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Biomarkers of IBD: from classical laboratory tools to personalized medicine

Emilie Viennois, PhD[1,2,*], **Yuan Zhao, MD, PhD**[1,3], and **Didier Merlin, PhD**[1,2]

[1]Institute for Biomedical Sciences, Center for Diagnostics and Therapeutics, Georgia State University, Atlanta, GA 30302 USA

[2]Atlanta Veterans Affairs Medical Center, Decatur, 30033 USA

[3]Department of Gastroenterology, Zhongshan Hospital, Fudan University, China

Abstract

Diagnostics of inflammatory bowel diseases (IBDs) currently relies on a combination of biological and morphological tests. The current method of diagnostic remains a critical challenge for physicians in part due to their invasiveness and also for their limitations in term of diagnosis, prognosis, disease activity and severity assessment and therapeutic outcomes. Laboratory biomarkers can be used in the diagnosis and management of IBD but none of them has been proven to be ideal. Increasing efforts are being made to discover new biomarkers that can discriminate between the types of IBD, predict future responses to treatment, and aid in differential diagnosis, treatment planning and prognosis prediction. This review addresses the potential for current biomarkers and the emergence of the concept of biomarker signatures in IBD diagnostic and personalized medicine.

Keywords

IBD; Biomarkers; signature

Introduction

IBDs are chronic inflammatory disorders of the gastrointestinal system that affect more than 1 million people in the United States and several million worldwide (1–4). The two major subtypes of IBD are Crohn's disease (CD) and ulcerative colitis (UC). IBD is a substantial public health problem that leads to considerable human suffering and high health costs. Furthermore, the intestinal inflammation associated with IBD is thought to underlie a significant portion of colonic neoplasia, which is a leading cause of mortality in developed countries (5). The diagnosis of IBD relies on a combination of biological and morphological tests, including gastrointestinal endoscopies and histology, and is based on standardized/validated diagnostic criteria (6). Even with these invasive methods, however, it is difficult to make the differential diagnosis between IBD and self-limited colitis, and to distinguish

*Author for correspondence: Institute for Biomedical Sciences, Georgia State University, Atlanta, GA, Tel: 404 413 3598; Fax: 404 413 3580, eviennois@gsu.edu.

between the two main forms of IBD. Furthermore, there are varying degrees of severity among IBD cases, and the responses to standard therapies can vary between patients.

Many aspects of IBD (e.g., diagnosis, prognosis, and the assessments of disease activity, severity, and therapeutic outcome) present challenges for physicians treating this disorder, especially given that there is no single “gold standard” test. Instead, physicians combine symptoms, clinical examinations, laboratory indices, radiological tests, and endoscopic/histologic results to make the diagnosis, assess severity, and predict the disease outcome. Many of these routine procedures are invasive.

Over the past decades, many researchers have sought to identify laboratory biomarkers for IBD, in the hopes of gaining an objective measurement of disease activity (as symptoms are often subjective) while avoiding invasive procedures that are often a burden to the patient. The ideal laboratory biomarker should be: disease-specific; able to identify individuals at risk for the disease; able to detect disease activity; able to monitor the effects of treatment; and prognostically valuable for assessing disease relapse or recurrence. The relevant biomarkers might be miRNAs or proteins found in biological samples such as serum, plasma or tissues. Increasing efforts are being made to discover new biomarkers that can discriminate between the types of IBD, predict future responses to treatment, and aid in differential diagnosis, treatment planning and prognosis prediction. To date, no single biomarker has been proven to possess all of the desired qualities. Some interesting biomarkers have been identified, however. In this review article, we will first provide an overview of the currently available biomarkers for IBD. Thereafter, we will detail and discuss the innovative concept of biomarker signatures, their potential relevance for IBD and the emerging idea of personalized medicine.

I- Currently available biomarkers

a- biomarkers capable of differentiating between CD and UC

Various serological tests have been assessed for their ability to improve the diagnosis of IBD and distinguish CD from UC. These include tests for perinuclear antineutrophil cytoplasmic antibodies (pANCAs) and anti-*Saccharomyces cerevisiae* antibodies (ASCAs) (7).

