Researchers advance understandings of the cellular mechanisms driving rheumatoid arthritis

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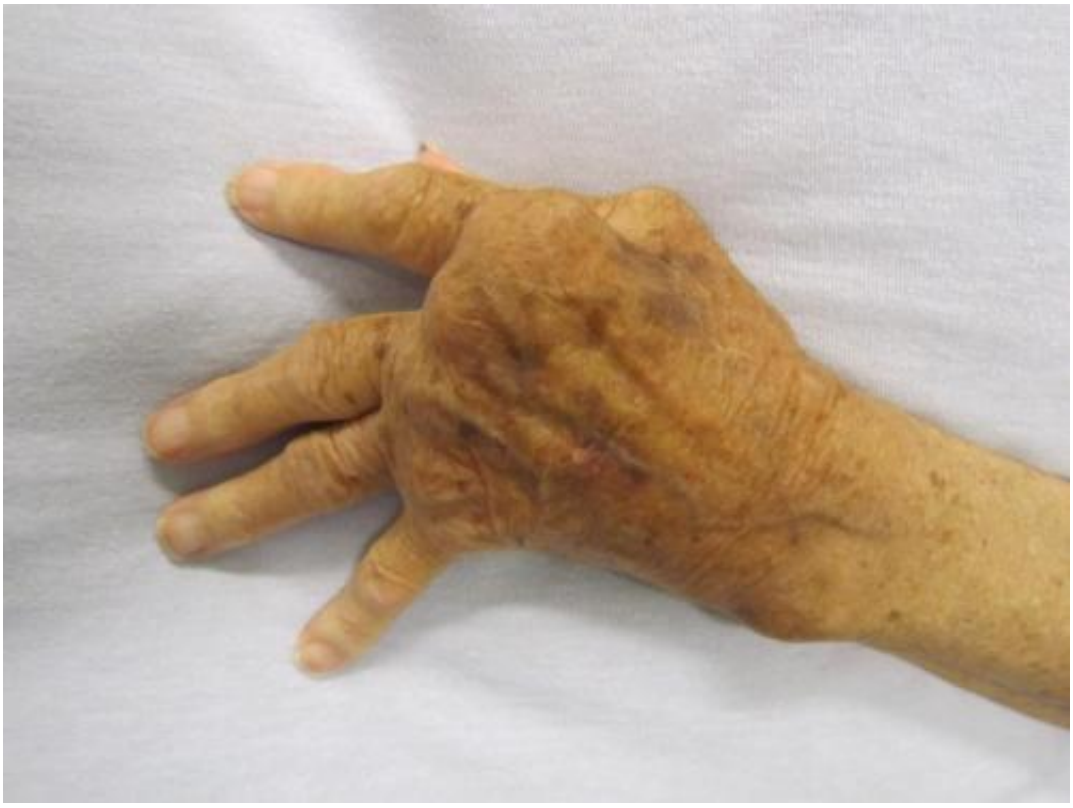

A hand affected by rheumatoid arthritis. Credit: James Heilman, MD/Wikipedia

Newly identified subsets of cell types present in joint tissue in people with rheumatoid arthritis and how they interact may explain why only some people respond to existing medications, according to two studies

by co-senior author Laura Donlin, Ph.D., Co-Director of the Derfner Foundation Precision Medicine Laboratory at Hospital for Special Surgery (HSS) and collaborating colleagues. The findings suggest exciting new targets for developing precision medicine strategies in the future.

Rheumatoid arthritis (RA) is an autoimmune disease that affects the joints. The immune system mistakenly perceives joint tissue as a harmful invader, like a bacteria or virus, and attacks it, causing inflammation, pain and swelling. RA affects an estimated 1.3 million Americans, about 1% of the population. Critical unmet needs in RA treatment are medications that effectively treat all people with RA, especially those who do not respond to disease-modifying antirheumatic drugs (DMARDs) or biologics.

