Single cell analysis paves the way for better treatments for IBD

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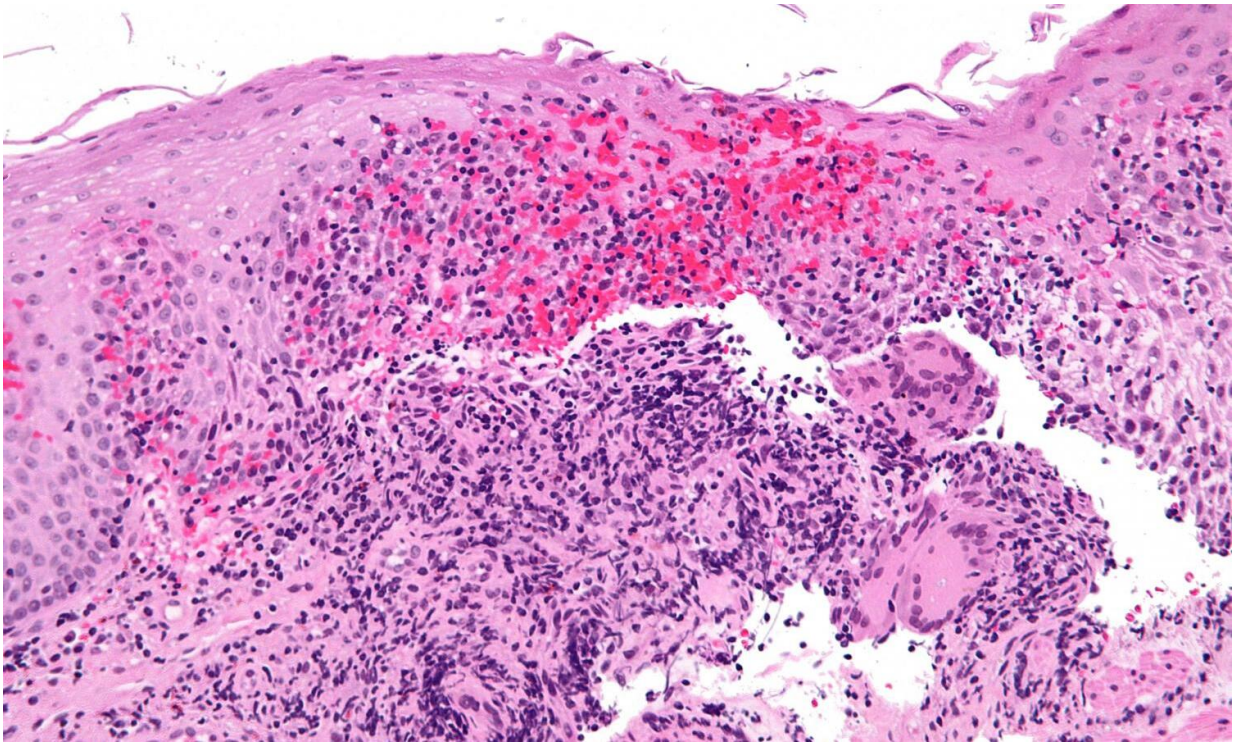

High magnification micrograph of Crohn's disease. Biopsy of esophagus. H&E stain. Credit: Nephron/Wikipedia

Researchers at MRC HIU examined the large intestine using sophisticated single cell technology, in work that paves the way for better treatments for IBD.

Inflammatory Bowel Disease (IBD) is a chronic inflammatory disease with limited treatment options. The two main forms of the disease, Crohn's disease and Ulcerative Colitis, affect more than 300,000 people in the UK. Up to 40% of patients with IBD fail to respond to conventional therapies, partly due to our limited understanding of the cells that form the large intestine, but also how they change in in patients affected by this disease.

A new study by the group of Professor Alison Simmons at the MRC Human Immunology Unit based in the MRC Weatherall Institute of Molecular Medicine paves the way for better treatments for IBD by providing the first detailed single cell resolution analysis of colon cells in health and disease.

The researchers specifically examined mesenchymal cells, a group of cells that play instrumental roles in innate immunity, immune regulation and epithelial barrier maintenance in the gut. These cells are known to be important, but it is unclear whether they constitute a homogeneous population of cells, and/or how they change in a disease context. The group led by Professor Simmons, Professor of Gastroenterology at the Nuffield Department of Medicine, examined these cells using sophisticated single cell technology that allows assessment of the characteristics of individual cells with incredible precision.

"Using cutting edge technologies such as single cell RNA sequencing, single molecule in situ hybridisation, organoid cultures and mass cytometry time-of-flight, we were able to examine functionally diverse mesenchymal cells in the colon and track their pathogenic changes during inflammation," explained the authors. "Colonic mesenchymal cells are a very complex cell type; precise RNA sequencing on a single cell level allowed us to segregate cells into functionally diverse categories for the first time. We then complemented this by using mass cytometry, which utilises stable metal isotopes coupled to antibodies to

detect cellular targets, to dissect the most biologically significant markers associated with IBD pathology. We further used techniques such as single molecule in situ hybridisation, immunohistochemistry and sophisticated three dimensional organoid cultures to interrogate the anatomical localisation of these functionally specialised subsets of cells and demonstrate their relative contributions to health and disease."

In total they examined 16,500 cells, assembling a detailed atlas of the colonic mesenchyme. Careful analysis of this atlas showed that, rather than a homogeneous group, mesenchymal cells actually fall into 5 categories, each with its unique characteristics, both in terms of gene expression, biological function and localisation. In particular they were able to show that one specific subset of these cells is dysregulated in patients with IBD, providing clues for how the disease emerges.

In addition, the researchers also compared the composition of the colon in human patients and mouse models of IBD. This work provides a detailed of understanding of the similarities and difference between the two species, essential as mice are vital models for the development and assessment of new drugs and treatments.

"This work has allowed us to highlight the most significant disease-associated features that we have identified as major drivers of chronic intestinal inflammation, many of which will open up new areas of drug targets for inflammatory bowel disease," they added.

The authors hope that this study provides the scientific community with a comprehensive atlas of the colon in health and disease, an important reference point for the development of future therapies for IBD but also for other conditions affecting the intestine.

The full paper, "Structural Remodeling of the Human Colonic Mesenchyme in Inflammatory Bowel Disease," is published in the

journal *Cell*.

More information: James Kinchen et al. Structural Remodeling of the Human Colonic Mesenchyme in Inflammatory Bowel Disease, *Cell* (2018). DOI: 10.1016/j.cell.2018.08.067