Review

Proteomics and Lipidomics in Inflammatory Bowel Disease Research: From Mechanistic Insights to Biomarker Identification

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Supplementary Tables

Supplementary Table S1. Proteomics and lipidomics studies for IBD. Studies identified via a PubMed search [("inflammatory bowel disease" OR "Crohn's disease" OR "ulcerative colitis") AND (LIPIDOMICS OR PROTEOMICS)] and complemented with Google Scholar search results.

Category[1]	Species	Sample Type	Groups[2]	Technology	Main Findings	Reference
BM	Human	Colonic mucosa biopsies	Discovery: CD (15), UC (15), HC (20) Validation: CD (15), UC (15), HC (19)	Proteomics LC-MS/MS	Five-protein panel able to discriminate IBD versus control cases with 95.9% accuracy, and a 12-protein panel discriminating between CD and UC patients with 80% accuracy in the validation cohort.	[1]
BM	Human	Blood/Serum	UC (30) HC (30)	Proteomics 2D-PAGE	Twelve serum proteins differed between UC and HC	[2]
BM	Human	Blood/Serum	UC (24) HC	Proteomics 2D-PAGE	Upregulation of ceruloplasmin and apolipoprotein B-100 specifically in children	[3]
BM	Human	Blood/Serum	Stricturing CD (9) Nonstricturing CD (9) UC (9)	Proteomics LC-MS/MS	Stratification of IBD patient subgroups	[4]
BM	Human	Blood/Serum	CD UC HC	Proteomics LC-MS/MS	Peptides of the secreted phosphoprotein 24 (SPP24) differentiated IBD from controls	[5]
BM	Human	Blood/Serum	CD with and without intestinal complications	Proteomics LC-MS/MS	Serology panel of three proteins to identify CD with complications	[6]
BM	Human	Blood/Serum	UC CD HC	Lipidomics	Thirty-three lipids (primarily ether-lipids) negatively associated with CD	[7]
BM	Human	Colon biopsies	UC CD	Proteomics MALDI imaging	Clear differences between UC and CD for stratification, but specific molecules not identified	[8,9]
BM	Human	Colonic mucosa biopsies	UC (4) CD (3) HC (3)	Proteomics LC-MS/MS	Twelve upregulated proteins were shared between the UC and CD cases	[10]

			UC-related inflammatory polyps (2)			
BM	Human	Intestinal mucosal-luminal interface aspirates	18 non-IBD 42 IBD	Proteomics LC-MS/MS	Two 4-protein panels that distinguished active IBD from non-IBD and pancolitis from non-pancolitis in UC, respectively (discovery cohort, limited validation for two proteins in stool samples)	[11]
BM	Human	Salivary exosomes	37 UC, 11 CD, 10 healthy individuals	Proteomics LC-MS/MS	PSMA7 increased in UC and CD	[12]
BM	Mouse interleukin-$10^{-/-}$ model	Blood/Serum	Longitudinal during development of IBD-like disorder	Proteomics 2D-PAGE	Candidate markers for global, intestinal, and chronic inflammation	[13]
BM	Mouse G-alpha(i2)$^{-/-}$ IBD model	Fecal samples	Diseased, non-diseased (wild-type) mice	Proteomics LC-MS/MS	Ten differentially abundant proteins, including higher levels of peptidase D in diseased mice	[14]
BM, TR	Human	Blood/Serum	CD with and without infliximab response (20)	Proteomics 2D-PAGE	Initial prediction model of treatment response, including platelet aggregation factor 4 (PF4)	[15]
BM, TR	Human	Blood/Serum	Infliximab responders in remission (6), responders (6), and non-responders (6) [16]	Proteomics 2D-PAGE	Candidate serum markers for treatment response	[16]
BM, TR	Human	Blood/Serum Inflamed colon biopsies	Infliximab responders, non-responses	Proteomics LC-MS/MS	Reduced tenascin-C level in biopsies and serum upon treatment	[17]
BM, TR	Human	Blood/Serum	Children with IBD, before and after treatment with corticosteroids (12) or infliximab (12)	Proteomics SOMAmer	Five proteins demonstrated consistent downregulation upon treatment and were associated with inflammatory processes	[18]
BM,DM	Human	Colon biopsies	Acute UC HC	Proteomics 2D-PAGE	Distinguish inflamed and non-inflamed samples, increase in energy metabolism and oxidative stress proteins in UC	[19]
DM	Human	Adenocarcinoma cell line Purified colon epithelial cells	Cytokine treated cell line/isolated cells from UC, CD, and HC	Proteomics 2D-PAGE	Indoleamine-2,3-dioxygenase (IDO1) upregulation in UC/CD, linked to immune-tolerance	[20]
DM	Human	Blood/Macrophages	Stimulation with heat-inactivated *Escherichia coli*	Lipidomics	Alteration in lipid levels, including ceramides	[21]
DM	Human	Endoscopic sampling of microbiome by mucosal lavage	UC CD HC	Proteomics (targeted & untargeted)	Protein modules associated with intestinal location and disease state	[22]

