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MINIREVIEWS

Proteomic insights on the metabolism in inflammatory bowel disease

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Abstract

Inflammatory bowel diseases (IBD) are chronic and relapsing inflammatory conditions of the gut that include Crohn's disease and ulcerative colitis. The pathogenesis of IBD is not completely unraveled, IBD are multi-factorial diseases with reported alterations in the gut microbiota, activation of different immune cell types, changes in the vascular endothelium, and alterations in the tight junctions' structure of the colonic epithelial cells. Proteomics represents a useful tool to enhance our biological understanding and to discover biomarkers in blood and intestinal specimens. It is expected to provide reproducible and quantitative data that can support clinical assessments and help clinicians in the diagnosis and treatment of IBD. Sometimes a differential diagnosis of Crohn's disease and ulcerative colitis and the prediction of treatment response can be deducted by finding meaningful biomarkers. Although some non-invasive biomarkers have been described, none can be considered as the "gold standard" for IBD diagnosis, disease activity and therapy outcome. For these reason new studies have proposed an "IBD signature", which consists in a panel of biomarkers used to assess IBD. The above described approach characterizes "omics" and in this review we will focus on proteomics.

Key words: Proteomics; Inflammatory bowel disease; Cronh's disease; Ulcerative colitis; Proteins; Biomarkers discovery

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Core tip: Patients' heterogeneity is a hallmark for inflammatory bowel diseases (IBD). Some patients present limited bowel involvement and a mild course of the disease, others develop very extensive, aggressive disease and variable response to therapy. In IBD, there is a great need of patient stratification and of new biomarkers as part of a personalized medicine approach to patient care. Biological therapies are more and more widely used for IBD patients, because of their efficacy in patient's refractory to other drugs; still, biological treatments fail in 20%-40% of patients and, to date, no reliable clinical or molecular predictor of response to biological therapeutic strategy has been described. This review aims to collect the "omics" approach for research of serological biomarkers of diagnosis, response to specific biological therapies in the IBD field.

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INFLAMMATORY BOWEL DISEASE

Ulcerative colitis (UC) and Crohn's disease (CD) are the two main inflammatory bowel diseases (IBD)[1-4]. Despite some shared characteristics, they can be distinguished by differences in genetic predisposition, risk factors, and clinical, endoscopic and histological features. CD is characterized by diffuse chronic inflammation throughout the gastrointestinal tract, in a non-continuous manner[5]; UC presents with inflammation limited to the colon, spreading continuously from the rectum[6]. The pathogenesis of IBD is at present not completely unraveled; however, genetically susceptible individuals seem to have a dysregulated mucosal immune response to the commensal gut flora, which results in bowel inflammation[7]. IBD are multi-factorial diseases[8] with reported alterations in the gut microbiota[9-12], activation of different immune cell types[13-15], changes in the vascular endothelium[16,17], and alterations in the tight junctions structure of colon epithelial cells[18-20].

Nowadays, the diagnostic and prognostic tools for IBD and the outcome of therapy are largely based on evaluation of clinical symptoms in combination with endoscopy, histology, radiology and non-specific biomarkers from serum or stools[21].

BIOMARKERS IN INFLAMMATORY BOWEL DISEASE

Inflammation in IBD is characterized by the increased levels of some molecules extensively validated but not all included in the laboratory routine. Some of them are related to the inflammatory acute-phase response, coagulation and fibrinolysis (fibrinogen, plasminogen, complement components), proteinase inhibitors (α1-antitrypsin and α1-anti-chymotrypsin), transport proteins (haptoglobin and ceruplasmin) and other serum proteins[22] and cytokines[23]. Elevated platelet and white blood cell counts may also indicate inflammation but they cannot be considered strictly related to bowel inflammation[23]. C-reactive protein (CRP), anti-*Saccaromyces cerevisiae* (ASCA) and anti-neutrophil cytoplasmic antibody are the most widely used indicators. CRP has a short reaction time (6-10 h) and it is useful for the identification of inflammatory disease activity especially in CD, but not in UC[24]. CRP has low specificity enabling to differentiate between CD, UC and infectious colitis[21], and also the 25% of IBD patients with demonstrable disease activity have CRP levels above the normal threshold[22]. ASCA is an antibody used for the identification of CD patients who are often positive (39%-79% of CD patients, 5%-15% UC patients)[25,26], however a large part of healthy controls is also positive (14%-18%) to this antibody, limiting the diagnostic value of its detection[27]. anti-neutrophil cytoplasmic antibodies are antibodies found in immune-mediated pathologies, such as rheumatoid arthritis and Wegener's granulomatosis[28], and have shown a different staining pattern in UC and CD patients[29-31], but as for ASCA 32% of healthy population is also positive to them[32].