Antineutrophil cytoplasmic antibodies (pANCAs)—These antibodies, which react to an antigen in the cytoplasm of neutrophil granulocytes, were first reported in 1990 as being found specifically in the sera of UC patients (8). Increased levels of pANCA are common in patients with UC or those with CD associated with UC-like pancolitis (7).

Anti-Saccharomyces cerevisiae antibodies (ASCAs)—ASCAs react to the mannan protein in the cell wall of *Saccharomyces cerevisiae.* Increased titers of ASCA were reported to identify patients with CD with high specificity (95%) but low sensitivity (50%) (7).

Testing for pANCA/ASCA status—The combined use of these two biomarkers appears to offer some benefits. In pediatric patients, testing for $pANCA^{+}/ASCA^{-}$ status identified

UC patients with 70% sensitivity and 93% specificity (9). A meta-analysis of 60 studies comprising 3,841 UC and 4,019 CD patients showed that the $ASCA^+/pANCA^-$ test offered the best sensitivity for CD (54.6%), along with 92.8% specificity (9). A prospective long-term study including 197 IBD-Unclassified (IBD-U) patients showed that half of the patients had negative results for both the ASCA and pANCA tests (10). However, 80% of the $ASCA^+/pANCA^-$ patients were later diagnosed with CD, and 64% of the $ASCA^-/pANCA^+$ patients were later diagnosed with UC. Thus, ASCA and pANCA appear to predict the disease type, but without 100% accuracy, specificity or sensitivity (10) (Table 1).

b- Biomarkers of inflammation

Various biomarkers have been proposed for the objective evaluation of disease activity or inflammation in IBD.

C-Reactive Protein (CRP)—CRP, which is one of the most important proteins of the acute-phase response (11), is a pentameric hepatocyte-secreted protein that is found at a low serum level (< 1 mg/L) under physiological conditions, but is rapidly increased under conditions of acute inflammation. Following an acute-phase stimulus, the CRP level may increase 10,000-fold, from less than 50 μg/L to more than 500 mg/L (12). The hepatocyte-specific production of plasmatic CRP is predominantly controlled at the transcriptional level by the cytokine, interleukin-6 (IL-6). The half-life of CRP is short (about 19 h) compared with other acute-phase proteins; its level increases early after the onset of inflammation and rapidly decreases after the inflammation is resolved (13). Importantly, the CRP response differs between CD and UC patients, who show strong CRP responses *versus* little to no CRP response, respectively (14). Furthermore, symptomatic Crohn's disease patients have significantly higher levels than similar patients with UC, and the levels in Crohn's disease patients correlate well with overall assessments of severity and disease activity (14). Indeed, CRP can not only be used to differentiate CD form UC; its correlation with colonoscopy findings suggest that it may also be used to distinguish quiescent from active disease (15). In addition CRP has been suggested as a useful laboratory tool for supplementing clinical scores in patients with CD, in monitoring the response to treatment and in helping to predict the course of the disease (16) (Table 1). However, CRP is a general biomarker of ongoing inflammation and/or tissue damage, and it is altered in other inflammatory diseases, various cancers (e.g., prostate, ovarian and lung cancers), diabetes, and cardiovascular diseases (17–24). Thus, it should not be taken as being specific to IBD.

Fecal biomarkers—An obvious advantage of fecal biomarkers is the easy access to stool samples from IBD patients. In addition, serum biomarkers might be increased by various inflammatory or pathological conditions other than gut inflammation. Therefore, fecal biomarkers could have a higher specificity for IBD in the absence of gastrointestinal infection. A number of neutrophil-derived proteins present in stools have been studied, including calprotectin and lactoferrin.

Fecal calprotectin: Calprotectin, which was first described in 1980 by Fagertol (25), is released by activated neutrophils and represents more than 60% of the cytosolic proteins in granulocytes. The presence of calprotectin in feces can therefore be considered directly

proportional to the migration of neutrophils to the gastrointestinal tract (13). The first study examining fecal calprotectin as a biomarker for IBD established that patients with Crohn's disease had calprotectin levels above the suggested reference limit of 6740 micrograms/L (26). Since then, fecal calprotectin has been shown to be a useful biomarker for various applications in IBD management, such as differentiating quiescent from active disease (27–30), assessing mucosal healing (31, 32), predicting relapse (33–36), and projecting the therapeutic response (37) (Table 1).

