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Analysis of intestinal tissue from newly diagnosed patients with inflammatory bowel disease reveals distinct proteomic profiles

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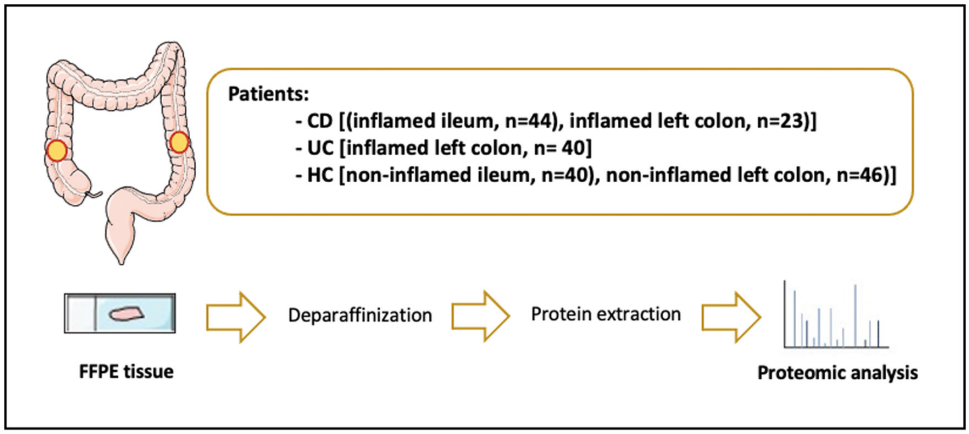

FIGURE 1. Experimental design and workflow of the study. CD: Crohn´s disease; HC: healthy control; UC: ulcerative colitis; FFPE: Formalin fixed paraffin-embedded.

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Background: Inflammatory bowel disease (IBD) is a complex multifactorial disease characterized by chronic inflammation of the gastrointestinal tract. Despite significant efforts to understand the pathogenetic mechanisms of IBD, the elucidation of its etiopathology and progression is far from fully understood. The direct analysis of the intestinal tissue from the endoscopy which leads to IBD diagnosis (before starting any treatment) would be the ideal sample to elucidate IBD pathogenesis.

Methods: High-throughput mass-spectrometry-based quantitative proteomic analysis was performed using formalin-fixed paraffin-embedded human intestinal samples from newly diagnosed patients to elucidate the potential mechanisms responsible for gut inflammation in Crohn´s disease (CD) and ulcerative colitis (UC). For this purpose, 192 formalin-fixed paraffin-embedded samples from 40 active UC patients, 67 active CD patients and 46 normal biopsies from healthy controls (HC) were analyzed (Figure 1). Proteins with p-value < 0.05 were considered as significantly dysregulated. Moreover, we used Ingenuity Pathway Analysis (IPA) to analyze the pathways and functions in different locations of the gut (ileum or left colon) that could be related to IBD pathogenesis.

Results: A total of 2,903 proteins were identified, of which 1,010 were differentially expressed between left colon from CD patients and HC. 1,242 proteins were differentially expressed between left colon from UC patients and HC, and 952 differential proteins discriminated between left colon from CD and UC patients. In the comparative study of ileum biopsies from Crohn's disease patients and healthy controls, 956 proteins were differentially expressed (Figure 2). IPA revealed multiple canonical pathways, including EIF2 signaling, regulation of eIF4 and serine/threonine kinase P7056K signaling, mitochondrial dysfunction, and oxidative phosphorylation altered in ileum biopsies from CD patients compared to HC (Figure 3). Regarding the proteomic study in left colon samples, the main canonical pathways enrichment in the comparison of UC and CD with HC were the following: neutrophil extracellular trap signaling pathways, fatty acid oxidation, sirtuin signaling pathway, tRNA charging, and mitochondrial dysfunction (Figure 4).

Conclusion: The proteomic results revealed dysregulated proteins and pathways in ileum and left colon biopsies from patients with active CD and UC compared to HC that may unravel key mechanisms contributing to the pathogenesis of these diseases. The results of the study serve as a starting point for hypotheses to understand the pathogenesis and search for therapeutic targets.