Another explored field in the search for IBD biomarkers is the analysis of stool proteins, which can be dysregulated or abnormally present in patients. Stool markers have the advantage of increased specificity for bowel inflammation and reflect any mucosal barrier disruption. Fecal markers can be useful to diagnose CD, where

inflammation is patchy and is possibly missed at endoscopy[33]. Fecal calprotectin (FC) accounts for up to 5% of the neutrophil granulocytes' protein content with chemotactic and antimicrobial activities. It is stable in stool for more than a week and can resists to bacterial degradation[34]. FC is not a specific marker for IBD, but it correlates with increased disease activity at least in adults[35], but not in pediatric patients where was found with high sensitivity (98%), but only modest specificity (68%)[36]. Disease location should also be taken into account when interpreting FC levels. Patients with ileal CD may have ulcers even in the absence of markedly elevated FC levels. Consequently, the cut-off values for ileal CD may differ from those with ileocolic disease[37,38]. A study conducted by De Vos *et al*[39] has demonstrated that Calprotectin decreased 2 wk after Infliximab administration predicts remission in anti-TNF-naïve patients with UC. The increase of FC can also be a suitable marker for the identification of relapse, given the fact that the levels are increased as early as 6 mo before clinical and endoscopic relapse[40]. Lactoferrin is an iron-binding protein expressed by neutrophils during inflammation and represents a defense against infection as part of the innate immune system[41,42]. As a biomarker, Lactoferrin can distinguish IBD from Irritable Bowel Syndrome, but not between CD and UC[27].

Although many non-invasive biomarkers have been described, none can be considered as the "gold standard" for IBD diagnosis, disease activity and therapy outcome. A single ideal biomarker is very unlikely to be found. As for other pathologies as pancreatic cancer[43-46], non-small cell lung cancer[47] and colorectal cancer[48] new studies have proposed the idea of a "Biomarker Signature", which consists in a panel of biomarkers used to assess various pathological conditions and response to therapy[49], and which is applicable also to IBD diagnosis and prognosis. Table 1 summarizes the biomarkers commonly used for IBD.

PROTEOMIC APPROACH TO INFLAMMATORY BOWEL DISEASE RESEARCH

Proteomics comprehensively studies the protein composition and abundance in a given cell population and its changes under biological perturbations[50,51]. The proteome may be considered the signature of a disease, in fact it is the result of the interactions between the genetic background and environmental factors[49]. The novel proteomic technologies now facilitate the analysis of transcriptome variations also in the IBD context and have already provided with new candidate biomarkers[52]. They help to investigate the inflammatory response, epithelial barrier function and gut microbiome from different biological samples, *i.e.*, serum/blood, colon samples and feces. The proteomic strategies can be bottom-up and top-down (Figure 1). In the bottom-up approach, purified proteins or complex protein mixtures are subjected to proteolytic cleavage and the peptide products are analyzed by mass spectrometry (MS). Conversely, the top-down approach is based either on the analysis of intact proteins followed by the direct measurement of fragment ions by MS or on the isolation of the protein by gel-based separative methods, protein gel elution and MS analysis.