Fecal lactoferrin: Fecal lactoferrin was first described as a biomarker for IBD in 1996 (38). Its levels are significantly increased in the active phase of the disease compared to the inactive phase in both UC and CD. Fecal lactoferrin has been shown to be 90% specific for identifying inflammation in patients with active IBD (39). Similarly to fecal calprotectin, fecal lactoferrin correlates with the response to therapeutics (37, 40), and can be used to differentiate quiescent from active disease (29, 30), assess mucosal healing (32), and predict relapse (34) (Table 1).

However, although fecal calprotectin and lactoferrin are useful tools for assessing the intestinal inflammation in IBD, they do not allow discrimination between CD and UC.

S100A12—S100A12 is part of the S100 calcium binding protein family, whose members participate in proinflammatory processes notably through the activation of the NF-κB pathway (41–43). A study in children described fecal S100A12 as a novel noninvasive biomarker that could be used to distinguish children with active IBD from healthy control subjects with high sensitivity and specificity (44). Fecal S100A12 is significantly increased in severe acute pediatric UC patients and decreases gradually when children are under clinical remission, but does not correlate with the therapeutic response (45). A recent study showed that the fecal S100A12 level is a reliable tool associated with the response to anti-TNF therapy of IBD (46). In addition to IBD, however, S100A12 is also increased in other inflammatory diseases, such as arthritis and Kawasaki disease (47, 48) (Table 1).

Lipocalin-2—Lipocalin-2 (Lcn-2), which is also known as neutrophil gelatinase-associated lipocalin (NGAL), belongs to a family of small secreted proteins that are expressed by a variety of cells, especially neutrophils (49). In UC patients, NGAL overexpression is reportedly upregulated in the colonic epithelium (50) and feces (51). In a study measuring serum and urinary NGAL levels in 181 IBD patients (93 with UC, and 88 with CD) and 82 healthy controls, serum NGAL was found to be elevated in IBD patients compared with healthy controls (52). There was no significant difference between UC and CD patients, but significantly higher levels of serum NGAL were observed in patients with active *versus* inactive IBD (52). In a study published in 2012, Chassaing *et al.* investigated the extent to which fecal Lcn-2 can serve as a sensitive and non-invasive biomarker for intestinal inflammation in the well-studied murine models of dextran sulfate sodium (DSS)-induced colitis and IL-10 deficient spontaneous colitis (53). They demonstrated that fecal Lcn-2 levels correlated with the degree of inflammation, and suggested that Lcn-2 could be a stable, rapid, sensitive and broadly dynamic biomarker for the non-invasive detection of both low-grade inflammation and severe colitis (53). However, Lcn-2 is non-specific, as it is altered in other inflammatory conditions, including chronic kidney injury, cardiovascular

disease, sepsis, chronic obstructive pulmonary disease, pancreatitis, and various cancers (54–58) (Table 1).

II- Biomarker signatures

Although numerous laboratory biomarkers have been investigated and some are currently used in clinic, none is an ideal tool. Some can distinguish between the different subtypes of IBD, indicate disease activity and/or predict relapse or the therapeutic response, but no currently known biomarker can assess all of the desired parameters (Table 1). Indeed, the search for a single ideal IBD biomarker might be an impossible quest. Thus, some researchers are seeking to develop the concept of a biomarker signature, in which a panel of biomarkers is used to assess IBD.

a- Biomarker signatures for various diseases

Numerous studies have sought to identify biomarker signatures for diverse diseases. Wingren *et al.* pointed out that the individual biomarkers that have been identified for pancreatic cancer [e.g., C-reactive protein (CRP), haptoglobin, IGF-binding protein (IGFBP)-1 and CA 19-9] all lack specificity, as they are elevated in both nonmalignant conditions (e.g., pancreatitis and acute cholangitis) and other gastrointestinal cancers (e.g., gastric cancer and colorectal cancer) (59). Thus, the authors set out to identify a serum protein biomarker signature. Using antibody microarray based serum-protein profiling, they identified a serum biomarker signature for pancreatic cancer diagnosis, and showed that it could discriminate between cancer and other inflammatory states of the pancreas (59, 60). Many other research groups have used similar conceptual approaches, focusing on biomarker signatures comprising serum miRNA and/or protein biomarkers.

