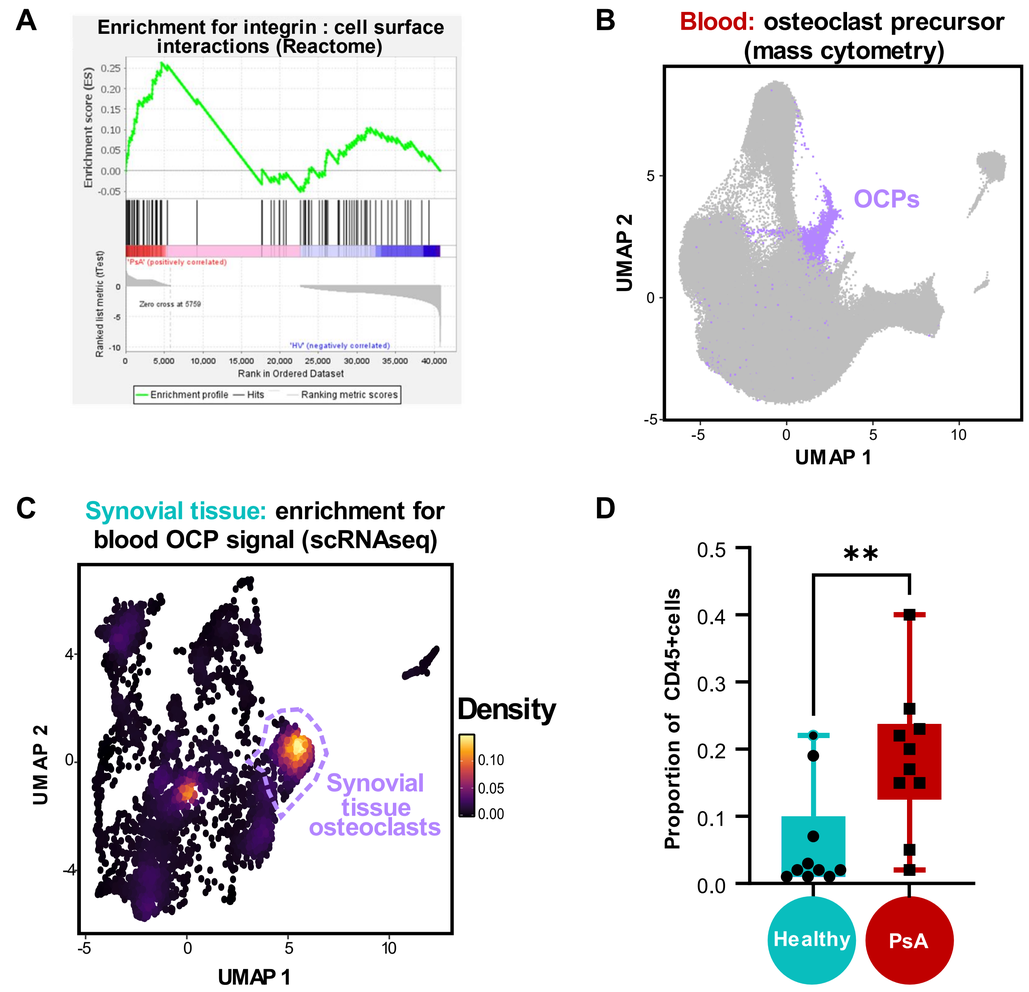


Figure 3 Novel osteoclast precursor population is enriched for key synovial tissue homing signal and is also found on infiltrating synovial myeloid cells. **(A)** UMAP projection showing enrichment for synovial tissue homing signal on 200,000 antigen presenting cells from the peripheral blood of N=10 healthy and N=10 donors with active treatment naïve PsA using AddModule score; OCP population highlighted by dotted purple lines. **(B)** UMAP plot of 4,442 synovial tissue myeloid cells from N=5 donors with psoriatic arthritis, enrichment for same synovial tissue homing signal using AddModule score and Nebulosa; key populations of interest highlighted.