Proteomics in the study of IBD pathogenesis

By LC-MS analysis of colon mucosal biopsies from 10 patients with UC, Bennike *et al*[53] identified 5711 quantifiable proteins classified by biological function, sub-cellular location and molecular function. Forty-six proteins demonstrated statistically significant changes in mean abundance between UC biopsies and control biopsies; among those proteins, the one with the largest mean fold abundance change was lactotransferrin, which was 219 times more abundant in the UC group. The relative abundance of lactotransferrin also correlated to the severity of tissue inflammation in the patients with UC, as determined by the colon inflammation grade score based on histology. Good correlation was found between the colon inflammation grade score and the relative abundance of lactotransferrin in the tissue (0.82)[53]. Eleven of the 46 proteins identified in the UC biopsies are present in neutrophils and are associated with the formation of neutrophil extra-cellular traps which are released from neutrophils in response to inflammatory stimuli[54,55], and are a sign of chronic inflammation even in the absence of visible inflammation[54,56,57].

Proteomics has also investigated IBD-related immune-cell responses. Riaz *et al*[58] compared Th1 and Th17 clones isolated from the intestinal mucosa of CD patients by means of label-free quantitative mass-spectrometry analysis, which led to the identification of a total number of 7401 unique protein groups and demonstrated that 334 proteins were differentially expressed. The largest differences between the two phenotypes were observed in such proteins with cytotoxic function as Granzyme B

Table 1 Biomarkers in inflammatory bowel disease

Marker	Setting	Diagnostic accuracy	Ref.
C-Reactive Protein (CRP)	Serum	Higher in CD *vs* UC	Henriksen *et al*[24], 2008
		25% IBD patients have levels above normal	Vermeire *et al*[22], 2004
Anti-*Saccharomyces cerevisiae* Antibodies (ASCA)	Serum	39%-79% CD positive	Peyrin-Biroulet *et al*[25], 2015;
		5%-15% UC positive	Reumaux *et al*[26], 2004
		14%-18% HC positive	Bennike *et al*[27], 2014
Anti-neutrophil cytoplasmic antibodies (ANCA)	Serum	Different pattern in CD and UC	Peeters *et al*[31], 2001;
			Peyrin-Biroulet *et al*[30], 2007;
			Reumaux *et al*[29], 2003
		32% HC positive	Bernstein *et al*[32], 2011
Calprotectin	Colorectal mucus	Higher in IBD *vs* HC	Loktionov *et al*[79], 2016
		Higher in UC *vs* CD	
Calgranulin C (S100A12)		Higher in UC *vs* CD	
Eosinophil-derived neurotoxin (EDN)		Higher in IBD *vs* HC	
		Higher in UC *vs* CD	
Fecal calprotectin (FC)	Stool	It correlates with disease activity in adults	Gisbert *et al*[35], 2009
Lactoferrin	Stool	It distinguishes IBD from IBS	Bennike *et al*[27], 2014

CD: Crohn's disease; UC: Ulcerative colitis; HC: Healthy controls; IBS: Irritable bowel syndrome; IBD: Inflammatory bowel disease.

and perforin, which are lower in Th17 cells than in Th1 cells. Other differentially expressed proteins with higher expression in the Th1 clones included several transcription factors with both known and unknown functions in $CD4^+$ T-cells. The most striking differences at quantitative analysis are about $CD4^+$ T cells with Th1 phenotype having a much higher degree of cytotoxic features as compared with Th1/Th17 phenotype[58].

