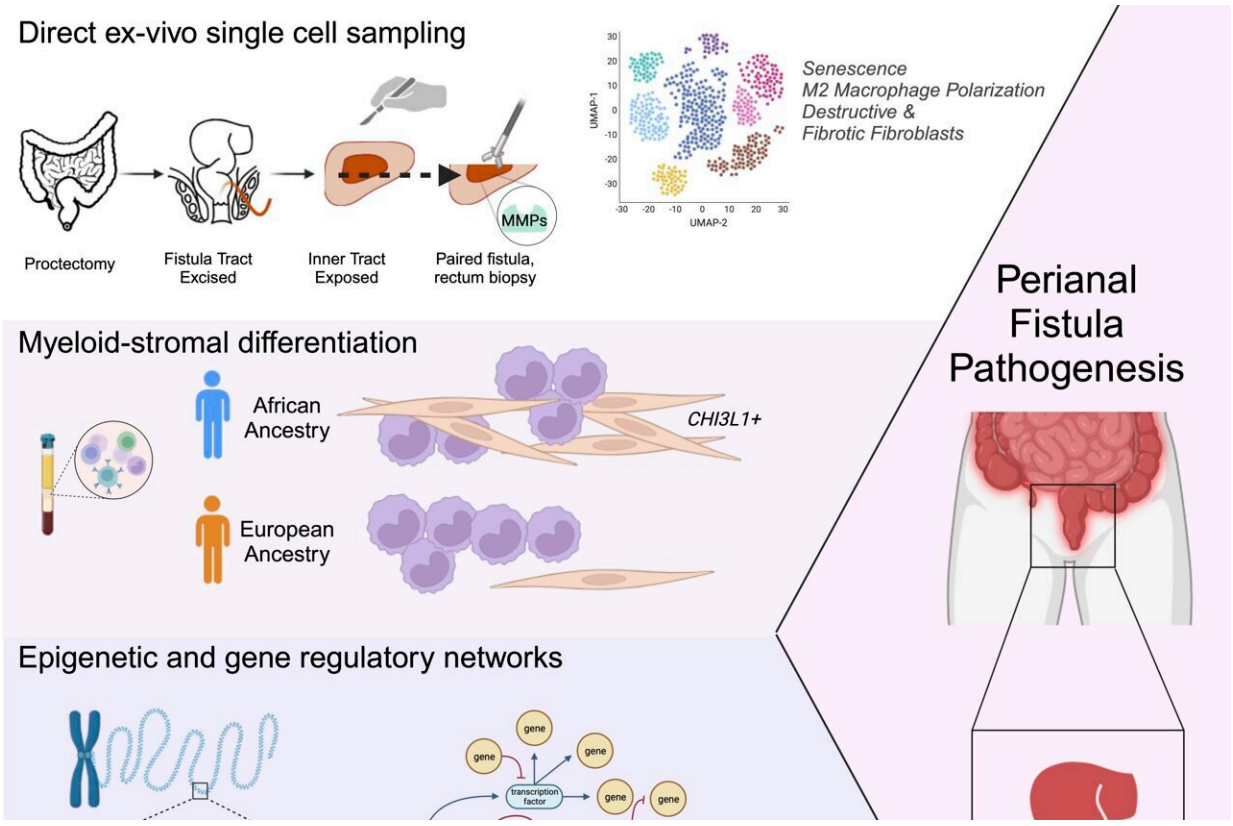
Single-cell analysis reveals mechanisms of a common complication of Crohn's disease

April 24 2024



Multimodal analyses of cells from abnormal tunnels in Crohn's disease converge to illuminate underlying pathomechanisms. Credit: Med/Cell Press (Elsevier)

Mount Sinai researchers have published the first study to use single-cell analysis in identifying several pathophysiological mechanisms of abnormal passageways in the digestive system known as perianal fistulae, a common complication of Crohn's disease. These findings were published in the journal *Med* on April 24.

Crohn's disease is an inflammatory bowel disease that causes chronic inflammation at any part of the gastrointestinal (GI) tract and impacts more than half a million people in the United States. Perianal fistulae, abnormal connections between the anal canal and perianal skin, are a common complication of Crohn's disease that often result in painful abscesses and impact patients' quality of life.

This Mount Sinai study is the first to apply single-cell transcriptomics of perianal fistulous tracts, and to recruit Black patients with the chronic condition for a diverse and comprehensive study cohort.

Patients with African ancestry have been substantially underrepresented in genome-wide association studies of Crohn's disease, and inflammatory bowel disease overall, reflecting in part the lower prevalence of Crohn's disease in African American populations compared to patients with European ancestry. However, patients of African ancestry are about twice as likely to have perianal fistulae, according to studies in adult and pediatric populations.

The researchers profiled more than 140,000 single cells from diverse Crohn's disease patients with perianal fistulae. The team identified several key pathways underlying fistulizing Crohn's disease, including cellular aging and loss of proliferation, reaction to microenvironmental stimuli, and a destructive gene signature in connective tissues that is unique to perianal fistulae.

The researchers also determined that subpopulations of fibroblasts—cells forming the connective tissues—with this destructive gene signature may originate from mononuclear cells in the immune system, a phenomenon observed in greater magnitude from patients with African ancestry. The experts found evidence for key transcription factor binding events in relevant gene promoter regions that suggests a potential epigenetic phenomenon underlying this apparent difference in cell behavior between patients of African and European ancestry.

"Circulating blood monocytes can traffic to disease tissues and form a critical first step in fighting microbes throughout the body," said corresponding author Judy H. Cho, MD, Dean and Ward-Coleman Chair in Translational Genetics at the Icahn School of Medicine at Mount Sinai.

"In this study, we have defined population-specific differences in how blood monocytes respond, which contribute to the higher rates of perianal fistulous complications in African American patients with Crohn's disease."

A range of anti-inflammatory medications can treat Crohn's disease, but they show limited efficacy for closure of perianal fistula tracts. In severe cases, patients may require surgical removal of all or part of the rectum. But researchers said their findings provide avenues to identify new therapeutic options.

The team said future studies should examine similar epigenetic patterns in white blood cells of the immune system from diverse, healthy patients and from patients with other immune-mediated inflammatory diseases to further explore the role of the transcription factor underlying race or ancestry-based disparities.

"We have leveraged transcriptomic, epigenetic, genetic, cellular, and

tissue-based data from patients with a history of this devastating complication to better understand reasons for the discrepancy in prevalence between Black and white patients," said first author Rachel M. Levantovsky, Ph.D., who is working on her MD in the Mount Sinai Medical Scientist Training Program.

"Our discovery of unique fistula fibroblasts, distinct monocyte differentiation in African-ancestry individuals, and key transcription factor binding events helps us illuminate mechanistic underpinnings of perianal fistula—critical for the optimization of future treatment."

More information: Multimodal single cell analyses reveal mechanisms of perianal fistula in diverse Crohn's disease, *Med* (2024). DOI: 10.1016/j.medj.2024.03.021. www.cell.com/med/fulltext/S2666-6340(24)00133-8

Provided by The Mount Sinai Hospital