A160

MOLECULAR ANALYSIS OF THE INJURY-REPAIR RESPONSE IN ULCERATIVE COLITIS REVEALS HETEROGENEITY IN DISEASE ACTIVIT

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Background: Ulcerative colitis (UC) is a chronic inflammatory condition affecting the colonic epithelium. We used an established microarray-based system to analyze a set of 128 UC biopsies (113 patients), assessing gene expression associated with the colon's response to injury in UC.
Aims: Our aim was to describe the burden of injury in UC biopsies and to explore molecular heterogeneity across disease activity, as assessed by the endoscopic Mayo score.
Methods: 128 UC colon biopsies were collected at the University of Alberta Hospital (Edmonton, AB) and Cedars-Sinai Hospital (Los Angeles, CA) during standard of care colonoscopy and processed using Affymetrix microarrays. Principal component analysis (PCA) and archetypal analysis (AA) visualized relationships between biopsies and previously annotated injury-associated transcript sets. AA assigned each biopsy to one of three groups, and scores to each biopsy relating it to all three groups.
Results: Spearman correlations (**Table 1A**) were highest between the endoscopic Mayo score and the injury-repair-associated transcripts (IRRAT, 0.64, $P=4.7x10^{-16}$), immunoglobulin transcripts highly associated with chronic injury and fibrosis (IGT, 0.63, $P=3.0x10^{-15}$), endothelial transcripts (ENDAT, 0.61, $P=1.8x10^{-14}$), and parenchymal dedifferentiation i.e. epithelial solute carrier loss (CT2, -0.60, $P=6.5x10^{-14}$).
PCA separated injury from no injury in PC1 (**Figure 1A**). T cell transcripts (QCATs), interferon-gamma inducible transcripts (GRITs) and targets of biologics (IL12, TNFA, ITGA4/B7) separated from injury transcripts in PC2.
We assigned three AA groups and visualized biopsies in PCA (**Figure 1B**, colored by AA membership). Group 1 (grey, N=44) biopsies had little parenchymal dedifferentiation and low expression of injury-associated transcripts. Groups 2 (red, N=44) and 3 (blue, N=40) had increased expression of injury-associated transcript sets and dedifferentiation compared to Group 1 (**Table 1**). Although Group 3 was endoscopically similar to Group 1 ($P>0.05$), Group 3 showed elevated injury-associated transcript set expression (e.g. IRRAT) and increased parenchymal dedifferentiation (CT2).
Conclusions: Assessment of UC biopsies using AA and previously annotated injury-associated gene sets reveals two groups of biopsies that are endoscopically similar though one group has increased molecular abnormalities, thus revealing heterogeneity unrelated to the Mayo score. A molecular system based around PCA and AA could enhance and refine UC disease assessment by allowing for quantitation and qualification of injury in biopsies obtained at endoscopy i.e. a level of resolution beyond conventional endoscopic scoring.