As discussed above, the disruption of the intestinal barrier is a typical event in IBD pathogenesis. The intestinal epithelium is the largest surface exposed and coming into contact with the external environment. The intestinal epithelial cells (IECs) are the main component of the physical barrier between the luminal micro-environment and the host and act as the host's first line-of-defense against potential harmful stimulants. They also represent the innate immunity within the gut mucosa[59]. Normally, the intestinal epithelium is covered by a single layer of IECs, which are characterized by a fast renewal rate, and act as a protective barrier against luminal antigens, but this barrier can be damaged, thus promoting a state of chronic inflammation due to mucosal immune cell infiltration, as is typically observed in IBD patients[59]. The molecular changes in the epithelial layer, extra-cellular matrix and junction proteins in inflamed and non-inflamed intestinal tissue have been only partially addressed to date. In 2012 Poulsen *et al*[60] analyzed the proteomic profiles of whole colonic biopsies from UC patients using 2D-gel electrophoresis and MALDI-TOF MS for the identification of differently expressed protein spots. Forty-three proteins were identified differentially expressed between UC inflamed and non-inflamed tissue, including proteins involved in the energy metabolism and in oxidative stress[60]. Proteomic studies on isolated IECs obtained from surgical specimens of full-thickness colonic tissues from UC-, CD-affected patients and non-inflamed controls were analyzed by gel-based stable-isotope label technologies (2D-DIGE and ICPL LC-MS/MS) and immunoblot assay to evaluate any proteome changes. Moreover, the results were verified on a group of patients not participating in the discovery phase[61]. The differential proteomic approaches have revealed changes in several molecules involved in extracellular matrix, mechano-transduction, metabolic rewiring and autophagy that characterize quiescent UC and quiescent CD epithelial cells and they may help understanding the complex mechanisms associated to IBD. UC patients are characterized by cytoskeletal rearrangement and increased level of specific enzymes that contribute to cell homeostasis, enabling cells to cope with energy requirements and macro-autophagy. CD patients are characterized by metabolic rewiring to sustain the cell metabolism, whereas autophagy and cell renewal are blunted[61-63]. Table 2 provides a summary of the proteins and pathways identified by the proteomic approach as involved in IBD pathogenesis.