Proteomic profiling has successfully identified serum protein signatures specific to various pathological conditions or therapeutic responses. Protein panels have been used to: predict which patient groups may benefit more from a certain chemotherapy in metastatic colorectal cancer (61); detect non-small cell lung cancer (62); and predict the disease prognosis in patients with advanced pancreatic cancer (63). Meanwhile, miRNA expression profiling has been shown to distinguish the diagnosis and tumor stage of cancers more accurately than traditional mRNA analysis (64). Hundreds of studies have sought to identify miRNA serum signatures/profiles for different pathological conditions (mostly cancers); such studies have used miRNA panels to detect breast cancer (65), identify metastatic prostate cancer (66), diagnose and predict recurrence for bladder cancer (67), stratify and predict risk in glioblastoma patients (68), detect colorectal cancer (69, 70), discriminate the metastatic subtype of colorectal cancer (71), predict the prognosis and distant metastasis of colorectal cancer (72), perform early detection of pancreatic cancer (73), accurately distinguish malignant cutaneous T-cell lymphoma from benign inflammatory skin disorders (psoriasis, atopic dermatitis, contact dermatitis) (74), and association to lupus nephritis (75). Indeed, Brand *et al.* recently showed that the use of a five-miRNA panel plus cytology improved preoperative pancreatic cancer diagnosis, correctly identifying pancreatic cancer in 91% of positive samples, compared to the 79% sensitivity seen for cytology alone. The combination of cytology and the miRNA signature had a positive predictive value > 99% (76). MiRNA biomarker discovery studies have also been performed using fecal samples for the screening

of colon cancer (77, 78) and pancreatic cancer (79). Together, these studies show that the use of protein and/or miRNA panels can improve the predictive values of the current procedures and out-perform the use of a single biomarker for classifying disease types, giving a prognosis or diagnosis, and predicting the therapeutic response. However, relatively fewer studies have focused on identifying biomarker signatures for IBD.

b- Biomarker signatures for IBD

Proteomic

Circulating protein signature: The proteome represents the net result of interactions between the genetic background and environmental factors, and may be considered as the signature of a disease. Several groups have focused on serum protein profiling in an effort to improve the diagnosis, classification and therapeutic response prediction of IBD. Using matrix-assisted laser desorption/ionization (MALDI) time-of-flight (TOF) mass spectrometry (MS), Nanni *et al.* analyzed serum from 15 CD patients, 26 UC patients and 22 healthy individuals, and were able to separate the three groups with 97% accuracy (80). Meuwis *et al.* used surface enhanced laser desorption ionization (SELDI)-TOF-MS to compare the protein profiles of 120 serum samples collected from four patient groups (Crohn's disease, UC, inflammatory controls and healthy controls) (81). They identified four relevant biomarkers: platelet aggregation factor 4, haptoglobin α2, fibrinopeptide A, and myeloid related protein 8. These proteins were all previously known to be associated with acute-phase inflammation, and the authors showed that their differential distribution among patient groups could help discriminate IBD patients from controls (81). However, this study did not consider changes related to treatment during the early stages of CD or UC. Another study investigated the proteomic profiles of early- *versus* advanced-stage CD in comparison to healthy controls, in order to explore the disease duration- and treatment-related differential expression of acute-phase proteins or protein isoforms characteristic of the pathological status (82). Two-dimensional (2D) electrophoresis followed by MALDI-TOF MS analysis of serum from 13 healthy controls, eight early-stage CD patients and 36 advanced-stage CD patients revealed between-group differences in the protein profiles, with important differences noted in haptoglobin, complement C3, and α1-anti-trypsin (82). Interestingly, complement C3 was specifically deregulated in early CD, suggesting that it could be used to discriminate between different stages of disease progression. In another study, Meuwis *et al*. analyzed whether sera from CD patients could be used to predict the response to anti-TNFα antibody-based (infliximab) treatment (83). Serum samples from 20 CD patients showing clinical responses or non-responses to infliximab were subjected to serum proteomic profiling by SELDI-TOF-MS. The authors verified the four previously identified biomarkers (81), generated a model for predicting the treatment response, and selected relevant potential biomarkers (including platelet aggregation factor 4, which was associated with non-response to infliximab) (83). In an effort to identify a panel of candidate protein biomarkers of CD that might predict the response to infliximab therapy, Gazouli *et al*. recently measured changes in serum protein levels in a small cohort of 18 CD patients, including six primary non-responders (meaning that they did not respond to classical induction therapy), six patients who had responded clinically and serologically to infliximab, and six patients who had achieved clinical and serological remission on infliximab (84).

