New work on precursors of inflammatory synovial macrophages sheds light on pathogenesis of rheumatoid arthritis

June 13 2024

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The exact origin and precursor differentiation route of tissue macrophages remains controversial. At the 2024 congress of EULAR—The European Alliance of Associations for Rheumatology—new work sheds light on blood precursors of pathogenic tissue macrophages.

Rheumatoid arthritis (RA) is an autoimmune disease that causes joint inflammation and destruction. There is currently no cure—and although there are many treatments, their effectiveness varies from person to person, suggesting an undefined pathogenic diversity.

Deep characterization of myeloid cell subsets by single cell RNA sequencing across healthy and inflamed tissues in RA has led to the identification of new pathogenic cell states and subsets—with data coming from five large-scale studies. But subset overlap across studies and compartments—such as in blood versus synovial tissue—has not yet been systematically investigated.

Presenting at the 2024 EULAR congress in Vienna, researcher Sebastien Viatte explained, "We wanted to map monocyte subsets and states across studies and compartments to identify blood monocyte precursors of inflammatory synovial macrophage subsets observed in people with RA."

With this in mind, the group set out to discover whether quiescent human blood monocyte states are pre-committed to an inflammatory synovial transcriptional program. First, peripheral blood mononuclear cells (PBMC) from healthy volunteers and RA patients with clinically well-controlled disease (quiescent PBMC) were enriched for monocytes by negative selection and subjected to single cell RNA sequencing. The researcher then used published myeloid cell subsets to map on to their template, based on the similarity of their expression scores.

Hierarchical methods were applied to merge similar clusters and create a consensus map, and random forests were used to merge over-clustered data and identify novel myeloid cell states—and generate a final taxonomy of monocyte states in healthy human blood. Finally, to provide experimental validation at the protein level, PBMC from 19 RA patients with uncontrolled inflammation were deeply immunophenotyped, and inflammatory cell states with increased abundance in RA were identified.

All told, this work generated an exhaustive reference atlas comprising a total of 11 monocyte states across anatomical compartments relevant for RA. For example, it was possible to show that different clusters in fact represent the same inflammatory synovial macrophage subset, and are transcriptionally similar to an IL1B+ monocyte subset present in quiescent peripheral blood.

The findings also revealed that four quiescent monocyte states present in the peripheral blood of both RA patients and healthy individuals expand in the blood of patients with uncontrolled RA. These likely represent blood precursors of pathogenic tissue macrophages.

This work is important, because it not only defines a new monocyte cell taxonomy relevant for RA—with 11 continuous cell states that dynamically transition into each other across anatomical compartments—but also identifies potential blood precursors of pathogenic tissue macrophages.

More information: E. Amies et al, OP0111 Quiescent human blood monocyte states are pre-committed to an inflammatory synovial transcriptional program, *Scientific Abstracts* (2024). DOI: 10.1136/annrheumdis-2024-eular.5134

Provided by European Alliance of Associations for Rheumatology (EULAR)