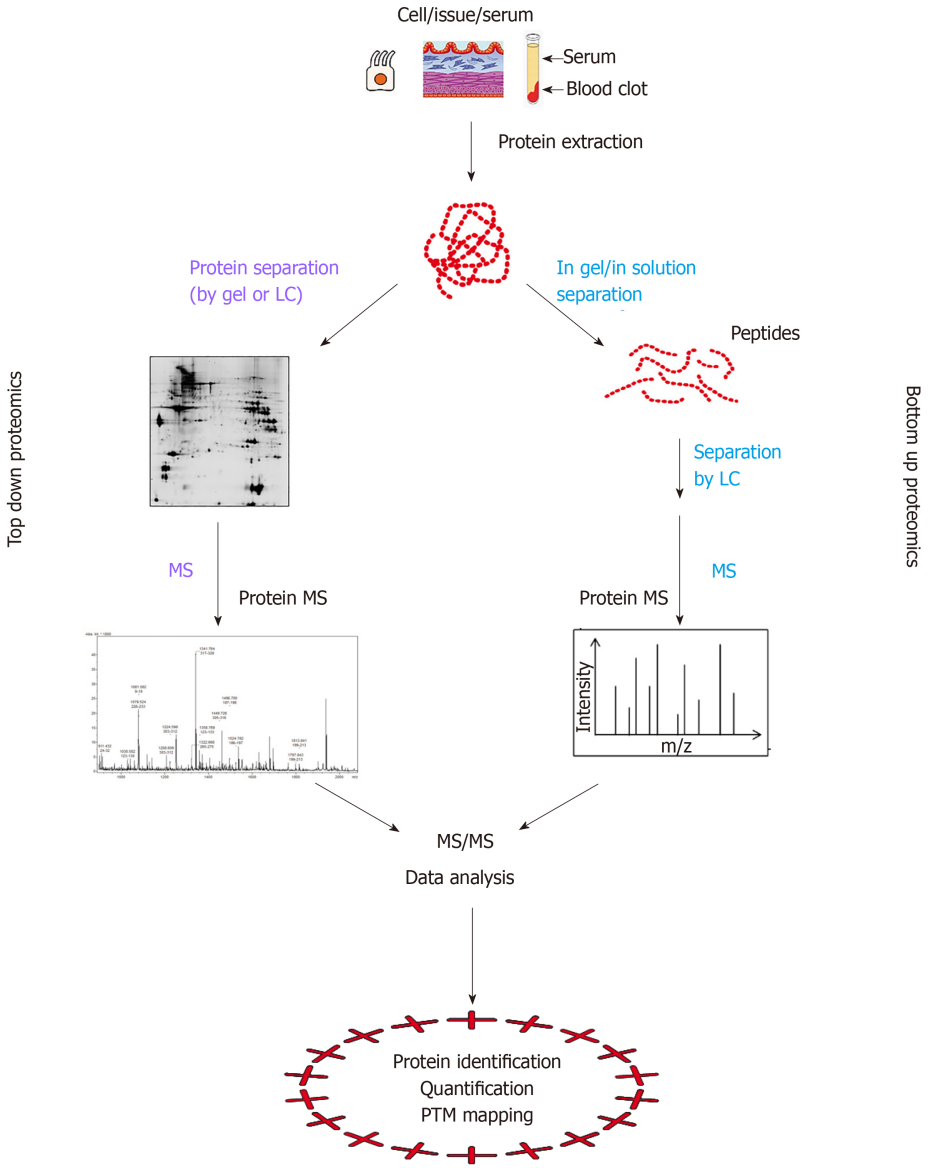

Figure 1 Schematic illustration of the difference between protein-based top-down and peptide-based bottom-up proteomics.

Proteomics for the identification of novel biomarkers

Another approach is the identification of biomarkers useful for the diagnosis, treatment selection and response monitoring. A recent study focused on diagnosis has identified a serological panel which demonstrates transmural intestinal injury and is able to indicate complications in CD patients with 70% sensitivity and 72.5% specificity[64]. The increase of circulating epithelial component proteins may be a sign of transmural intestinal injury and stricturing or fistulizing intestinal complications. The serum biomarkers for the stratification of IBD patients are unable to distinguish between CD and UC[65], while the proteomic profiles of colon biopsies can identify a more precise signature of these diseases[61,66,67]. In 2016 Starr *et al*[68] established two candidate biomarker panels: A 5-protein panel to discriminate IBD from control patients and a 12-protein panel to distinguish CD from UC patients in children with a new IBD diagnosis.

Proteomics has been applied to the identification of treatment-response biomarkers. The anti-TNF drug called Infliximab is one of the most used drugs in IBD, but the factors predicting the response and the molecular mechanisms that are related to the loss of response or non-responsiveness are not completely known. Meuwis *et al*[69] have analyzed sera from responder and non-responder CD patients at baseline and then comparing sera throughout the induction period (week 4 for non-fistulizing and week 10 for fistulizing patients) and have shown that the platelet aggregation Factor 4 (PF4) was higher in non-responders than responders to Infliximab therapy (both before and after treatment). PF4 is considered as an acute-phase reactant because its level increases with general inflammation, as already observed in the plasma of CD

Table 2 Proteomics in inflammatory bowel disease pathogenesis

Protein	Setting	Diagnostic accuracy	Ref.
Lactotransferrin	UC *vs* HC biopsies	It correlates to the colon inflammation grade score	Bennike *et al*[53], 2015
Neutrophil extracellular traps (NETs)		Sign of chronic inflammation	
Granzyme B and Perforin	CD Th1 and Th17 clones from intestinal mucosa	Higher in Th1 *vs* Th17	Riaz *et al*[58], 2016
RORC and FOXP3			
Glycerol-3-phosphatedehydrogenase	UC biopsies inflamed *vs* non-inflamed	Higher in inflamed *vs* non-inflamed tissue	Poulsen *et al*[60], 2012
Alphaenolase		Lower in inflamed *vs* non- inflamed tissue	
Keratins 10, 14, 19	UC intestinal epithelial cells	Higher in QUC vs HC	Moriggi *et al*[61], 2017
Keratin 8		Lower in QUC *vs* HC	
Tricarboxylic acid cycle enzymes			
Oxidative phosphorylation enzymes			
Vinculin and α-tubulin			
Keratin 8, 18	CD intestinal epithelial cells	Lower in QCD *vs* HC	
Heat shock cognate-70 (HSC70)			
Vinculin and α-tubulin		Higher in QCD *vs* HC	
Fibrinopeptide A (FPA)	CD serum	Higher in CD *vs* HC	Nanni *et al*[62], 2009
Complement 3 protein (C3)			
Apolipoprotein A-IV			
Apolipoprotein E		Lower in CD *vs* HC	
L-lactate dehydrogenase	IBD and HC intestinal epithelial cells	Higher in IBD *vs* HC; Higher in CD *vs* UC	Shkoda *et al*[63], 2007
Carbonyl reductase			
Keratin 19			
Rho-GDI dissociation inhibitor α			
Annexin 2	UC intestinal epithelial cells	Higher in UC *vs* HC	
Programmed cell death protein 8 (PDCD8)			