RA involves a complex interplay between many different types of cells—including T cells, B cells, monocytes and fibroblasts—but the specific subtypes that drive disease progression are largely undefined. Understanding these cell types more precisely may hold valuable information in developing new treatments.

"Right now, the standard approach for treating patients is a trial and error approach. We try the first-line of medication for three months and if it does not work, we try the next one," says Dr. Donlin. "Sometimes it can take a year or more to find an effective treatment. Meanwhile, the disease progresses to the extent of irreversible damage in some of the cases."

For the first paper, published in the May 6, 2019 issue of *Nature Immunology*, co-senior author Dr. Donlin collaborated within the Accelerating Medicines Partnership (AMP) in Rheumatoid Arthritis and Lupus Network (AMP RA/SLE consortium) to create a comprehensive "map" of the cells found in RA joint tissue using advanced sequencing

technologies. The AMP RA/SLE consortium is a unique public-private partnership that was created to find new ways to identify and validate promising biological targets for diagnostics and drug development.

The researchers identified 18 unique cell populations in synovial tissue provided by 36 patients with RA. Several of the cell types were present in higher amounts in people with RA compared to control samples from patients with osteoarthritis, a degenerative joint disease that results from deterioration of cartilage due to injury or wear over time. For example, Dr. Donlin and colleagues identified a subset of fibroblasts, cells that make connective tissue, in 15 times greater quantities in RA tissues compared to OA tissues. This fibroblast subset is a major producer of the pro-inflammatory cytokine called interleukin-6 and thereby represents a cell type that may be important to focus on in the development of medications for RA patients.

Dr. Donlin and colleagues were also the first to identify the presence of a subset of autoimmune-associated B cells in synovial tissue. These too were found in large quantities in the RA samples, indicating that this subtype may also be a promising target for future drug development.

"Cutting-edge single-cell RNA sequencing technology allowed us to see the complexity of the cell populations in RA tissue for the first time," says Dr. Donlin. "However, determining whether these expanded cell populations are a cause or an effect of the disease, will require further research."

For the second paper, published May 8, 2019 in the journal *Science Translational Medicine*, co-senior author Dr. Donlin and HSS colleagues conducted additional research using results from the AMP consortium to home in on a particular disease-associating cell type. They discovered an abundant subset of macrophages they referred to as HBEGF+ inflammatory macrophages in the RA tissue samples. Macrophages are

white blood cells that readily tailor their actions to signals from other cells. In chronically inflamed RA tissue, macrophages are a known source of tumor necrosis factor (TNF), a small protein or cytokine that is involved in inflammatory responses in RA.

Next, the researchers tested how clinically-effective RA medications impacted the HBEGF+ inflammatory macrophages and thereby disrupt the disease at the cellular level. They were surprised to discover that COX inhibitors known as nonsteroidal anti-inflammatory drugs (NSAIDs) did significantly alter these macrophages, but they did not stop TNF responses. "This finding may explain why NSAIDs treat pain but are not disease-modifying in RA," says Dr. Donlin. "A better approach may be to use NSAIDs in combination with anti-TNF medications to shut down both inflammatory pathways."

An experimental drug developed for cancer treatment, an epidermal growth factor receptor (EGFR) inhibitor called AG-1478, was able to successfully reverse the activity of the HBEGF+ inflammatory macrophages in cell studies. "Our experiment demonstrated that it is possible to target activity of these cells, but this drug has significant systemic side effects in people," says Dr. Donlin. "Our work sets the stage for developing better drugs in the future that could target the same mechanism but in a more specific fashion."

"Overall, our work to date on these two papers has identified previously unknown subsets of cells and provided new insights about how some of these cell types interact with each other to drive RA," says Dr. Donlin. "We hope that through a better understanding of the cell populations in individual patients we can provide a means by which we can treat them with precision medicine strategies at the earliest stages of disease."

More information: David Kuo et al. HBEGF+ macrophages in rheumatoid arthritis induce fibroblast invasiveness, *Science Translational*

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