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Defining the host mucosal and gut microflora interactions in Crohn's disease using redundancy analysis on microarray datasets

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Abstract

Introduction: Crohn’s disease (CD) is an inflammatory bowel disease that is characterised by chronic relapsing inflammation of the digestive tract. There is a significant body of evidence that suggests the intestinal mucosal microbiome interacts with the immune response to produce pathological inflammation and together these factors play a major role in the pathogenesis of CD. The aim of this study is to investigate interactions between the human intestinal mucosal transcriptome and mucosal microbiome using multivariate redundancy analysis on microarray datasets.

Methods: DNA and RNA were extracted from the same mucosal biopsies collected from CD patients (terminal ileum: n=5 from sites with active disease, n=4 from inactive sites (tissue with normal histology); colon: n=8 from active and n=6 from inactive sites). RNA was used to study the human intestinal mucosal transcriptome (Affymetrix GeneChip® Exon 1.0 ST arrays) and DNA was used to study the resident microbiota using a custom phylogenetic microarray. The latter was designed using published gastrointestinal microbiota 16S rRNA sequences with ~ 40-mer oligonucleotides targeting 765 bacterial species. Through examining the expression arrays, 30 differentially expressed inflammatory response genes of interest were selected. Correlations between expression patterns for these genes were assessed. Representatives (TNFRSF1B, IL2RA, IL8) of three groups of inflammatory genes with highly correlated expression and three uncorrelated genes of interest (CXCL11, IL- 13RA1 and TIRAP) were used. Multivariate relationships between the expression of the six representative inflammatory response genes and the abundance of microbial species in colon or terminal ileum, in patients with active or inactive disease was examined using redundancy analysis using the vegan package in R1. Correlations between the expression of individual inflammatory response genes and the abundance of individual microbes were also investigated.

Results: There appears to be a significant relationship between changes in the abundance of some microbial species in intestinal mucosa with active disease and the expression of the six representative inflammatory response genes. However, this was not the case in the normal (inactive) mucosa of these patients. Where there was active disease the expression of the six genes were predicted by members of the sulfite-reducing bacteria Clostridia class (p-value 0.02-0.005) in the colon, and the Betaproteobacteria (p-value 0.02) and Clostridia (p-value 0.03) class members in the ileum. In the normal (inactive) mucosa of CD patients, there were no bacterial species that significantly predicted the expression of inflammatory immune response genes. There was also some evidence that the expression of the pro-inflammatory cytokine, IL8, predicted changes in the abundance of microbes in inactive colon (p-value 0.04) and that TIRAP (toll-Il1 receptor domain containing adaptor protein), involved in the innate immune system’s recognition of microbial pathogens, was predictive of the pattern of microbial abundance in active ileum (p-value 0.05).

Conclusions: Our findings begin to define the unique hostmicrobial responses associated with CD.

Keywords

microarray, defining, datasets, host, mucosal, gut, microflora, interactions, crohn, disease, redundancy, analysis

Disciplines

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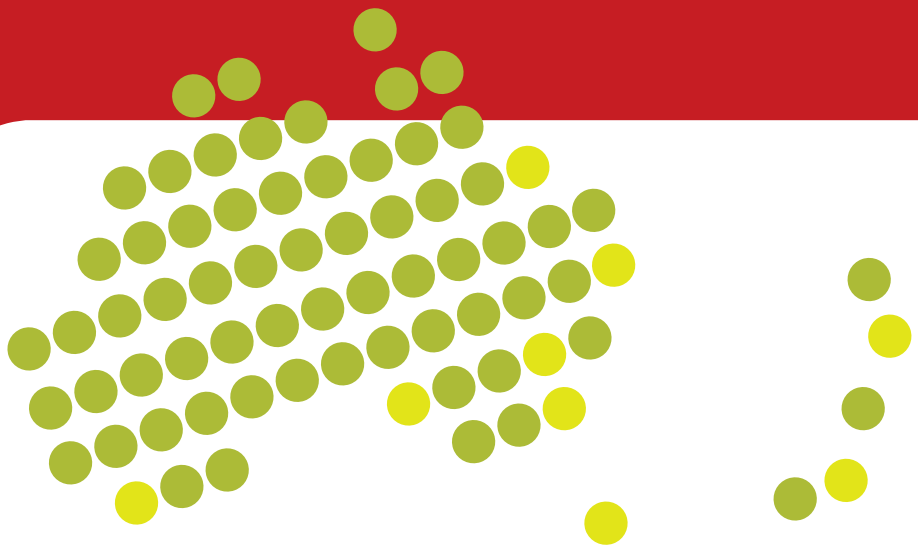

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