Intestinal Microbiota and miRNA in IBD

Subjects: Gastroenterology & Hepatology

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Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC) and comprises a chronic gastrointestinal tract disorder characterized by hyperactive and dysregulated immune responses to environmental factors, including gut microbiota and dietary components.

intestinal microbiota microRNA dysbiosis inflammatory bowel disease

1. Introduction

Inflammatory bowel disease (IBD) comprises a chronic gastrointestinal tract disorder characterized by hyperactive and dysregulated autoimmune responses and increased intestinal permeability related to environmental factors, including gut microbiota and dietary components, which includes Crohn's disease (CD) and ulcerative colitis (UC), which differ in their pathophysiological and clinical characteristics [1][2].

The current incidence of CD has increased by 11% compared to the incidence three decades ago [3][4]. The etiology is unknown, and genetic, immunological, and environmental factors contribute to the risk of disease onset and progression. A cure remains elusive, and the efficient management of CD requires a multidisciplinary and interprofessional approach [4][5]. The disease can extend to all segments of the gastrointestinal tract, most commonly the terminal ileum and colon. Inflammation is typically segmental, asymmetrical, and transmural, but over time complications such as strictures, fistulas, or abscesses will develop in half of the patients who often require surgery [4][6][7]. Patients with CD frequently suffer from malnutrition and psychological issues and may have to live with a stoma, which could cause significant morbidity and impact the patients' quality of life [4][7]. Current therapeutic strategies aim to prevent disease-related complications and interrupt the disease's recurrence process by prolonging the remission period, whereas personalized medicine and the treat-to-target approach have been the most effective strategies adopted for the control of the inflammatory process [4][7].

UC is a chronic inflammatory condition that causes inflammation of the colon, manifested by continuous lesions and superficial inflammation, which can lead to erosions, ulcers, and bloody diarrhea [8]. The disease is characterized by a relapsing and remitting course, and curative medical therapy is not yet available. Patients with mild or moderate activity are usually unremarkable, apart from blood on rectal examination, whereas patients with a severe attack may exhibit fever, tachycardia, weight loss, abdominal tenderness, abdominal distension, and reduced bowel sounds [8][9].

The management of CD and UC has evolved from the mere treatment of symptoms and induction of clinical remission to more stringent outcomes, including the maintenance of steroid-free remission, the reduction in the number of hospitalizations and surgeries, mucosal and histological healing, improvement in patient-reported outcome, such as the patients' quality of life [7][8][9][10][11], as well as the control of the risk factors associated with the development of colorectal cancer (CRC). The CRC risk is associated with the duration, extent, severity, and persistence of inflammatory activity [8][12], and it is estimated that CRC can account for up to 10% of deaths in patients with IBD [13].

As the etiology of IBD is not fully understood, it is believed that the interaction among genetic, immunological, and environmental factors, such as intestinal microbiota, can trigger the disease. Chronic gut dysbiosis has also been associated with autoimmune diseases such as eczema, asthma, celiac disease, and type-1 diabetes, as well as with diseases related to the consumption of an unbalanced diet, increased inactivity, age, obesity, type 2 diabetes, metabolic and cardiovascular diseases [14][15], liver disorders such as non-alcoholic liver steatosis [16], cancers such as colorectal cancer, and psychological diseases such as depression, anxiety, autism and Alzheimer's disease [17][18][19].

During inflammation in IBD, oxidative stress promotes an increase in pathogenic bacteria at the expense of beneficial bacteria. This can cause an imbalance in the intestinal microbiota, potentially making it a useful biomarker and predictor for stratifying patients with IBD [20][21][22]. Further, microbiota-modulating therapies such as diet, fecal microbiota transplantation, pre- and probiotics, symbiotics, and antibiotics have been studied as potential therapies, thereby demonstrating the importance of intestinal microbiota in IBD patients [22][23][24][25][26].

miRNAs are potential disease markers that have been studied in recent years. miRNAs have been involved in the pathogenesis of IBD and their role has been studied both as a diagnostic biomarker and also as therapeutic targets [27][28]. miRNAs may represent a useful tool in the differentiation between UC and CD, besides being adopted as biomarkers of disease activity, of response to therapy as well as the potential to be used as prognostic markers of disease severity and the presence of complications such as stenosing, penetrating disease and CRC.

