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Review

Diagnostic and therapeutic value of micro-RNAs in inflammatory bowel disease

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ABSTRACT

Inflammatory bowel disease (IBD) is a heterogeneous chronic idiopathic inflammatory disease that includes ulcerative colitis (UC) and Crohn's disease with uncertain etiology and pathogenesis. The prevalence of IBD has steadily increased worldwide, affecting numerous groups of people in both developed and developing countries. Current guidelines are being re-defined with the aim for patients with established IBD to achieve mucosal healing and complete morphological figures with minimal drug toxicity, to diminish the likelihood of extra-intestinal manifestations and dysplasia/ colorectal cancer, and to prevent the need for surgery. Many patients with established IBD may require conventional treatment, as well as alternative treatment, due to non-response, loss of response, or intolerance to treatment regimen. In this context, stratification of risk and management of IBD could be based on personified strategy predominantly allocated to core components of pathogenesis of the disease. MicroRNAs (miRNAs) are defined as non-coding short RNAs which are involved in various stages of the natural evolution of IBD. Recent animal and clinical studies have shown the role of single nucleotide polymorphisms (SNPs) and signature of miRNAs in susceptibility to IBD, risk of clinical and histological exacerbation, and remission. The aim of the review is to summarize the knowledge regarding use of miRNAs as biomarkers and molecular targets in IBD.

Key words: inflammatory bowel disease, ulcerative colitis, Crohn's disease, miRNAs, biomarkers, prediction, prognosis

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INTRODUCTION

Inflammatory bowel disease (IBD) is defined as a group of complex and heterogeneous chronic idiopathic inflammatory diseases that includes ulcerative colitis (UC) and Crohn's disease[1]. The prevalence of IBD appears to be steadily growing worldwide and affecting people of all ages, sexes, and ethnicities[2]. It has been suggested that several environmental, genetic and immunological factors, as well as particularities of diet, smoking, and metabolic comorbidity states (*e.g.* abdominal obesity, diabetes mellitus, etc.) can modify endothelial expression of pro-inflammatory cytokines and adhesion molecules, thereby playing a pivotal role in the initiation and development of IBD[3–6]. Current guidelines are being re-defined with the aim for patients with established IBD to achieve mucosal healing and have complete morphological figures with minimal drug toxicity. The goal also is to diminish the probability of extra-intestinal manifestations and dysplasia/ colorectal cancer, while preventing the need for surgery[7].

Although the main principles of diagnosing and managing IBD have been well-reported in numerous studies and clinical guidelines[8–10], there is still a lack of clear understanding of the precise etiology and pathogenesis of IBD, which warrants further investigations into novel innate molecular mechanisms of the pathogenesis of the disease[11]. New molecular targets are needed as the basis for targeted therapies as well as for biological markers for risk stratification during treatment[12]. Indeed, new biotechnological drugs, predominantly those such as monoclonal antibodies (mAbs), bispecific antibodies, specific blockers of interleukin [IL]-23, and tumor necrosis factor-alpha (TNF-α), have effectively changed the treatment paradigm for IBD patients previously allocated to be refractory to conventional treatment with corticosteroids and sulfasalazine (5-ASA). Moreover, these new drugs have opened possibilities to reduce surgery rate and hospital admissions, as well as improving quality of life; however, other approaches including risk stratification, treatment efficacy and safety monitoring are still needed in combination[13–15].

In this context, biological markers reflecting several stages of pathogenesis of IBD could be used to individualize risk assessment and created personalized treatment schemes. MicroRNAs (miRNAs) are non-coding RNA molecules involved in the conduction of gene expression, predominantly as negative feedback

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regulators[16]. There is large body of evidence regarding altered miRNA expression and miRNA-related single nucleotide polymorphisms (SNPs) in immunocompetent cells, intestinal cells, resident cells and tissue mononuclear cells; they are drivers for impaired Treg, Th1 and Th17 cell function, B-cell activation and blast transformation, over-expression of inflammatory genes (*e.g.* TNF-α, IL-1β, IL-18, IL-22, IL-23, type I and II interferons IFNβ and IFNγ, etc.) and transcription factors (*e.g.* nuclear factor-κB, Stat1/Stat3, *etc.*), and worsening of post-transcriptional regulation of IL-10 release[17–19]. All these processes are crucial for IBD initiation and development. The aim of the review is to summarize the knowledge regarding use of miRNAs as biomarkers and molecular targets in IBD.

