A70

MOLECULAR ARCHETYPE HETEROGENEITY IN ULCERATIVE COLITIS BIOPSIES

K. Madill-Thomsen[3], S. Withecomb[3], M. Parkes[3], V. Jovanovic[2], J. Venner[1], R. Fedorak[2], P. Halloran[3], B.P. Halloran[1]

1. Medicine, Divison of Gastroenterology, University Of Alberta , Edmonton, AB, Canada; 2. Gastroenterology, University of Alberta, Edmonton, AB, Canada; 3. Medicine, University of Alberta, Edmonton, AB, Canada

Background: The assessment of patients with ulcerative colitis (UC) remains a challenge despite rapidly evolving medical therapy. Current assessment with endoscopic scoring and histopathology lacks the granularity to correlate strongly with response to therapy.
Aims: Utilizing a microarray based system for colonic epithelial assessment we looked for stratification of endoscopically similar UC biopsies using molecularly heterogeneous archetypes.
Methods: Molecular data from 71 UC biopsies (from 61 patients) was obtained from microarray analysis. The top 300 genes correlating with the endoscopic Mayo score (2/3 vs 0/1) were used for an unsupervised analytical method called archetypal analysis, and grouped the biopsies into three distinct clusters. Logistic regression modeling was used to compare archetype scores or cluster membership to endoscopic Mayo score and PC1 in predicting mucosal healing. A contingency table was generated to show evidence of mucosal healing within each of the archetype clusters. We then assessed a subset of biopsies from the original set of 71 (selected due to the availability of biopsies before and after therapy, all on TNF therapy) plus one IBDU case. Patients were classified as 'responders' (Mayo 2/3 score to Mayo 0/1 score by last obtained biopsy or scope) or 'non-responders' (Mayo 2/3 score that did not decrease to 0/1 by last obtained biopsy or scope).
Results: We found three unique groups of biopsies using archetypal analysis (A1: lack of inflammation, A2: inflammation and response to wounding, A3: inflammation). Logistic regression showed that the only models with statistically significant predictive value (p-value < 0.05) were those that contained archetype scores or cluster membership. Response rates differed between archetype clusters with statistical significance (Table 1), while the mayo score distribution within these clusters was not statistically different. In our subset of serial biopsies, the majority of initial biopsies were found to have an A2 archetype, moving to an A1 archetype in follow-up that mirrored response to treatment (Figure 1).
Conclusions: This archetypal analysis suggests there is potentially important heterogeneity in UC biopsies that is not accessible by endoscopic Mayo score. Serial biopsies showed dynamic shifts in the archetype composition between biopsies. This may be a useful tool for both initailly prognosticating patients and assessing response to treatment over time with increased granularity and reliablity.

UC Patient Response to Therapy Assessed by Initial Archetype Cluster

Archetype Cluster (Total cases)	# of cases improved*
A1 (4)	4 (100%)
A2 (16)	10 (62%)
A3 (6)	1 (17%)

All cases had a Mayo score of 2-3 on initial endoscopy. *score of 0-1 on follow up endoscopy . Pearson's Chi-Squared = 7.222, df = 2, p = 0.027

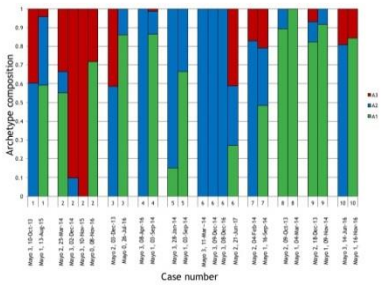

Figure 1. Stacked and group bar charts showing archetype composition of biopsies in 10 UC patients taken over time (2-4 serial biopsies/patient).

Funding Agencies: None