Both the intestinal microbiota and miRNAs have been the target of recent studies aimed at gaining an appreciation of their roles and relationship with IBD [29][30][31][32]. Considering that intestinal microbiota and miRNAs are both strongly related to IBD, understanding the role of each in the IBD process can provide vital information that could result in the development of more effective and accurate diagnostic tools and target treatments for patients with IBD.

2. MicroRNAs in Inflammatory Bowel Disease

miRNAs are a group of small (18–24 nucleotides), single-stranded, non-coding RNA molecules that can act as potent negative regulators in gene expression [33][34]. Each miRNA can target hundreds of mRNAs within a given cell type, and a single mRNA is often the target of multiple miRNAs. Thus, miRNAs contribute to the regulation of >30% of protein-coding genes [35]. Several biological processes are regulated by miRNAs, including cell survival,

differentiation, proliferation, apoptosis, cell cycle control, and homeostasis; additionally, specific miRNAs regulate the differentiation of intestinal epithelial cells [33][34].

miRNAs have been extensively studied in multiple types of cancer and have been reported as regulators of tumor suppressors and oncogenes [35]. Although most studies are focused on their aforementioned role, the impact on autoimmune diseases and especially IBD is not fully investigated (**Table 1**). It has been suggested that the critical function of these small RNAs is to contribute to the establishment of immunological homeostasis at mucosal sites [33].

The first study reporting miRNA alterations in IBD patients revealed 11 different expressed miRNAs in patients with UC vs. controls. The miRNAs miR-16, miR-21, miR-23a, miR-24, miR-29a, miR-126, miR-195, and let-7f were increased, whereas miR-192, miR-375, and miR-422b were reduced [36]. Subsequently, several studies have been conducted with the aim of characterizing such alterations in the expression of miRNAs [37][38][39] and, consequently, several of these miRNAs have been suggested as potential biomarkers for CD or UC both in colonic tissues and non-invasive samples such as blood and feces [39][40][41][42].

The distinct miRNA expression was described in tissues from different intestinal regions in patients with active ileal or colonic CD [37]. Three miRNAs were increased (miR-31, miR-215, miR-22), and one miRNA (miR-19b) was decreased in the terminal ileum compared to those in the colon, supporting the likelihood that miRNAs influence different inflammation-related gene expression in each IBD subtype [37].

Another study reported miR-223 as a potential biomarker in the serum of patients with IBD [42]. Patients with IBD had significantly increased serum levels of miR-223 to controls, showing a positive correlation with disease activity in patients with CD and UC. Moreover, miR-223 showed a better disease activity correlation in patients with CD compared to erythrocyte sedimentation rate and high-sensitivity C-reactive protein [42]. In another study, the circulating miR-320a levels were strongly correlated with endoscopic disease activity in patients with CD and UC, highlighting its potential as a non-invasive biomarker in monitoring the control of the inflammatory process [43].

In addition to their potential role in monitoring disease activity, whether in clinical [42], biochemical [42], or endoscopic activity [43], miRNA can also be used as predictors of response to therapy. When evaluating patients with severe UC, Morilla et al. [44] identified 15 miRNAs associated with the response to corticosteroids, 6 miRNAs associated with the response to infliximab, and 4 associated with the response to cyclosporine, in those patients unresponsive to initial corticosteroid therapy, thereby highlighting the role of miRNA as a predictor of response to therapy in IBD. In other study including children with IBD (CD: 17 and UC: 2) who received prednisone or infliximab, miR-146a, miR-320a, and miR-146b decreased with both drugs, correlating to the control of the inflammatory process, and miR-486 showed a significant change in response to prednisone but not to infliximab [45].

