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Summary

NEUTROPHIL-DRIVEN INFLAMMATION AND METABOLIC REPROGRAMMING CHARACTERIZE FISTULIZING CROHN'S DISEASE: A LARGE-SCALE MULTI-OMIC ANALYSIS

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Multi-omic profiling of 2,889 UK Biobank Crohn's disease patients (217 with fistulas) identifies a distinct molecular signature in fistulizing disease characterized by neutrophil activation, impaired epithelial repair, extracellular matrix remodeling, and metabolic reprogramming.

KEY POINTS

- Fistulizing Crohn's disease showed elevated neutrophil-associated and inflammasome-related proteins (MPO, MMP9, LCN2, CASP8, ZBP1) and increased cytoskeletal and extracellular matrix remodeling proteins (ARHGAP5, EFNB2, STX3, STX7), while proteins associated with epithelial integrity and repair (KRT18, ROBO1, GALNT10, MAN1A2) were reduced.
- Metabolomic profiling revealed decreased HDL-related lipid fractions and selected amino acids alongside increased VLDL lipids, branched-chain amino acids, acetate, and citrate, indicating a pro-inflammatory, energy-demanding metabolic state.
- Integrated analysis demonstrated neutrophil-derived proteins clustered with oxidative stress and NAD^+ metabolic activation markers (NAMPT, NMNAT1), with dysregulated molecules mapping to MMP9-mediated matrix degradation, NAMPT-driven NAD^+ metabolism, and branched-chain amino acid-dependent mTOR signaling pathways.
- Independent spatial transcriptomics validation showed neutrophils significantly associated with chemokine signaling and fistula-associated stromal cells, with MMP9 and COL7A1 associated with the neutrophil module.
- The study included all fistula types without differentiation by anatomic location and used unpaired circulation and tissue data from separate cohorts.

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