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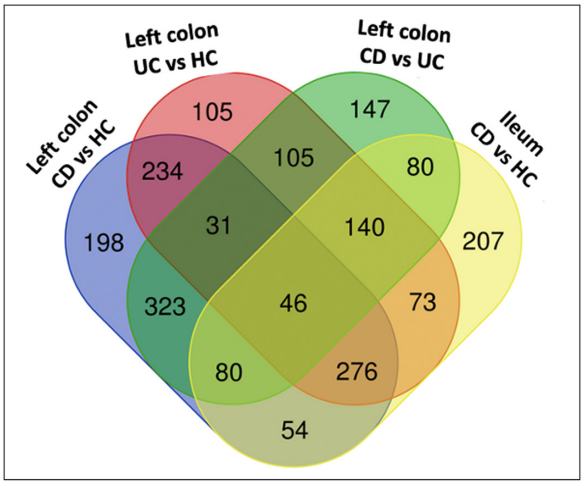

FIGURE 2. Venn diagram of the differentially expressed proteins identified by proteomics between different study comparatives. CD: Crohn´s disease; HC: healthy control; UC: ulcerative colitis.

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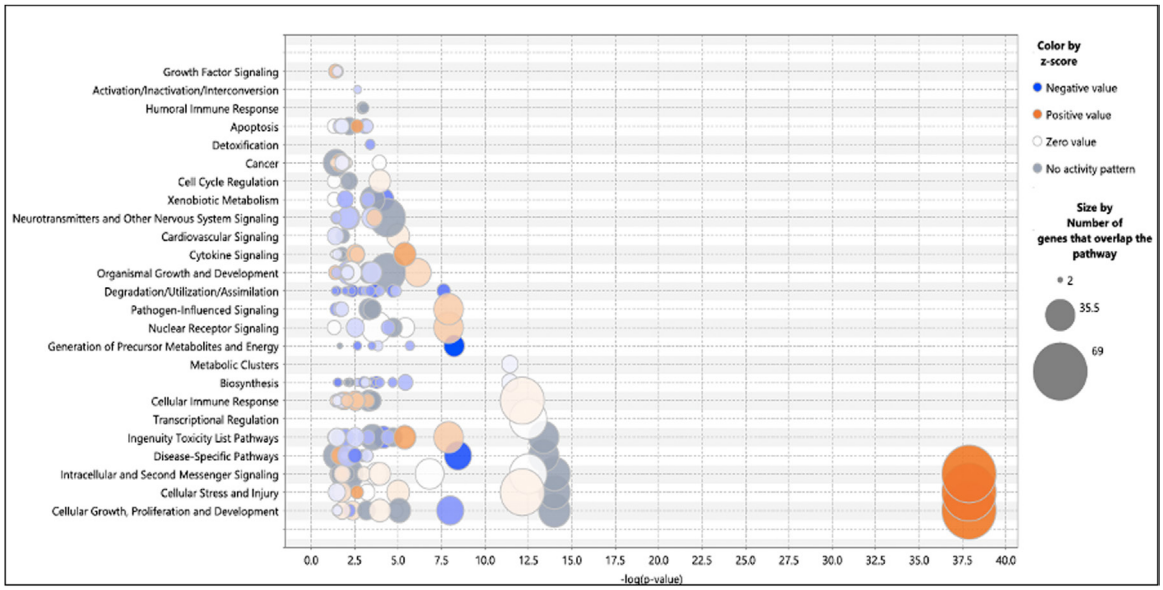

FIGURE 3. Canonical Pathway scores from proteomic data plotted in the comparison of Ileum from Crohn's disease patients compared to healthy controls. The colors indicate the z-score (see legend at top right), and the size of the bubble increases with the number of overlapping genes. Therefore, the large orange bubbles of the chart represent statistically significant pathways, are predicted to be activated and have many overlapping genes with the dataset.