DM	Human	Intestinal biopsies	Th1 and Th1/Th17 T-cell clones from CD	Proteomics LC-MS/MS	Only subgroup of Th1 expresses cytotoxic features	[23]
DM	Human	Isolated intestinal epithelial cells (inflamed and non-inflamed regions)	CD UC CRC (control)	Proteomics 2D-PAGE	Alterations in signal transduction, stress response, and energy metabolism in IBD	[24]
DM	Human	Isolated intestinal epithelial cells	CD HC	Proteomics LC-MS/MS	Upregulation of protein folding and ubiquitin processes in CD	[25]
DM	Human	Lymphocytic cell line	IL-23 stimulation	Proteomics LC-MS/MS (phospho-proteomics)	STAT3 involvement, regulatory role of pyruvate kinase isozyme M2	[26]
DM	Human	Mucosa biopsies	Active UC Inactive UC Nonspecific colitis HC	Proteomics 2D-PAGE/MS	Colonocyte mitochondrial dysfunction and perturbed mucosa immune regulation in the pathogenesis of UC	[27]
DM	Human	Mucosa biopsies (non-inflamed)	UC HC	Proteomics LC-MS/MS	Role of neutrophil extracellular traps in UC	[28]
DM	Human	Mucosa biopsies	UC HC	Lipidomics	Inflamed mucosa in UC with elevated levels of seven eicosanoids	[29]
DM	Human	Mucosa biopsies	UC	Proteomics LC-MS/MS (label-free)	168 differentially abundant proteins between UC and HC	[30]
DM	Human	Mucosa biopsies	CD HC	Proteomics LC-MS	Downregulation of mitochondrial proteins in CD, including H_2S detoxification enzymes	[31]
DM	Human	Rectal mucus	UC CD HC	Lipidomics	Lower levels of PC and lyso-PC in UC	[32]
DM	Human (twin pairs)	Stool samples/Microbiome	CD HC	Proteomics LC-MS	CD associated with alterations in bacterial carbohydrate metabolism and bacterial-host interactions; and increase in host proteins involved in epithelial integrity and function	[33]
DM	Human	Treg cells and conventional T lymphocytes ($CD4^+Foxp3^-$)	Isolated cell populations	Proteomics LC-MS/MS	Themis protein as a checkpoint control in the suppressive function of Treg cells	[34]
DM	Human cell line	Adenocarcinoma cell line	Cytokine treated Untreated	Proteomics 2D-PAGE (ubiquitin staining)	Ubiquitin-mediated regulation of chaperones in inflammatory response	[35]

DM	Mouse TNF transgenic	Microbiome	IBD and control mice	Proteomics LC-MS	Metaproteomics complemented genomics methods for the analysis of microbial communities	[36]
DM	Mouse adoptive T-cell transfer model	Microbiome	IBD and control mice	Proteomics LC-MS (activity-based probes for enzyme classes)	Quantitative alterations in both host and microbial proteins due to intestinal inflammation	[37]
DM	Mouse	Serum	DSS-treatment & recovery period	Lipidomics	Involvement of lipid mediators (such as resolving D1) in intestinal healing process	[38]
DM	Primary murine bone marrow– derived macrophages	Cell culture	Wild-type and Atg16l1 (autophagy-related gene) knockout	Proteomics LC-MS/MS	Limited set of differentially abundant proteins upon Atg16l1 knockout, prominently sequestosome-like receptors	[39]
GA	Human	Serum	CD UC HC	Proteomics Antibody microarray	SNP in CD regulated levels of MST1 in serum	[40]
GA	Human	Serum	Diverse	Proteomics SOMAmer	Genome-proteome-disease sub-network that associated CD with four genomic loci (MST1, IL23R, IL18R1, and C7)	[41]
TR	Mouse Mdr1a$^{-/-}$ model	Colon	Polyphenol-treatment	Proteomics 2D-PAGE	Treatment decreased inflammatory and fibrinogenesis proteins and increased xenobiotic metabolism enzymes	[42]
TR	Mouse Mdr1a$^{-/-}$ model	Colon	Curcumin treatment	Proteomics 2D-PAGE	Treatment decreased inflammatory proteins and increased xenobiotic metabolism enzymes	[43]
TR	Mouse DSS-model	Colon	Celastrol treatment	Lipidomics	Celastrol treatment restored control-like lipid profiles	[44]

