Pathway Enrichment Analysis Reveals Ulcerative Colitis Patients with Non-response to TNFi Therapy May Have More Biological Dysregulation

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BACKGROUND

Tumor necrosis factor-α inhibitors (TNFi) are essential to ulcerative colitis (UC) management, however only 50% of patients will achieve a clinical response during induction therapy. There is an unmet need to identify and predict UC therapy response. This study aims to analyze potential etiologies for lack of TNFi response using pathway enrichment analysis.

METHODS

Differential expression analysis between TNFi responders, non-responders, and healthy controls was conducted using the limma package from Gene Expression Omnibus (GEO) UC patient cohorts. All datasets contained post-treatment mucosal gene expression data and corresponding response, defined as endoscopic healing at 4 to 8 weeks after treatment initiation. Enrichment analysis of signaling pathways from the Kyoto Encyclopedia of Genes and Genomes (KEGG) database was performed to compare the gene expression profile dysregulation severity between responders and non-responders. Genes exclusive to each group for select significantly enriched pathways were identified. The difference between the number of responder and non-responder exclusive genes was computed and assessed using the random label permutation test. Significantly different pathways between non-responder-exclusive genes and responder-exclusive genes were reported.

Table 1. UC patient baseline mucosal biopsy datasets were used to identify differential gene expression between responders and non-responders to TNFi therapy

TNFi	Dataset	Control	Responders (R)	Non-responders (NR)
Infliximab	GSE16879	6	8	16
	GSE23597	-	24	7
Golimumab	GSE92415	21	32	27

RESULTS

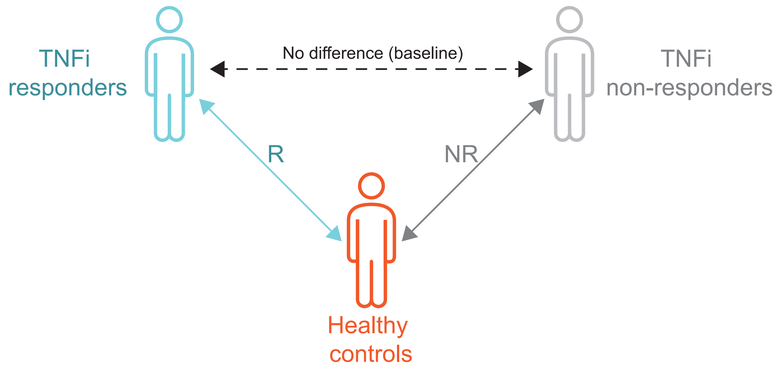
Differentially expressed genes between responders and healthy controls (R) and between non-responders and healthy controls (NR) were identified (Figure 1A). Multiple overlapping dysregulated genes were observed between the two groups. Non-responders had significantly more differentially expressed genes (Figure 1B). Pathway enrichment analysis on the R- and NR-sets demonstrated that 40 of 282 KEGG pathways were significantly enriched with non-responder genes ($p < 0.05$). Of the 40 pathways, 28 had significantly more NR-exclusive genes than R-exclusive genes ($p < 0.05$) (Figure 1C). The NR-set included unique differentially expressed genes involved in cytokine signaling, receptor mediation, and signal transduction.

CONCLUSIONS

UC-relevant KEGG pathways are significantly more enriched and disrupted in non-responders compared to responders, suggesting that non-responders have more dysregulated biological pathways. Other enriched pathways highlight the role of inflammation, barrier integrity, and the intestinal microbiome in UC. This study illustrates precision medicine's potential value in predicting clinical response to TNFi in UC patients.