DEFINITION OF MIRNA

By definition, miRNAs are non-coding short RNAs about 24–30 nucleotides long, which shape RNA-protein complexes to mediate and predominantly negatively regulate epigenetic and post-transcriptional gene silencing[20]. According to contemporary nomeclature, miRNAs are a subtype of non-coding RNAs, which also includes other types of these molecules, such as endogenous small interfering RNAs (endo-siRNAs), Piwi-interacting RNAs (piRNAs), and long non-coding RNAs (lncRNAs)[21]. There are two alternative pathways to produce miRNAs: canonical and non-canonical[22]. The most transcribed miRNAs are a result of primary transcription of precursors of miRNA in the canonical pathway, which is characterized by consequently involving RNAse III, DROSHA, and specific microprocessor complex in cell nucleus to cleave pro-molecule and shape miRNA. The canonical biogenesis of miRNA is illustrated in **Figure 1**. First, in the nucleus, Drosha associated with DiGeorge syndrome critical region 8 protein shapes precursor miRNAs (pre-miRNA) from primary miRNA (pri-miRNA) transcripts. The next step in the transcription of miRNA is export of pro-molecule (pre-miRNA) into the cytoplasm with further shortening processing, which is conducted by specific RNase III enzyme Dicer. This enzymatic cascade shapes a respectively unstable, short, double-stranded molecule of miRNA that gives yield to the mature miRNA. The next step affects the incorporation of the single-stranded mature miRNA into the RNA-induced silencing complex, which is the primary target which cleaves the standing miRNA.

An alternative non-canonical biogenesis of miRNA is based on independent mechanisms including both DROSHA and DICER processes in the synthesis of miRNA. In fact, miRNAs are core post-translational regulators of cell functions through modulating activity of the nuclear transcription factor kappa-beta (NF-κB) pathway and promoting development of IBD.

Previous studies have revealed that there have been cell type-specific effects of miRNAs, while numerous miRNAs have not demonstrated tissue specificity; they have exhibited universal effects regardless of the multi-functional crosslink to metabolic responses[23]. The miRNAs are involved in numerous biological processes, such as immunity, cell growth, inflammation, differentiation, proliferation, and apoptosis[24]. Additionally, miRNAs have been discussed as a key player in tumorigenesis through remarkably promoting clonogenicity, cell migration, and invasion[25]. Immune function and biological roles of miRNAs in IBD are presented in **Figure 2**. Development of IBD have been correlated to increased circulating levels of several miRNAs (*e.g.* miRNA-28-5p, miRNA -103-2, miRNA -126, miRNA -151-5p, miRNA -199a-5p, miRNA -320, miRNA -340, miRNA -362-3p, and miRNA -532-3p), and numerous miRNAs have been found in lowered concentrations (*e.g.* miRNA-505)[26]. Although these findings have been revealed to be associated with IBD in the population of patients with known diagnosis, they have not explained whether signature miRNAs or SNPs of miRNAs have caused IBD.

SUSCEPTIBILITY FOR IBD AND SIGNATURE OF MIRNAS

Previous studies have shown that IBD is associated with sophisticated changes in structure and function of intestinal cells and that this process affects expression of several constitutive and inducible enzymes, including metabolizing enzymes (*e.g.*, CYP2C9 and UGT1A1), membrane-associated co-transporters (*e.g.* ABCB1, ABCG2, monocarboxylate transporter 1, organic anion-transporting polypeptide 2B1, and organic cation transporter-like), as well as inflammatory cytokines (*e.g.* IL-33), which were all under control of microRNAs[27–29]. There is an assumption that altered cooperation between inflammatory-induced miRNA expression and membrane-associated regulatory molecules, enzymes and peptides has been implicated in susceptibility of IBD. Yet, SNPs of miRNAs may influence miRNA expression and/or maturation which, if as speculated, is able to translate into specific phenotypic changes.