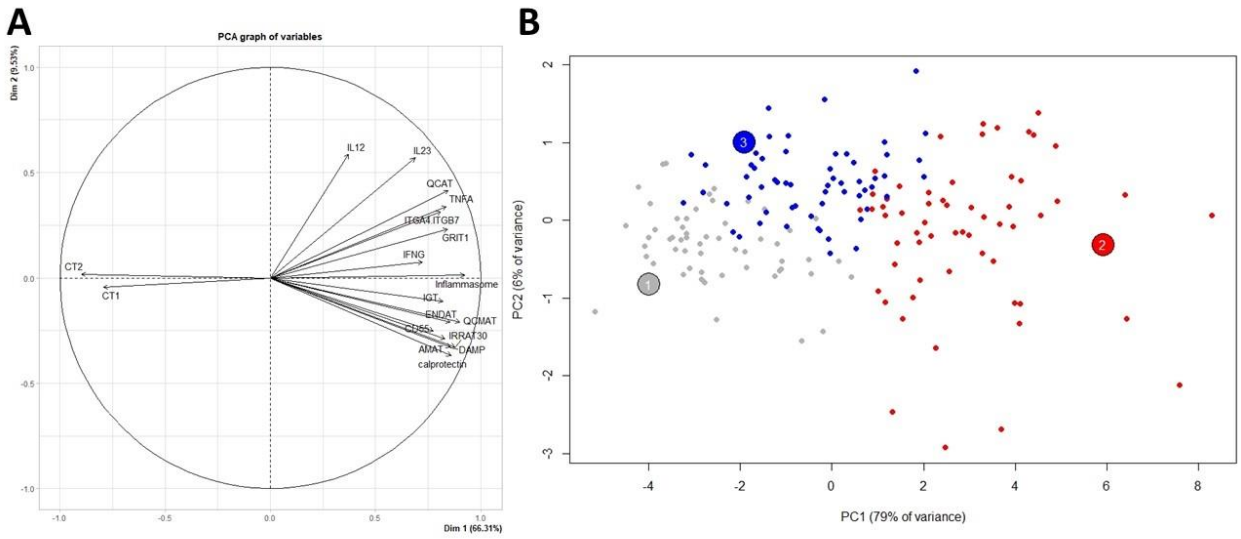

Figure 1. (A) Correlation of transcript set expression to PC1 and PC2. PCA separated injury from no injury in PC1. T cell transcripts (QCATs), interferon-gamma inducible transcripts (GRITs) and targets of biologics (IL12, TNFA, ITGA4/B7) separated from injury transcripts in PC2. **(B) Archetypal analysis (AA) is used to assign the 128 UC biopsies to three groups and are visualized in PCA space.** Group 1 (grey), group 2 (red), group 3 (blue). The number of groups was chosen based on a scree plot showing the residual sum of squares (not shown).
PC, principal component.

Table 1. Mean transcript set scores (expression) and clinical mean scores/counts in each of the three Archetype Groups

	Feature/Score	Group 1 (Grey) Normal (N=44 biopsies)	Group 2 (Red) Injury 1 (N=44 biopsies)	Group 3 (Blue) Injury 2 (N=40 biopsies)
Clinical Features (Counts)	Endoscopic Mayo 0 biopsies (N)	15	0	9
	Endoscopic Mayo 1 biopsies (N)	13	3	14
	Endoscopic Mayo 2 biopsies (N)	14	18	13
	Endoscopic Mayo 3 biopsies (N)	2	23	4
Clinical Features Mean (median)	Endoscopic Mayo Score	1.07 (1.0)	2.45 (3.0)	1.3 (1.0)
	Total Mayo Score	3.2 (2.0)	7.2 (7.0)	4.4 (3.5)
Molecular Features (Mean)	Colon-associated – solute carriers (CT2)	0.04	-0.53	-0.15
	Injury-repair-associated (IRRAT)	-0.14	0.80	0.34
	Endothelial-associated (ENDAT)	-0.03	0.49	0.17
	Danger-associated molecular patterns (DAMPs)	0.07	0.71	0.38
	Alternative Macrophage Activation-associated (AMAT)	-0.12	0.60	0.22
	Macrophage-associated (QCMAT)	-0.05	0.64	0.21
	Immunoglobulins (IGT)	0.05	1.21	0.31
	T cell-associated (QCAT)	0.02	0.67	0.37
	IFNG-inducible (GRIT)	0.15	0.65	0.34

*Note: Groups 2 *vs.* 1 and 2 *vs.* 3 differed in total Mayo score (P=7.5x10^{-6} and 1.0x10^{-3}, respectively), and in endoscopic Mayo Score (P=4.1x10^{-12}, and 9.2x10^{-9}). Groups 3 *vs.* 1 were not significantly different in Total Mayo Score (P=0.2) or endoscopic Mayo score (P=0.25).

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