Table 1. The main microRNA involved in Inflammatory Bowel Disease patients.

miRNA	In IBD	Target	References
miR10a	Decrease	Inhibit NOD2	[46]
miR-16	Increase in UC	T-cell sub-types	[36]
miR-19b	Decrease in CD		[37]
miR-21	Increase in UC	T-cell sub-types	[36]
miR-22	Increase in CD	Th17 cell	[37]
miR-23a	Increase in UC		[36]
miR-24	Increase in UC		[36]
miR-29	Decrease IL-12 and IL-23 in CD	Through activation of NOD2	[47][48]
miR-29a	Increase in UC	NOD2	[48]
miR-31	Increase in CD		[37]
miR-107	Decrease	IL-23p19 (a subunit of IL-23)	[49]
miR-126	Increase	Regulates VCAM-1	[36][50][51]
miR-143/145	Decrease	Inhibit IGFBP5 (regulate IGF pathway in intestinal epithelial regeneration)	[32][52]
miR-146a	Increase	TNF-α	[45]
miR-146b	Increase	TNF-α	[45]
miR-150	Increase intestinal permeability	c-Myb	[32][53]
miR-155	Increase in UC	SOCS1	[54]
miR-192	Decrease in UC	MIP-2α	[36]
miR-195	Increase in UC		[36]
miR-215	Increase in CD	MIP-2α	[37]
miR-223	Increase	Claudin-8 (a TJ-integral protein)	[42]
miR-320a	Increase		[43][45]
miR-375	Decrease in UC	inhibit KLF5 (antagonist of the goblet cell–differentiation factor KLF4)	[32][36]

miRNA	In IBD	Target	References
miR-422b	Decrease in UC		[36]
miR-486 [48][50]	Increase		[45]
let-7f	Increase in UC	T-cell sub-types	[36]

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olecule-1
(VCAM-1) [50][51], the same mechanism of action of the vedolizumab, also indicated for the treatment of moderate to severe IBD. The miR-155 Suppressor of Cytokine Signaling 1 (SOCS1) targets a regulatory protein of the Janus kinase (JAK) signaling pathway [54], mimicking the use of JAK inhibitors currently available for UC treatment. A review published by Moein et al. [55] clarified the relationship among various miRNAs and the mechanisms involved in the pathogenesis of IBD, including modulations of the inflammatory response through dendritic cells, macrophages, neutrophils, natural killer cells and T cells, dysregulation of TJs, formation of the mucous barrier, and regulation of apoptosis. The elucidation of the role of miRNAs in the inflammatory cascade opens new innovative perspectives for the treatment of IBD, for example, by providing the enhancement of miRNAs that act by inhibiting the inflammatory response (using RNA mimics) or inhibiting the miRNAs that act to perpetuate the inflammatory response (using antagonists of miRNAs).

Relationship of main microRNA with decreased or increased activity in Inflammatory Bowel Disease (IBD). CD: Crohn's disease; IGFBP5: insulin-like growth factor-binding protein 5; KLF5/4: Kruppel-like factor 5 and 4; MIP-2α: macrophage inhibitory peptide; NOD2: nucleotide-binding oligomerization domain 2; SOCS1: Suppressor of Cytokine Signaling 1; Th17: T helper 17; TJ: tight junction; TNF-α: tumor necrosis factor alpha; UC: ulcerative colitis; VCAM-1: Vascular Cell Adhesion Molecule-1.

Changes in the profiles of miRNAs could represent a useful tool in the differentiation of UC and CD, providing important information about the pathophysiology of each disease, prognosis, and response to therapy. Moreover, the identification of the dysregulated miRNA may represent new targets for new therapies focusing on modulation of the inflammatory process via miRNA regulation. Future studies are required for better characterization of the miRNA profile in IBD patients and to clarify the role of miRNAs in triggering and maintaining the inflammatory process in IBD patients and their applications in clinical practice.

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