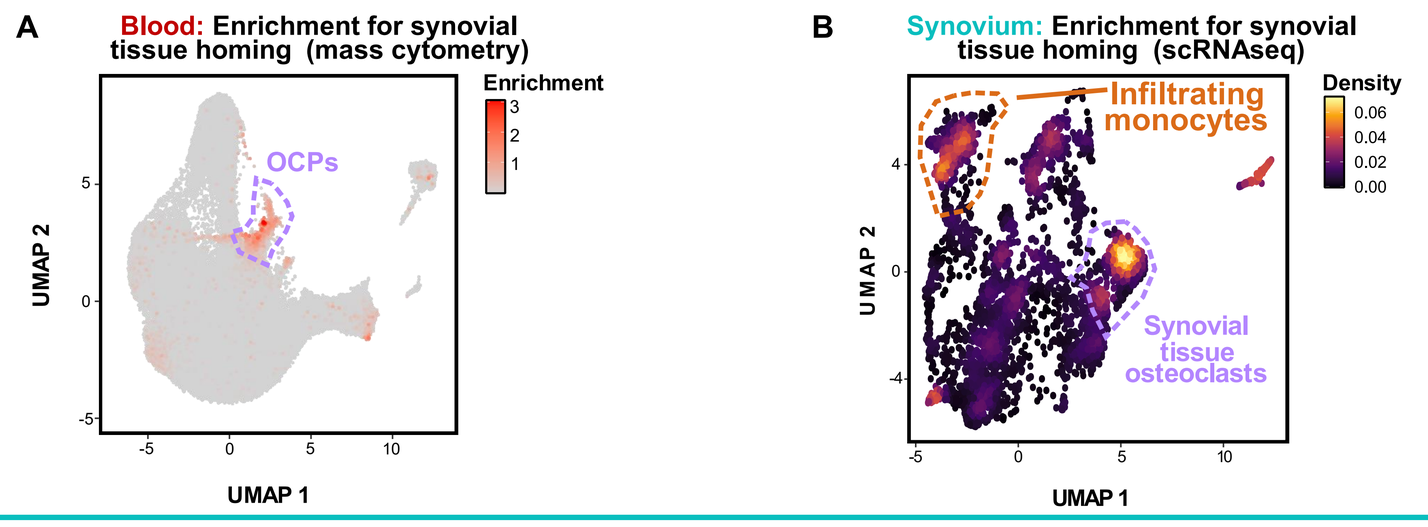
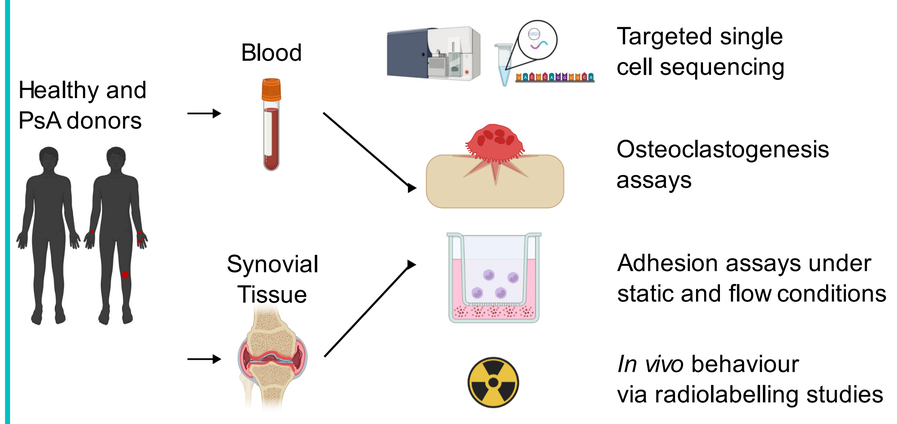


Figure 4 Next research steps.



Conclusions

Circulating MPS are abnormal in active treatment naïve PsA.

Circulating OCPs are expanded and have a synovial tissue homing signal in PsA.

The same tissue homing signal is found on infiltrating cells and osteoclasts in psoriatic synovium.