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EDITORIAL

Use of blood based biomarkers in the evaluation of Crohn's disease and ulcerative colitis

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Abstract

Despite significant improvements in our understanding of Crohn's disease (CD) and ulcerative colitis (UC) in recent years, questions remain regarding the best approaches to assessment and management of these chronic diseases during periods of both relapse and remission. Various serologic biomarkers have been used in the evaluation of patients with both suspected and documented inflammatory bowel disease (IBD), and while each has potential utility in the assessment of patients with IBD, potential limitation remain with each method of assessment. Given these potential shortcomings, there has been increased interest in other means of evaluation of patients with IBD, including an expanding interest in the role of gene expression profiling. Among patients with IBD, gene expression profiles obtained from whole blood have been used to differentiate active from inactive CD, as well as to differentiate between CD, UC, and non-inflammatory diarrheal conditions. There are many opportunities for a non-invasive, blood based test to aid in the assessment of patients with IBD, particularly when considering more invasive means of evaluation including endoscopy with biopsy. Furthermore, as the emphasis on personalized medicine continues to increase, the potential ability of gene expression analysis to predict patient response to individual therapies offers great promise. While whole blood gene expression analysis may not completely replace more traditional means of evaluating patients with suspected or known IBD, it does offer significant potential to expand our knowledge of the underlying genes involved in the development of these diseases.

Key words: Inflammatory bowel disease; Ulcerative colitis; Gene expression analysis; Whole blood gene expression analysis; Biomarkers; Crohn's disease; Gene

profiling

Core tip: Questions remain regarding the best approaches to the assessment and management of patients with inflammatory bowel disease (IBD) during periods of both relapse and remission. Given the existing limitations of other serologic biomarkers, the development of whole blood gene expression profiling as a non-invasive method of assessment of patients with IBD is appealing. In an era of increased focus on personalized medicine, the potential expansion of our understanding of the genes underlying these diseases and their potential utility in predicting an individual's disease course or response to therapy offers great promise.

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INTRODUCTION

Though great strides have been made in our understanding of Crohn's disease (CD) and ulcerative colitis (UC) in recent years, questions remain regarding the best approaches to assessment and management of these chronic diseases during periods of both relapse and remission. These two subtypes of inflammatory bowel disease (IBD) have a presumed genetic predisposition, which when combined with multiple environmental exposures including changes to the gut microbiome, lead to clinically evident CD or UC. While the traditional evaluation of patients with IBD has been largely centered on endoscopic and radiographic examination, along with histological assessment of biopsy specimens, newer techniques focusing on gene expression profiling have been increasingly utilized to examine the differential expression of genes between disease states and normal. The use of gene expression profiling has significant potential within the field of IBD, both in differentiating CD and UC from non-IBD conditions, as well as determining activity of disease and response to treatment.

CURRENT APPROACHES TO EVALUATION

Various serologic biomarkers have been used in the evaluation of patients with both suspected and documented IBD. Erythrocyte sedimentation rate and C-reactive protein (CRP) are non-specific markers of inflammation that can be elevated in patients with active CD and UC. Although CRP can be useful in differentiating IBD from other non-inflammatory gastrointestinal conditions[1], given their non-specific nature, reliance on these biomarkers alone can be problematic. While CRP is an acute phase protein thought to increase in patients with active IBD, up to 50% of patients with an active flare of UC can demonstrate normal CRP levels[2]. In patients with clinically active CD, normal CRP levels can be noted[3,4], as biomarker levels are not necessarily correlated with mucosal lesions noted on endoscopy[3]. Additionally, certain populations of patients with CD can demonstrate persistently low CRP levels in the setting of active disease, including patients with an ileal disease distribution or low body mass index[5].

