Cellular 'atlas' built to guide precision medicine treatment of rheumatoid arthritis

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Rheumatoid arthritis (RA) is an autoimmune disease characterized by inflammation that leads to pain, joint damage, and disability, which affects approximately 18 million people worldwide. While RA therapies

targeted to specific inflammatory pathways have emerged, only some patients' symptoms improve with treatment, emphasizing the need for multiple treatment approaches tailored to different disease subtypes.

To more precisely define cellular drivers of RA, an international research consortium co-led by researchers from the Broad Institute of MIT and Harvard and Brigham and Women's Hospital, a founding member of the Mass General Brigham health care system, analyzed tissues from RA donors at the single-cell level, integrating multiple forms of analysis to stratify RA by six subtypes of inflammation.

Findings, published in *Nature*, shed new light on the variety of cellular causes of RA, which may inform more targeted, effective and patient-tailored therapeutic approaches.

"In the treatment of individuals with rheumatoid arthritis, we struggle to find the right treatment for the right patient," said corresponding author Soumya Raychaudhuri, MD, Ph.D., of the Brigham's Division of Rheumatology, Inflammation and Immunity and the Broad Institute, where he is an institute member.

"We aimed to determine why some subsets of patients don't respond to conventional treatments by looking at the subtypes of inflammation. We did so from many different angles, using multiple cutting-edge, single-cell techniques and integrating results in a way that hasn't been done before for an inflammatory disease."

The findings from the study represent a major milestone in the Accelerating Medicines Partnership Rheumatoid Arthritis and Systemic Lupus Erythematosus program, a public-private partnership launched in 2014 to advance molecular- and cellular-level understandings of autoimmune diseases and identify promising drug targets.

Through collaboration with researchers and clinicians across the U.S. and U.K., the investigators analyzed 79 donor samples of synovial tissue, the inflamed tissue in RA that normally helps cushion and sustain joints. In particular, the researchers examined tissue from patients with new-onset disease and from patients unresponsive to treatment to better identify both the initial drivers of RA as well as those of refractory disease.

To "deconstruct" RA pathology on a cellular level, the researchers combined surface protein data and histologic analysis with multiple forms of single-cell RNA-sequencing and bulk RNA sequencing. Despite the variety of methods used to analyze over 314,000 cells, the researchers consistently found evidence of six major types of inflammation, which they stratified by associated cell type, called cell-type abundance phenotypes (CTAPs).

While some CTAPS, such as those enriched with T and B cells, were expected finding for an autoimmune disease like RA, the researchers were surprised to see CTAPs associated with structural cells such as fibroblasts and endothelial cells, with relatively few inflammatory leukocytes. They also found that patients' CTAPs were dynamic and could change over time in response to treatment.

Going forward, the researchers aim to expand upon their knowledge of the cell types involved in RA by studying how interconnections between cells promote disease states. Furthermore, they hope this work will encourage increased synovial tissue analysis in RA patients, which is currently not standard practice. While blood tests are more common in RA patients, findings from this study and others emphasize that the cellular profile of synovial tissue differs substantially from that of blood.

"What this study shows is that the tissue matters," said co-senior author Michael Brenner, MD, of the Brigham's Division of Rheumatology,

Inflammation and Immunity.

"Our findings point to the value of getting synovial tissue biopsies to evaluate the nature of the pathological process, which can be so different across patients. Clinical trials going forward will benefit greatly from assessing tissue characteristics alongside responses to a therapy. By providing this atlas of cell types and pathways involved in RA, we are better able to pursue our precision medicine goal of being able to select the right drug for the right patient and achieve a high response rate."

More information: Soumya Raychaudhuri, Deconstruction of rheumatoid arthritis synovium defines inflammatory subtypes, *Nature* (2023). DOI: 10.1038/s41586-023-06708-y. www.nature.com/articles/s41586-023-06708-y

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