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; QCD: Quiescent Crohn's disease; QUC: Quiescent ulcerative colitis; HC: Healthy controls; CRC: Colorectal carcinoma.

patients[70-72] . Gazouli *et al*[73] have compared sera before treatment and after IFX induction (week 12) and successfully identified 15 proteins that were differentially accumulated in the sera, most of them modifying the activation of monocytes /macrophages and directly and indirectly regulating the differentiation and activation of CD4+ T-lymphocytes. Also, a recent study by Magnusson *et al*[74] reported on the proteomic analysis on biopsies obtained from 6 UC patients (3 responders and 3 non-responders) treated *in vitro* with or without Infliximab and also from 43 UC patients' sera at different time points: Baseline, week 2 and week 14. Those authors have shown that the response in UC patients is associated with reduced monocyte activation 2 wk after therapy initiation, suggesting that the monocytes of these patients are less responsive to inflammatory stimuli when reaching the intestinal mucosa. In therapy responders Infliximab has had influence on Tenascin C, which might be a down-regulator of the two chemokines CCL2 (mcp-1) and CXCL10 (IP-10)[74], which are produced by inflammatory cells and stromal cells, recruit leucocytes, and are induced in inflamed UC mucosa[75-77]. Table 3 summarized the potential biomarkers identified by proteomics in IBD.

CONCLUSION

In the IBD micro-environment a multitude of components interact. No information about a single gene, a single molecule or microbe can exhaustively explain the events that result from such a complex signaling. Also, the wide range of variability between patients' disease features and medical histories makes it difficult to understand how every component of IBD acts and influences other components. On the other hand,

Table 3 Proteomics in inflammatory bowel disease diagnosis and response to therapy

Proteins	Setting	Diagnostic accuracy	Ref.
Platelet aggregation factor 4 (PF4)	Responder *vs* non-responder's CD serum	Higher in non-responders	Mewuis *et al*[69], 2008
Proteins that regulate $CD4^+$ T-cell activation	Serum before IFX treatment *vs* serum after IFX induction period	Higher before treatment	Gazouli *et al*[73], 2013
Proteins that regulate monocytes/macrophages activation			
Tenascin C	Responder *vs* non-responder's UC serum	Higher in non-responders	Magnusson *et al*[74], 2015

CD: Crohn's disease; UC: Ulcerative colitis.

even if the diagnostic gold standard is endoscopy, the introduction of novel molecular biomarkers in clinical practice has always nurtured hopes for new tools that can lead to improvements in diagnostic accuracy. However, the low diagnostic performance of the available markers strongly limits their use in clinical practice. Still, it is reasonable to hypothesize that combining the modification of several biomarkers may identify a sort of fingerprint for IBD with specific disease features.

Indeed, techniques and methodologies that can deal with a very large volume of data and describe a wide picture, rather than focus on single alteration, are likely to represent the necessary step forward in describing and comprehending IBD[78]. For all these reasons omics can support the discovery of novel molecular interactions through a better definition of relevant biological pathways and interactions, rather than the analysis of the role of the perturbation of a single element. Omics can lead to the identification of representative patterns of disease which may replace simple biomarkers in clinical practice for the diagnosis, monitoring of IBD and for the personalization of therapies and treatments. Exploiting omic techniques and mastering big data analysis will help researchers to embrace the complexity and overcome the limitations of deciphering inflammatory disorders away from any restricted point of view. Table 3 provides a summary of the potential biomarkers identified by proteomics in IBD.

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