Other strategies have been developed in attempts to use serologic testing to differentiate CD from UC, such as the tests for anti-Saccharomyces cerevisiae antibodies (ASCAs) and perinuclear antineutrophil cytoplasmic antibodies (pANCAs). Increased titers of ASCA have been associated with CD, whereas increased levels of pANCA are more commonly seen in patients with UC[6]. However, when evaluated in a meta-analysis of 60 studies, the sensitivity and specificity of a $ASCA^+/pANCA^-$ pattern for identification of CD was only 55% and 93% respectively[7]. In addition to ASCA, multiple other antibodies to bacterial proteins (Omp-C and I2), flagellin (CBir1), and bacterial carbohydrates have been studied and associated with CD, including laminaribioside (ALCA), chitobioside (ACCA[2]) and mannobioside (AMCA). These existing serological markers tend to have low sensitivity and specificity due to the potential for elevation in levels caused by autoimmune diseases, infectious processes, and inflammation outside the GI tract[8].

In contrast to the serologic biomarkers, fecal markers such as fecal calprotectin (FC) and fecal lactoferrin are more specific for intestinal inflammation. FC serves as an indirect estimate of the neutrophil infiltrate in the bowel mucosa. When evaluating a patient with suspected IBD, one meta-analysis concluded that measuring FC can be used as a screening tool for identifying patients who are likely to need endoscopy for further evaluation of suspected IBD[9]. Among patients with previously diagnosed IBD, FC serves as a reliable indicator of disease activity, though it's greatest utility may be in the evaluation of UC[10]. While FC has demonstrated significant utility in differentiating IBD from other chronic abdominal syndromes such as Irritable Bowel Syndrome[1,11], FC does not reliably differentiate between UC and CD[12].

DEVELOPMENT OF NEW BIOMARKERS

Given the shortcomings of these established serologic and fecal biomarkers in the evaluation of a patient with suspected or documented IBD, there has been an increased interest in other means of evaluation, including gene expression profiling. One of the more recent advances in this field has been the development of techniques allowing for the evaluation of mRNA extracted from whole blood[13,14]. The use of whole blood

mRNA gene expression methodology has been validated and utilized to stratify an individual into high and low risk groups for the development of colorectal cancer[15], as well as to predict an individual's current risk for having colorectal cancer[16], Additionally, RNA expression profiles obtained from whole blood have been used to identify patients with other conditions such as lung cancer[17], bladder cancer[18], kidney diseases[19,20], cardiovascular diseases[21-23], osteoarthritis[24], and psychiatric disorders such as schizophrenia and bipolar disorder[25,26]. Among patients with IBD, gene expression profiles obtained from whole blood have demonstrated the ability to differentiate active from inactive CD[27], as well as the ability to differentiate between CD, UC, and non-inflammatory diarrheal conditions[28].

The ability of a blood based biomarker to differentiate active from inactive disease states, as well as the ability to differentiate between CD, UC, and non-inflammatory conditions, holds great promise as a clinical tool in the evaluation of patients with suspected or known IBD. While mucosal biopsy and histologic evaluation remains a gold standard in the traditional evaluation of patients with IBD, the ability of a non-invasive, blood based test to differentiate disease states could indicate significant promise as a tool for monitoring IBD disease activity and predicting response to therapy.

Few studies have evaluated whole blood gene expression analysis as a biomarker and clinical tool in the evaluation of patients with UC and CD. One recent study utilized Affymetrix GeneChip technology to generate genome-wide expression profiles used in the prediction of disease activity in patients with UC and CD[8]. In this study, whole blood gene panels reliably distinguished UC and CD, in addition to determining the activity of disease with high sensitivity and specificity[8]. As previously noted, whole blood gene panels have previously demonstrated the ability to differentiate active CD from CD in remission[27], as well as UC from CD and non-inflammatory diarrhea[28]. One early study utilized transcriptional profiling of peripheral blood mononuclear cell RNA to distinguish UC from CD with high accuracy[29]. Another study used peripheral blood-derived mononuclear cells to evaluate mRNA expression levels among patients with IBD, rheumatoid arthritis, and psoriasis[30]. Using this technique, the authors were able to identify disease specific gene panels that could differentiate each disease type and could separate the disease state from healthy controls[30]. Other authors have used peripheral blood MicroRNAs (miRNAs) to distinguish active CD and UC from healthy controls[31]. Finally, in an evaluation of pediatric patients with IBD, patients in clinical remission had distinct gene expression profiles obtained from peripheral blood leukocytes when compared to healthy controls[32].