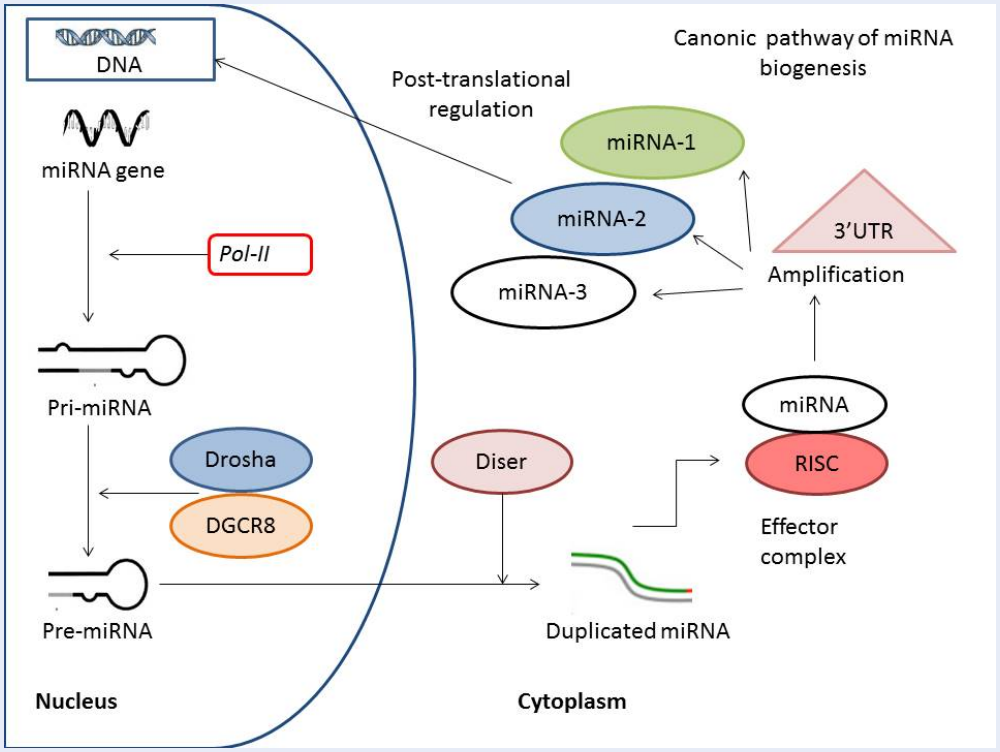

Figure 1: **Biogenesis of miRNA: a canonical pathway. Abbreviations**: DGCR 8: DiGeorge syndrome criticalregion 8 protein, 3′ UTR - 3′: untranslated region, RISC: RNA-silencing complex

Table 1: Most common SNP of miRNAs having clinical significance for patients with IBD

miRNA	SNP	Relation	Significance	Reference
miRNA-146a	rs2910164	Asian population	↓ UC risk	[18]
miRNA-146a	rs2910164	Caucasian population	↓ UC risk	[19]
miRNA-196a2	rs11614913	Asian population	↓colorectal cancer risk	[18]
miRNA-196a2	rs11614913	Caucasian population	↓ UC risk ↓colorectal cancer risk	[19] [28]
miRNA-196a-2	rs11614913	North Indian population	↑UC risk	[29]
miRNA-499	rs3746444	North Indian population	↑UC risk	[29]
miRNA-146a	rs2910164	Chinese population	↑UC risk	[30]
miRNA-149	rs2292832	Chinese population	↑UC risk	[30]
miRNA-196a	rs11614913	Chinese population	↑ risk of transformation of UC into colorectal cancer	[30]

