2021 International Conference on Human Genetics and Genomics
1-2 December
Yazd University

Achieving the pathogenesis of inflammatory intestine (bowel) disease by tissue proteome

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Background

Inflammatory bowel diseases (IBD) encompass a group of chronic idiopathic gastrointestinal disorders including Crohn disease (CD) and ulcerative colitis (UC). Although the IBD burden is rising globally, it is higher in westernized areas. It is estimated that more than 2 million people in North America and 3.2 million people in Europe have IBD, with the overall incidence ranging between 5 and 15 per 100,000 person-years for both forms (CD and UC). In Spain, the incidence of IBD is 16 patients/100,000 person-years, highlighting the strategic importance of IBD for society, including both patients' perspective and health care systems. Currently, there is no curative treatment for IBD, so the main goal in IBD management is to achieve control of inflammation to avoid future complications. Even though biologic drugs are considered the most effective treatment option for disease control, two-thirds of treated patients do not achieve clinical remission. Furthermore, there are no useful biomarkers of clinical response to different biologic therapies in IBD. The complexity and costs associated with these treatments place a great burden on public health systems, with a direct health care cost of 5.6 billion euros per year in Europe. Although the exact etiology of IBD remains vastly unclear, it is well-known that it involves the complex interaction between the patient's genetic predisposition, environmental factors, gut microbiota, and the immune system.

Materials and Methods

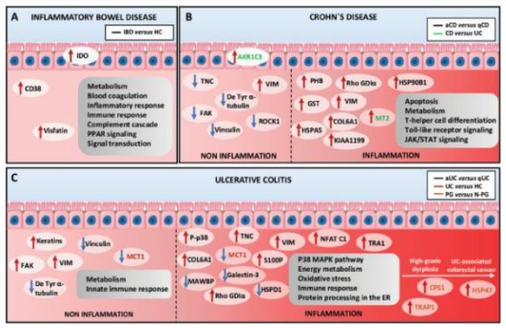

FIGURE 2. Integrated results from tissue proteomic studies in IBD. Several differentially expressed proteins confirmed by orthogonal techniques and biological pathways involved in IBD assessed by comparison of different study groups. Change of protein expression indicated as increase (↑) or decrease (↓) in patients with IBD vs HC (A), inflamed vs noninflamed tissue from patients with CD (B), and aUC vs qUC and UC-associated colorectal cancer (C). Comprehensive protein information and biological findings are detailed in the main text. aCD indicates active Crohn disease; aUC, active ulcerative colitis; de tyr α-tubulin, de-tyrosinated α-tubulin; ER, endoplasmic reticulum; AKR1C3, aldo-keto reductase family 1-member C3; CPS1, carbamoyl-phosphate synthase 1; COL6A1, collagen type VI alpha 1 chain; FAK, focal adhesion kinase; GST, glutathione S transferase Pi; HSPA5, heat shock 70 kDa protein 5; HSPDI, heat-shock protein 60; HSP47, heat-shock protein of 47 kDa; IDO, indoleamine-2,3-dioxygenase; HSP9OB1, heat shock protein 90 kDa beta member 1; JAK, Janus kinase; MCT1, monocaboxylate transporter 1; N-PG, nonprogressors; PG, progressors; PHB, prohibitin; PPAR, peroxisome proliferator-activated receptor; qCD, quiescent Crohn disease; qUC, quiescent ulcerative colitis; MAWBP, MAWD binding protein; MT2, metallothionein-2; NFAT C1, nuclear factor of activated T-cells cytoplasmic 1; Rho GDI alpha, Rho-GDP dissociation inhibitor α; ROCK1, Rho associated protein Kinase 1; STAT, signal transducer and activator of transcription; S100P, S100 calcium binding protein P; TNC, tenascin-C; TRA1, tumor rejection antigen 1; TRAP1, TNF receptor-associated protein 1; VIM, vimentin.