Gene expression profiling from mucosal biopsies has also been an area of increasing interest. One prior study utilized gene expression profiling from mucosal biopsies to differentiate between normal mucosa, adenoma, colorectal cancer and IBD[33]. Other studies have utilized gene expression profiles obtained from mucosal biopsies to differentiate patients with UC from controls[34], patients with IBD from infectious colitis[35], and patients with IBD from normal controls[36]. Arijs *et al*[37,38] have published data demonstrating the ability of mucosal gene expression profiles to predict response to infliximab in patients with UC and CD. While each of these studies is indicative of the significant promise for gene expression analysis as a clinical tool in predicting disease activity, response to therapy, and disease course in patients with IBD, the fact that they require mucosal biopsy for analysis makes the non-invasive option for gene expression analysis *via* whole blood potentially more attractive.

When evaluating specific patterns identified by gene expression profiling, trends along biological processes have been identified. In an evaluation of response to infliximab among patients with UC[37] using mucosal biopsies, patterns along several biological functions were identified including immune response, cell to cell signaling, cellular movement, cell death and tissue morphology and development. In addition, there was considerable overlap when the gene sets used in this study were compared to the gene sets identified in patients with the colitis subtype of CD[38]. When evaluating patterns identified by whole blood gene expression analysis, a similar trend around immune functions has been demonstrated. A four gene panel used to differentiate UC from CD included *CD300A* which potentially plays a role in modulating proinflammatory stimuli among neutrophils, as well as *IL1R2* which is involved in cytokine-cytokine receptor interactions[28]. In an evaluation of the ability of biomarkers to predict disease activity among patients with UC and CD, some of the genes that were identified within groups of patients with active disease had previously been associated with UC and CD[39]. These target genes included *NLRP12* (a member of the Nod-like receptor family) and *TAGAP*, which is one of 22 genes previously identified as downregulated at week 8 and week 30 among responders to infliximab in the Active Ulcerative Colitis Trial 1 (ACT 1)[39].

CONCLUSION

Given these recent successes, there remain many opportunities for further utilization of whole blood gene expression analysis to evaluate and treat patients with IBD. Current work is ongoing to evaluate the ability of whole blood gene expression analysis to predict response to biologic therapy for UC and CD. Additionally, given the initial success in differentiating UC from CD and other non-inflammatory diarrheal illnesses, further attention will be paid to the potential clinical utility of whole blood gene expression as a clinical biomarker used in the assessment of patients with IBD. Recent work has demonstrated the utility of whole blood gene expression analysis as a measure of effectiveness of

novel therapies such as leukocytopharesis for UC[40], and further studies will be necessary to evaluate the utility of gene expression biomarkers in monitoring clinical improvement in that population.

Despite the recent successes, some limitations of this expanding area of research must be identified. To date, the majority of the studies evaluating the use of whole blood gene expression analysis in the evaluation of patients with IBD have examined small populations. These small study populations may lead to evaluations of heterogenous patient groups, including patients with varying degrees of disease activity. This introduces heterogeneity into the ultimate population of cells used for the sample analysis, and thus larger studies are still necessary for further exploration. In addition, when target genes have been identified in IBD and other inflammatory conditions, difficulty in the evaluation of which genes represent underlying etiologies and which represent consequences of the disease remains[30].

Each of the significant developments outlined indicates the potential for this non-invasive serologic test to become an important blood based biomarker in the evaluation of patients with IBD. While we do not expect whole blood gene expression analysis to completely replace the traditional means of evaluating patients with suspected or known IBD, it does offer significant potential to expand our knowledge of the underlying genes involved in the development of these diseases. Perhaps most promising, whole blood gene expression analysis offers a non-invasive method of evaluation that may ultimately lead to personalized predictions of disease activity, disease course, and response to therapy.

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