Abbreviations: UC: ulcerative colitis

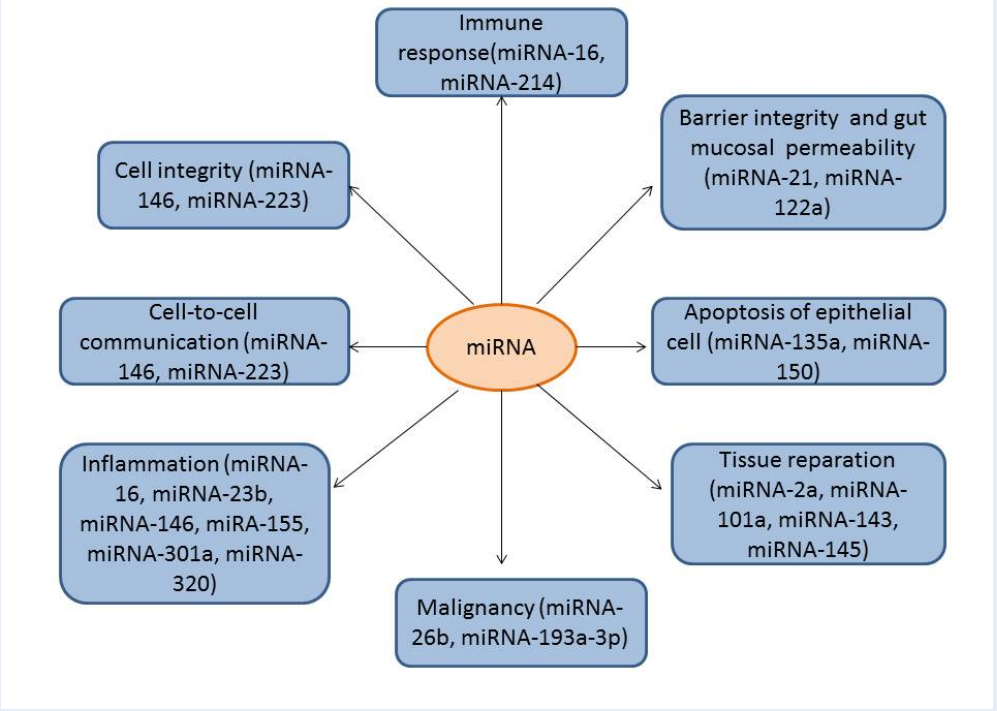

Figure 2: **Immune function and biological role of miRNAs in IBD.**

Table 1 shows the clinical significance of several miRNA polymorphisms in the context of increased susceptibility to IBD and the resulting complications, including colorectal cancer. It has been found that SNP of miRNA-146 rs2910164, but not miR-196 rs11614913, was associated with lowered risk of UC in the Asian population, but not Caucasian population[18]. On the contrary, in the Caucasian population, both miRNA-196 rs11614913 and miRNA-146a rs2910164 polymorphisms were found to be predictors of lowered risk of UC[19]. Moreover, miRNA-196a2 rs11614913 was associated with a lowered risk of colorectal cancer in UC patients, whereas miRNA-146a rs2910164 did not have a similar relation[28]. In a study by Ranjha R *et al.* (2017)[29], SNPs of miRNA-196a-2 rs11614913 and miRNA-499 rs3746444 were found as predictors of risk and prognosis of IBD in the North Indian population. In the Chinese population, SNPs of miRNA-146a rs2910164 and miRNA-149 rs2292832 were found to correspond to risk for developing IBD[30]. Additionally, the authors reported that SNP miRNA-196a rs11614913 indicated a progression of IBD to colorectal cancer[30]. Fisher, SA *et al.* (2008)[31], using genome-wide association scan (GWAS) technique, identified several risk loci (IL-23R, IL-12B, HLA DRB1, and transcription factor genes NKX2-3 and MST1), which were common to UC and Crohn's disease, whereas autophagy genes ATG16L1 and IRGM, along with NOD2, were specific for Crohn's disease only. Therefore, the authors did not observe SNPs in miRNAs genes which corresponded to development of IBD[31]. In fact, SNPs of miRNAs for several pro-inflammatory genes were strongly associated with ethnicity, while the phenotyping equivalent for majority of them have not been sustainable identified. Overall, it has been suggested that the genetic predisposition for IBD could be reflected in specific pre-existing miRNA profiles.