[1] Categories: disease mechanisms (DM); candidate biomarker identification (BM); treatment response characterization (TR); genotype association (GA). [2] Group abbreviations: healthy control (HC); colorectal carcinoma (CRC). Phosphatidyl-choline (PC).

Supplementary Table S2. IBD biomarker products.

PRODUCT	ASSIGNEE	MARKER(S)	MATRIX	APPLICATION	PATENT IDENTIFIED	FDA APPROVED
ASCA-CHEK™	TECHLAB INC.	ASCA	Feces	CD	Yes	Yes
COLOGUARD	EXACT SCIENCES	DNA mutation/methylation and hemoglobin	Feces	Colorectal cancer	Yes	Yes
LACTOFERRIN CHEK®	TECHLAB INC.	Lactoferrin	Feces	IBD & treatment response	Yes	Yes
LACTOFERRIN EZ VUE®	TECHLAB INC.	Lactoferrin	Feces	IBD	Yes	Yes
LACTOFERRIN SCAN®	TECHLAB INC.	Lactoferrin	Feces	IBD & treatment response	Yes	Yes
PHICAL TEST	CALPRO AS	Calprotectin	Feces	IBD	Yes	Yes
CALPROLAB™ ELISA TEST (ALP/HRP)	CALPRO AS	Calprotectin	Feces Blood Tissue fluids	IBD & treatment response	Yes	
CALPROTECTIN ELISA	EUROIMMUN	Calprotectin	Feces	IBD & treatment response		
CROHN'S PROGNOSTIC	PROMETHEUS LAB INC.	Antibodies and genetic markers	Serum	CD complications	Yes	
DIBICOL	INDEX PHARMACEUTICALS	Gene panel	Colon biopsy	IBD, UC vs. CD	Yes	
ELIATM CALPROTECTIN TEST	NAVIGENICS INC.	Calprotectin	Feces	IBD		
EXAIBD™	EXAGEN DIAGNOSTICS	Gene panel	White blood cells	IBD		
EXAUC/CD™	EXAGEN DIAGNOSTICS	Gene panel	White blood cells	UC vs. CD		
FECAL MPO SAMPLE COLLECTION KIT	EPITOPE DIAGNOSTICS	Myeloperoxidase (MPO)	Feces	IBD inflammation		

GLYCOMINDS IBDX®	GLYCOMINDS	ASCA, ALCA, ACCA, AMCA, Anti-L, Anti-C	Serum	IBD, UC vs. CD	Yes
HUMAN CROHN'S DISEASE RT2 PROFILER PCR ARRAY	MOLECULAR STAGING	84 gene panel		Research	Yes
HUMAN FECAL NGAL (LCN2) ELISA KIT	EPITOPE DIAGNOSTICS	NGAL, LCN2	Feces	IBD	Yes
IBD BIOCHIP	UNIVERSITY OF CALIFORNIA	C-reactive protein and calprotectin	Feces	IBD	
IBD SGI DIAGNOSTIC®	PROMETHEUS LAB INC.	Combined protein and genetic markers	Serum/ whole blood	IBD, UC vs. CD	Yes
MONITR™	PROMETHEUS LAB INC.	13 protein biomarkers	Serum	Mucosal healing in CD	Yes
PROMETHEUS® ANSER® VDZ TEST	PROMETHEUS LAB INC.	Antidrug antibodies	Serum	Treatment resistance	Yes
Q-FOB™ QUANTITATIVE FECAL OCCULT BLOOD TEST KIT	EPITOPE DIAGNOSTICS	Hemoglobin	Feces	IBD	Yes
QUANTITATIVE FECAL CALPROTECTIN ELISA KIT	EPITOPE DIAGNOSTICS	Calprotectin	Feces	IBD	Yes
QUANTITATIVE FECAL/URINE MYELOPEROXIDASE ELISA KIT	EPITOPE DIAGNOSTICS	MPO	Feces, Urine	Gut inflammation	
RAID-CD	GOODGUT	Specific biomarkers	Feces	CD	Yes

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