Results

TABLE 1. Human Tissue Proteomic Studies in IBD

Reference and Publication Year	Proteomic Approach	Biological Sample	Sample Size (discovery phase)	Biological Findings
Barceló-Batllori et al[95] 2002	2DE	DLD-1 (cell line) and intestinal epithelial cells	7 IBD, 4 DIV, and 4 HC	Differential protein expression associated with metabolism in IBD (TrpRS, IDO, JKTBP, ASS, LMP2, and IFP35). IDO overexpression confirmed in purified epithelial cells by Western blot.
Hsieh et al[96] 2006	2DE	Intestinal biopsies	4 UC, 3 NSIC, and 5 HC	A total of 19 proteins were differentially expressed in active mucosa of patients with UC. Several are mitochondrial enzymes or proteins related to energy generation, clearance of ROS, and cellular stress response. Moreover, TRA1, PVRL1, galectin-3, and NFAT C1 may serve as potential therapy target molecules in UC.
Berndt et al[97] 2007	MELC	Intestinal biopsies	10 CD, 10 UC, and 10 HC	Increased number of $CD3^+$ $CD45RA^+$-naïve T cells in inflamed mucosa of patients with CD. Expression levels of Bax, active caspase-3, or active caspase-8 downregulated only in activated memory T cells. Caspase-8 activity increased in $CD4^+$ Th cells coexpressing PARP and NF-ĸB in UC samples. Number of $CD4^+$ $CD25^+$ regulatory T cells increased only in UC.
Shkoda et al[98] 2007	2DE	Intestinal epithelial cells	6 CD, 6 UC, and 6 NC	Identification of 4 proteins (L-lactate dehydrogenase, NADPH prostaglandin E2 reductase, keratin 19, Rho GDI α) differentially altered in patients with inflamed IBD related to signal transduction, stress response, and energy metabolism. PCD8 and ANXA2 overexpressed in inflamed tissue.
Fogt et al[99] 2008	2DE	Intestinal epithelial cells	5 UC	Four of the proteins identified (protocadherin, α-1 antitrypsin, tetratricopeptide repeat domains, and caldesmon) associated with inflammation. Mutated form of desmin may be involved in development or course of UC.
Nanni et al[100] 2009	1DE	Intestinal epithelial cells	2 CD and 2 HC	Several proteins involved in inflammatory processes were altered in CD (different histones, UBIQ, ATPB, HSPA5, ANXA1, and MDHM).
Brentnall et al[101] 2009	iTRAQ	Intestinal epithelial cells	5 UC per group (HGD, NEG, Non-P, and Nl)	Identification of CPS1 and S100 proteins, which could be candidate biomarkers for identifying a patient risk for UC dysplasia.
Araki et al[102] 2009	2DE	UCCA and KE (cell lines)	UCCA-3, UCCA-21, and UCCA-24 and KE-43P, KE-43W, and KE-24)	Significant upregulation of HSP47 in UC-associated cancer. This protein may be a candidate biomarker of UC-associated carcinoma with potential clinical applications.
Zhao et al[103] 2011	2DE	Intestinal biopsies	12 UC and 12 HC	Identification of 26 differentially expressed proteins. A molecular signature of the P38 MAPK pathway (consisting of P-p38, MAWBP, and galectin-3) may be potential biomarker for evaluation of UC risk.
May et al[104] 2011	LC-MS/MS	Intestinal epithelial cells	5 UC per group (NP, P-NEG, and P-HGD)	Proteins related to mitochondria, cytoskeleton, RAS superfamily, apoptosis, and metabolism identified in nondysplastic and dysplastic tissues of UC progressors. TRAP1 and CPS1 displayed differences between different study groups. These findings suggested that rectal CPS1 could be a potential predictive biomarker of dysplasia or colon cancer.
M'Koma et al[105] 2011	MALDI-MS	Intestinal biopsies	24 CC and 27 UC	Three significant discriminatory peaks (m/z of 31752, 4939, and 5677) identified between CC and UC, with an accuracy of 70%. However, future analysis and protein identification will be necessary.
Presley et al[106] 2012	OFRG and SELDI-TOF	Intestinal MLI	21 UC, 14 CD, and 16 HC	High frequency of bacteria (35%) could discriminate between disease types. Analysis of MLI could elucidate host-relevant networks of bacterial taxa associated with IBD.

Conclusion

We have presented different proteomic approaches for the analysis of intestinal mucosa from patients with UC and CD and outlined potential future directions for this research basedon the aforementioned limitations.

Note that future studies will be needed to validate the novel differentially expressed proteins discovered in the previous studies.Efforts should be made to translate the validated biomarkers into routine clinical practice,improving clinical management and outcomes in patients with IBD. Further multicenter and multi-omics studies in large populations are required for the comprehensive molecular characterization of disease biology in real time with future impact on early detection,disease monitoring, and prediction of clinical outcome.

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