Table 2: Interrelationship between miRNAs expression and IBD developing

miRNA	Type of dysregulation	Gene target	Relation	Significance for IBD	Reference
miRNA-15	downregulation	adenosine A2a receptor	Inflammation-associated processes	Predict gut inflammation	32
miRNA-23b	downregulation	Marcksl	Altered intercellular communication	Predict gut inflammation	33
miRNA-26b	downregulation	E3 ubiquitin ligase DIP1	Inflammation-associated processes	discriminate between UCC and the sporadic colon cancer	34
miRNA-193a-3p	downregulation	IL-17RD	Inflammation-associated processes	Predict neoplasia and colorectal cancer	35
miR-320	upregulation	IL-33/ST2	Gut repair	Predict gut inflammation	36
miRNA-146	upregulation	MyD88; NF-κB; other genes in barrier function and immune protection	Altered proportion of Th17 / Treg and B cells (CD220+) populations	Increasing susceptibility to UC	37,38
miRNA-143 / 145	downregulation	IRS-1, K-RAS, API5, and MEK-2	Expression of IRS-1, K-RAS, API5, and MEK-2 in target cells (HCT116 and HCA7 cells)	predispose to chronic inflammation and neoplastic progression in IBD	39
miRNA-21	upregulation	RhoB	Reduces intestinal barrier function	Predict gut inflammation	40,41
miRNA-28-5p	downregulation	STAT	Inflammation-associated processes	Predict gut inflammation	42
miRNA -142-3p	downregulation	NOD2	autophagy-related pathways	Predict gut inflammation	42
miRNA -122a	downregulation	Occludin	TNFα-induced gut mucosal permeability	Predict gut inflammation	43
miRNA -124	downregulation	AHR	Reduces intestinal barrier function	Predict gut inflammation	44
miRNA -126	downregulation	EGFL7	Regulating cellular adhesion, proliferation, migration and invasion	Apoptotic- and inflammatory-induced tissue injury	42
miRNA -141	downregulation	CXCL12β	Leukocytes tissue infiltration	Predict gut inflammation	45
miRNA -146	downregulation	MIR155 MIR155HG	Impaired barrier function, regulator of inflammation and innate immune system	Predict gut inflammation	38,46

Continued on next page

Table 2 continued

miRNA	Type of dysregulation	Gene target	Relation	Significance for IBD	Reference
miRNA -150	downregulation	C-Myb	Apoptotic-induced gut mucosal permeability	Predict gut inflammation	41
miRNA -214	downregulation	PDLIM2	Inflammatory-induced gut mucosal permeability	Predict gut inflammation	44
miRNA -151-5p	downregulation	FOXO3a	TNF-α-induced gut mucosal permeability	Predict gut inflammation	42
miRNA -155	downregulation	FOXO3a	TNF-α-induced gut mucosal permeability	Predict gut inflammation	47
miRNA -192	downregulation	NOD2	autophagy-related pathways	Predict gut inflammation	42
miRNA -199a-5p	downregulation	IL-17	Gut inflammation	Predict gut inflammation	42
miRNA -301	downregulation	BTG1	Gut inflammation	Inflammatory-induced colon cancer	48
miRNA -320	downregulation	NOD2	autophagy-related pathways	Predict gut inflammation	42
miRNA -375	downregulation	IL-10	Gut inflammation	Inflammatory-induced colon cancer	46

Abbreviations: UC: ulcerative colitis; UCC: associated colorectal carcinoma; DIP1: ubiquitin protein ligase 1; MyD88: Myeloid differentiation primary response 88 protein; NF-kB: nuclear factor kappa beta.