Serum samples were analyzed using 2D polyacrylamide gel electrophoresis (PAGE), and 240 protein spots were selected for in-gel digestion and MALDI-TOF-MS. The authors successfully identified 15 proteins that were differentially accumulated in the sera of infliximab-responsive and -non-responsive CD patients. Among them, apolipoprotein A-I, apolipoprotein E, basic complement C4, plasminogen, serotransferrin, beta-2-glycoprotein 1, and clusterin were found to be more abundant in the primary non-responder and clinical/serological responder groups compared to the clinical/serological remission group, whereas leucine-rich alpha-2-glycoprotein, vitamin D-binding protein, alpha-1B glycoprotein and complement C1r subcomponent were more abundant in the latter group (84). This study thus showed the feasibility of identifying serum biomarkers capable of predicting treatment outcomes.

The above-described studies used the global serum proteomes of human IBD patients, and yielded results suggesting that it may be possible to identify novel biomarkers for diagnosing disease, differentiating patient groups and predicting therapeutic responses. However, they failed to identify biomarkers capable of predicting disease occurrence. Such information could be highly interesting and could reflect a new potential role for biomarkers.

A longitudinal study to identify protein biomarkers at different stages of the disease: To examine disease activity at different stages, researchers must perform longitudinal studies investigating the same individuals over time. As it would be a complex undertaking to collect serum samples from patients who have not yet developed IBD, researchers have turned to murine colitis models for protein biomarker studies. Multiple animal models of IBD have been developed (85). Although these models do not adequately recapitulate the full complexity of the human disease, they are valuable and indispensable tools for investigating the involvement of various factors in the pathogenesis of IBD. For example, the predictable timing of colitis in the interleukin-10 knockout (IL-$10^{-/-}$) mouse model allows longitudinal assessment of blood samples at various stages of colitis progression. Additionally, the use of a mouse model for IBD biomarker discovery offers researchers a number of benefits, including: easy access to large numbers of samples from a uniform genetic background; a controlled environment; and uniform sample collection. Our group recently published a study in which 2D-differential gel electrophoresis (DIGE) and MALDI-TOF/TOF were used to identify a total of 15 proteins that were differentially accumulated in serum samples from mid- to late-stage colitis in IL-10−/− mice compared to early non-inflamed IL-10−/− mice (86). The identified proteins included alpha-1-B glycoprotein, serpin peptidase inhibitor-clade A-member 1, collagen-type I-alpha 1, contrapsin, haptoglobin, pregnancy zone protein, hemoglobin-alpha-1, histocompatibility-2-Q region locus 10, complement component 3, peroxiredoxin-2, inter-alpha-trypsin inhibitor-heavy chain 4, transferrin, hemopexin, kininogen 1 and thrombospondin 1. The power and innovation of our study rested in the use of a combination of several biomarkers to define a signature for IBD. Studies in two other models of inflammation [dextran sodium sulfate (DSS)-induced colitis and collagen antibody-included arthritis] showed that the biomarker panel identified for IBD included some global inflammation biomarkers, some intestinal inflammation-specific biomarkers, and some chronic intestinal inflammation biomarkers.

This combination of specific and non-specific biomarkers yielded a powerful panel with a unique signature, developed based on longitudinally collected serum samples (86).

