Genetic variants synthesize to produce paneth cell phenotypes that define subtypes of Crohn’s disease.

VanDussen KL¹, Liu TC¹, Li D², Towfic F³, Modiano N⁴, Winter R⁴, Haritunians T⁵, Taylor KD⁵, Dhall D⁶, Targan SR⁶, Xavier RJ⁷, McGovern DP⁷, Stappenbeck TS⁸.

Author information

*¹Department of Pathology and Immunology, Washington University School of Medicine, St Louis, Missouri.
*²The F. Widjaja Foundation Inflammatory Bowel and Immunobiology Research Institute, Cedars-Sinai Medical Center, Los Angeles, California; Medical Genetics Research Institute, Cedars-Sinai Medical Center, Los Angeles, California.
*³Center for Computational and Integrative Biology, Massachusetts General Hospital, Harvard Medical School and Broad Institute, Boston, Massachusetts.
*⁴The F. Widjaja Foundation Inflammatory Bowel and Immunobiology Research Institute, Cedars-Sinai Medical Center, Los Angeles, California.
*⁵Medical Genetics Research Institute, Cedars-Sinai Medical Center, Los Angeles, California.
*⁶Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, California.
*⁷The F. Widjaja Foundation Inflammatory Bowel and Immunobiology Research Institute, Cedars-Sinai Medical Center, Los Angeles, California; Medical Genetics Research Institute, Cedars-Sinai Medical Center, Los Angeles, California. Electronic address: Dermot.McGovern@cshs.org.
*⁸Department of Pathology and Immunology, Washington University School of Medicine, St Louis, Missouri. Electronic address: stappenb@pathology.wustl.edu.

Abstract

BACKGROUND & AIMS:

Genetic susceptibility loci for Crohn’s disease (CD) are numerous, complex, and likely interact with undefined components of the environment. It has been a challenge to link the effects of particular loci to phenotypes of cells associated with pathogenesis of CD, such as Paneth cells. We investigated whether specific phenotypes of Paneth cells associated with particular genetic susceptibility loci can be used to define specific subtypes of CD.

METHODS:

We performed a retrospective analysis of 119 resection specimens collected from patients with CD at 2 separate medical centers. Paneth cell phenotypes were classified as normal or abnormal (with disordered, diminished, diffuse, or excluded granule phenotypes) based on lysozyme-positive secretory granule morphology. To uncover the molecular basis of the Paneth cell phenotypes, we developed methods to determine transcriptional profiles from whole-thickness and laser-capture microdissected, formalin-fixed, paraffin-embedded tissue sections.

RESULTS:

The proportion of abnormal Paneth cells was associated with the number of CD-associated NOD2 risk alleles. The cumulative number of NOD2 and ATG16L1 risk alleles had an additive effect on the
proportion of abnormal Paneth cells. Unsupervised clustering analysis of demographic and Paneth cell data divided patients into 2 principal subgroups, defined by high and low proportions of abnormal Paneth cells. The disordered and diffuse abnormal Paneth cell phenotypes were associated with an altered transcriptional signature of immune system activation. We observed an inverse correlation between abnormal Paneth cells and presence of granuloma. In addition, high proportions of abnormal Paneth cells were associated with shorter time to disease recurrence after surgery.

CONCLUSIONS:

Histologic analysis of Paneth cell phenotypes can be used to divide patients with CD into subgroups with distinct pathognomonic and clinical features.

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KEYWORDS:

CD; Crohn's disease; Diagnosis; IBD; Inflammatory Bowel Disease; Pathogenesis; Prognostic Factor; UC; inflammatory bowel disease; ulcerative colitis