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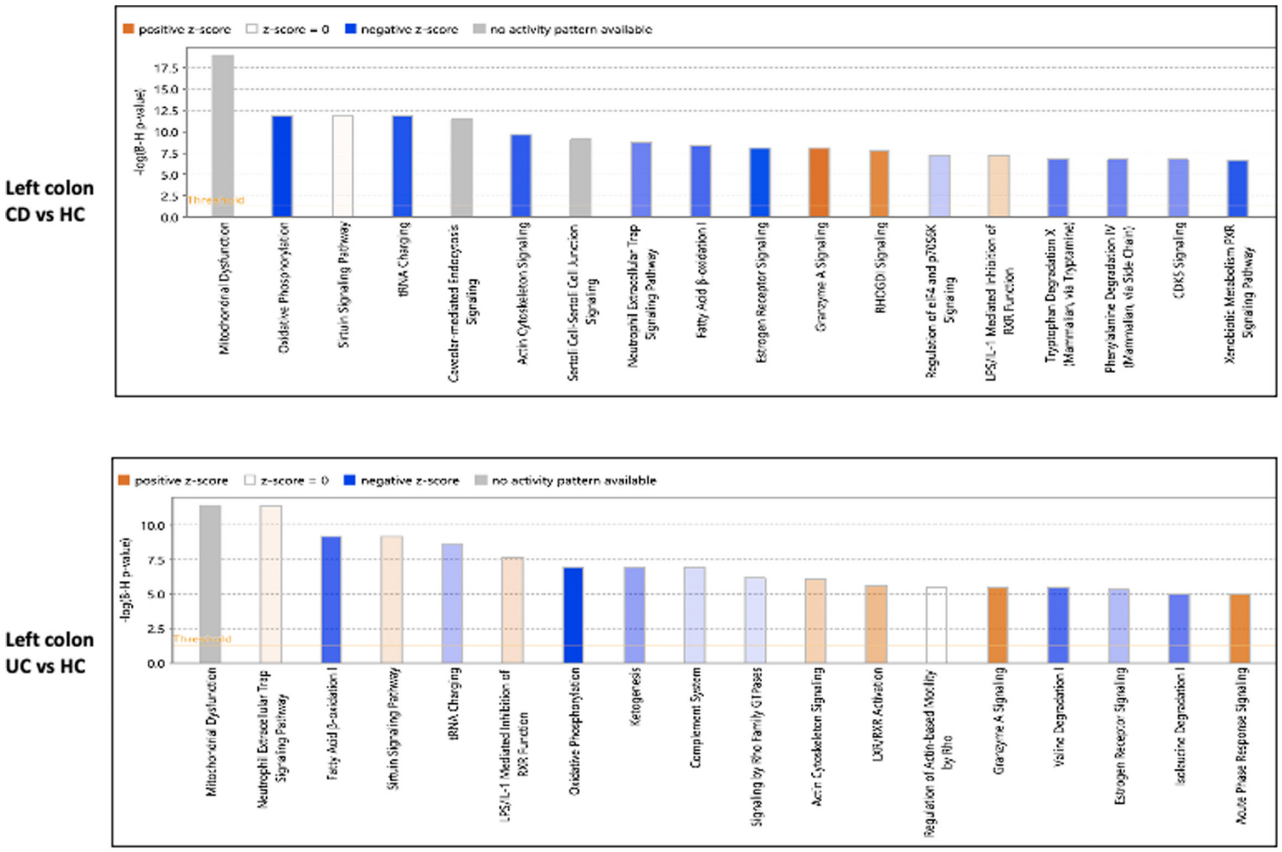

FIGURE 4. Canonical pathways determined by Ingenuity Pathway based on proteins identified in the dataset intestinal samples. The significance values (p-value of overlap) for the canonical pathways are corrected for multiple testing using the Benjamini-Hochberg (B-H) false Discovery rate. CD: Crohn´s disease; HC: healthy control; UC: ulcerative colitis.