MiRNA

Colonic tissue miRNA profiles: Wu *et al.* were the first to examine whether miRNAs were differentially expressed in colonic mucosa samples from IBD patients (87). They demonstrated that active UC was associated with the differential expression of 11 miRNAs, three and eight of which were significantly decreased and increased, respectively, in UC tissues. Of the active UC-associated miRNAs identified in human colonic tissues, miR-192 and miR-21 were the most highly expressed, and macrophage inflammatory peptide-2α, a chemokine expressed by epithelial cells, was identified as a target of miR-192 (87). Other studies focused on specific miRNAs and their associations with target genes. For example, Pekow *et al*. reported that miR-143 and miR-145 were downregulated in UC (88). Another study from our group identified miR-7 as a promising target for therapeutic modulation of CD98, since decreased levels of miR-7 were associated with upregulation of CD-98 in actively inflamed CD colonic tissues compared to healthy patient tissues (89). These two studies identified unique miRNA targets for potential exploitation in therapeutic interventions, but the identified miRNAs might not be valid biomarkers for IBD. In many other studies, differentially expressed miRNA panels have been identified in colonic tissues of IBD patients. For example, Wu *et al.* assayed the expression of 467 miRNAs in patients with sigmoid CD and active terminal ileal CD, and identified five miRNAs associated with active sigmoid CD (miR-19b, miR-629, miR-23b, miR-106a and miR-191) and four miRNAs significantly increased in active ileal CD (miR-16, miR-21, miR-223 and miR-594), compared to control tissues (90). A similar study evaluating the expression of 321 miRNAs in colonic tissue samples from UC and CD patients identified a set of eight miRNAs that defined quiescent IBD *versus* controls, and a distinct subset of 15 miRNAs that could differentiate between quiescent UC and CD (91). Differentially expressed miRNAs were also observed in biopsies from the sigmoid colon of active UC patients, and quantitative PCR analysis confirmed the presence of two deregulated (both upregulated) miRNAs: miR-21 and miR-155 (92). A recent study comparing colonic mucosa biopsies from active UC or CD patients, quiescent UC or CD patients, and healthy controls, identified miR-20b, miR-99a, miR-203, miR-26b, and miR-98 as being upregulated in active UC compared to quiescent UC, CD, and controls (93). Two miRNAs, miR-125b-1* and let-7e*, were upregulated in quiescent UC compared to active UC, CD, and controls (93). In the same year (2013), another paper showed that four miRNAs (miR-18a*, miR-629*, let-7b and miR-140-3p) were higher and three miRNAs were lower (miR-422a, miR-885-5p and miR-328) in the mucosa of active CD patients compared to quiescent CD patients, and two miRNAs were higher (miR-650 and miR-548a-3p) and three miRNAs were lower (miR-630, miR-489 and miR-196b) in the mucosa of active UC patients compared to quiescent UC patients (94). Another study of 2013 focused on five of the miRNAs that Wu *et al.* (90) had identified as being differentially expressed in colonic mucosal tissue of CD active patients compared with healthy controls or UC patients (miR-19b, miR-629, miR-23b, miR-106a and miR-191), and further examined their ability to distinguish classically diagnosed indeterminate IBD (95). The expression levels of miR-19b, miR-106a and miR-629 were found to differ significantly between the UC and CD groups; all five miRNAs differed

significantly between the indeterminate colitis and CD groups; and no significant difference was observed between the indeterminate and UC groups (suggesting that most cases of indeterminate colitis are likely to represent UC) (95). Together, these studies illustrate that miRNAs have potential value as biomarkers and could possibly be developed into miRNA profile-based diagnostic tools. However, the analysis of miRNA profiles in colonic tissues requires the collection of biopsies by colonoscopy, making this an invasive diagnostic method.