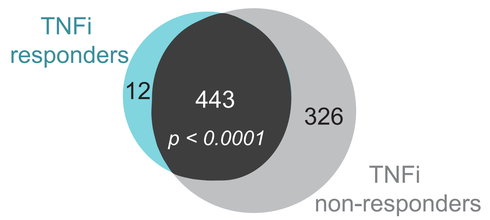
FIGURE 1

A



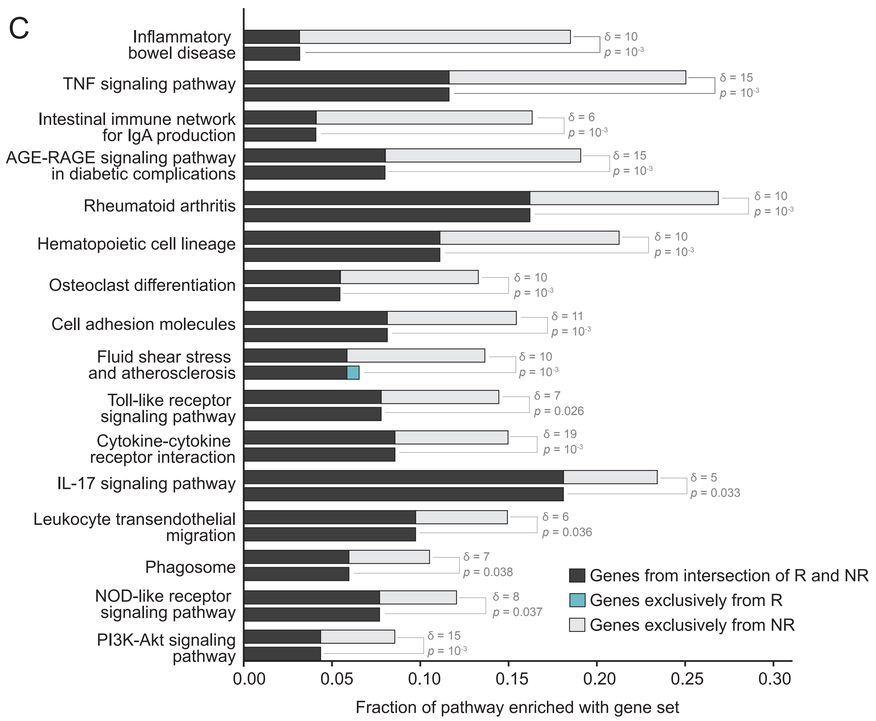
Differential expression gene sets were obtained by comparing different pairs of baseline gene expression data from TNFi responders, TNFi non-responders, and untreated healthy controls

B



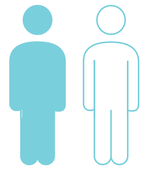
When baseline gene expression from UC patients who will (blue) or will not (grey) respond to TNFi therapy is compared to that of healthy controls, a significant number of genes are differentially expressed

C



KEGG pathways significantly enriched with NR-gene set that also have significantly more NR-exclusive genes than R-exclusive genes

DISCUSSION

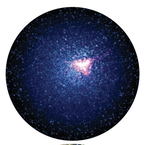


50% of patients who are primary non-responders to infliximab therapy will undergo colectomy in 3.2 years[1]

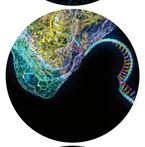
Achieving mucosal healing early has been associated with a decreased risk of future colectomy[2]

A precision medicine test that predicts treatment response could help guide therapy selection in patients with UC before treatment begins

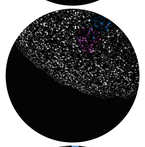
Ghiassian *et al.,* 2022 described a tissue-based precision medicine test that predicts inadequate response to infliximab therapy in biologic-naïve adult patients with active UC so an alternative therapy can be selected before treatment begins



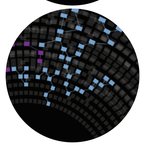
Used the Human Interactome network map of protein interactions to reveal mechanisms of UC and the biology that drives them[3-5]



Identified gene expression features relevant to UC disease biology[6,7]



Genes with RNA expression that significantly correlated with infliximab response outcomes were mapped onto the Human Interactome to identify a subnetwork of proteins indicative of infliximab response status in UC[8]



Gene expression levels within the subnetwork were fed into a probabilistic neural network model to generate a classifier that predicts inadequate response to infliximab[8]

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Conflict of interest: All authors are full-time employees and shareholders of Scipher Medicine Corporation