Circulating miRNA profiles: In contrast to colonic miRNA, circulating miRNA levels appear to have great potential for use as a semi-invasive (i.e., sampling of whole blood) diagnostic method. Wu *et al.* performed a microarray-based study on whole blood from IBD patients and found a panel of differentially expressed miRNAs that enabled them to distinguish active IBD subtypes from each other and from controls (96). Five miRNAs were significantly increased and two miRNAs (miR-149* and miRplus-F1065) were significantly decreased in the blood of active CD patients compared to healthy controls; 12 miRNAs were significantly increased and one (miR-505*) was significantly decreased in the blood of active UC patients compared to healthy controls; and 10 miRNAs were significantly increased and one was significantly decreased in the blood of active UC patients compared to active CD patients (96). In a similar study, higher concentrations of 11 miRNAs (miR-16, let-7b, miR-195, miR-106a, miR-20a, miR-30, miR-140, miR-484, miR-93, miR-192 and miR-21) were found in the sera of pediatric CD patients *versus* controls (97). Recently, another group identified 11 circulating miRNAs (miR-16, miR-23a, miR-29a, miR-106a, miR-107, miR-126, miR-191, miR-199a-5p, miR-200c, miR-362-3p and miR-532-3p) as being differentially expressed in blood samples from active CD patients *versus* controls, and six miRNAs (miR-16, miR-21, miR-28-5p, miR-151-5p, miR-155 and miR-199a-5p) that were significantly elevated in active UC patients *versus* healthy controls (98). Similarly, Duttagupta *et al*. found seven differentially expressed circulating miRNAs (miR-188-5p, miR-22, miR-422a, miR-378, miR-500, miR-501-5p, miR-7695p and miR-874) expressed in UC patients *versus* controls (99). A recent study identified different serum miRNA expression profiles in UC and CD patients *versus* controls and between UC and CD patients (94). Among the 768 miRNAs analyzed in this study, 21 were differentially expressed between CD (both active and quiescent) and healthy subjects; of them, 14 were expressed commonly in the peripheral blood of CD and UC patients, while the remaining six were expressed specifically in CD patients. Furthermore, six miRNAs were expressed differentially in the serum of active CD patients compared with quiescent CD patients, while 25 miRNAs were expressed specifically in UC patients. Finally, 13 miRNAs were commonly altered in both UC and CD patients (94).

Although relatively few studies have quantitatively assessed circulating miRNA in IBD patients, the results from these experiments demonstrate that it may be possible to develop a semi-invasive test based on miRNAs that are differentially expressed in peripheral blood.

The need for a longitudinal study to identify miRNA biomarkers at different stages of the disease: The existing studies that have focused on circulating miRNA profiles have been performed using IBD patient samples, limiting the feasibility of longitudinal studies. In the

future, it would be useful to perform similar miRNA profiling in blood or serum from mouse models that develop colitis over time. *In vivo* analyses in such models would have the advantage of giving miRNA prediction of the disease development on an individual basis. The development of a concept of biomarker signature from a longitudinal based study can bring the idea of individual signature.

III- Conclusion

Although various biomarkers have been investigated as diagnostic tools for IBD, none has proven ideal to date. Thus, a biomarker signature (protein- and/or miRNA-based), as has been investigated for many other diseases, holds promise for diagnosing IBD, predicting the occurrence of the disease, distinguishing IBD subtypes (CD or UC), and predicting the therapeutic response. Protein biomarkers may be measured for absolute quantification, while miRNA microarrays allow for massive parallel and accurate relative measurement of all known miRNAs, but are less useful for absolute quantification. Our group and others are currently seeking to develop new technologies (e.g., microelectrode miRNA sensors) capable of performing absolute quantification of miRNAs.

Personalized medicine is “an emerging practice of medicine that uses an individual’s genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease” (National Institutes of Health; http://www.genome.gov/glossary/). In the past decade, significant advances have been achieved in personalized medicine in several biomedical domains, particularly oncology (100). In the context of IBD, however, personalized medicine is still in its early stages. A goal of personalized medicine is to identify high-risk patients who would benefit most from aggressive treatment and medication. Circulating miRNAs or protein profiles that can stratify asymptomatic patients or predict therapeutic outcomes have the potential to detect patients at high risk, and thus appear to be promising tools for directing patient management. It is also conceivable that miRNA and protein profiles could be used as prognostic biomarkers and/or to identify patients who would benefit from certain treatments.

In sum, the results of the studies reviewed herein suggest that circulating protein or miRNA signatures may have potential clinical applications and may help in the management of patients with different subtypes of IBD. Compared to the biomarkers currently used in the clinic, biomarker panels should offer increased sensitivity and specificity.

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Table 1

Current biomarkers

Biomarker name	Distinguish CD vs UC (Yes/No)	Specificity for IBD (Yes/No)	Sensitivity (Low/high)	Predictive potential (Yes/No)	Reference
pANCAs ASCAs	Yes Yes	Yes Yes	Low Low	Yes Yes	(7, 9, 10) (7, 9, 10)
CRP	No	No	high for CD Low for UC	Yes	(14–16)
Fecal Calprotectin	No	Yes	High	Yes	(32–36)
Fecal Lactoferrin	No	Yes	High	Yes	(33, 36, 39)
S100A12	No	No	High	No	(43–45)
Lipocalin 2	No	No	High	No	(49–52)

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