MIRNAS AS A DIAGNOSTIC AND PREDICTIVE TOOL FOR IBD AND ITS COMPLICATIONS

miRNAs are core regulators of inflammation in IBD, which suggests they mediate the process of IBD-to-colorectal cancer transformation. Taking into consideration these findings, miRNAs might have diagnostic and predictive values for patients with established diagnosis of IBD. **Table 2** shows the interrelationship between miRNA expression and IBD development. Benderska, N *et al.* (2015)[34] reported that miRNA-26b, which down-regulates E3 ubiquitin ligase DIP1 in cells of mucosa lamina of intestines, turns out to be a good biological marker for inflammation-associated processes and can be used to predict sporadic colon cancer in patients with established IBD. Pekow, J *et al.* (2017)[35] found that miRNA-193a-3p was downregulated in UC neoplasia and attenuated malignancy in colon through up-regulation of IL-17RD. Notably, this transformation may be maintained not just by altered miRNA expression but by inflammation-associated dysbiosis in the gut lumen via co-stimulation of TLR/NFκB signaling pathway[49]. Meanwhile, epithelial repair and restitution are reported as crucial elements in gut mucosal healing, and antigen stimulation produced by microbiota acts as a modulator of the IL-33/ST2 axis. Thus, miRNAs are warranted for evaluation as a resolution for bowel inflammation. Indeed, epithelial-derived miR-320 has been shown to be able to promote epithelial repair through activation of IL-33/ST2 cooperation; as well, deficiency of miR-320 is considered as a marker of increased inflammatory response[36]. It has been revealed that miRNA-146a was over-expressed in distal colon and in ileum of IBD patients[37]. In fact, miRNA-146a can be found in hematopoietic cells in a microbiota-independent manner[50]. In animal studies, miRNA-146a sufficiently restricted the expansion of numerous T cell gut populations, such as Th17, Tregs, and Tfh cells. Consequently, an association was established between expression of barrier cells and deficiency of miRNA-146a in the intestine[37]. As a result, it has been suggested that miRNA-146a could be involved in the regulation of gut homeostasis besides impacting mucosal surfaces and mediating susceptibility to IBD, although this assumption is needed to be confirmed in clinical studies.

Previously, it has been reported that miRNA-143 and miRNA-145, which promote gut cell repair during stress and injury, could be feedback regulators of inflammatory-induced malignancy in IBD[39,51]. Indeed, miRNA-143 and miRNA-145 were down-regulated in patients with IBD and mediated expression of IRS-1, K-RAS, API5, and MEK-2 in epithelial cells of gut, thereby predicting inflammation and colon cancer[39]. In another study, exaggerated levels of miRNA-21 in UC biopsy materials were found[40]; this molecule mediated intestinal barrier function by acting via target GTPase RhoB. In fact, over-expressed miRNA-21is considered as a key regulator of intestinal epithelial tight junction permeability that increases susceptibility to malignancy. Additionally, down-regulated miRNA-122a was associated with TNFα-induced gut mucosal permeability and maintained gut inflammation[43]. In some animal studies, over-expressed miRNA-150 and miRNA-214 found in UC biopsy materials were associated with apoptotic-induced changes in gut barrier function[41,44]. Although it remains to be established whether these findings are essential for evolution of IBD in humans, there is evidence that transcription of both miRNAs-150 and -214 can be supported by IL-6-upregulated STAT3 in colon tissues[44]. As a result of this action, reduced levels of tensin homolog and PDZ and LIM domain 2 (PDLIM2) can result, leading to phosphorylation of AKT, switch on of NF-κB, and increased activity of IBD. Moreover, expression of miRNA-214 has been well-correlated with morphological changes in the gut of patients with established UC[44]. He, C *et al.* (2017)[48] reported that miRNA-301A could be a promoter of gut inflammation and UC-associated malignancy, resulting in the inhibition of BTG1. Other miRNAs that are potential candidates as inflammatory response promoters (as confirmed in clinical studies) are miRNA-141[45], miRNA-146[38], miRNA-155[47], miRNA-124[44], and miRNA-23b[33]. Zhang & Li (2018)[32] have shown that miRNA-15, which is expressed in colonic tissues of IBD patients, inversely affected the expression of adenosine A2a receptor and also mediated NF-κB cascade which supports inflammation. However, there have been numerous miRNAs up-and down-regulated in IBD and whose diagnostic and predictive roles in UC and Crohn's disease are uncertain. Thus, further investigations are required to scrutinize the complete signature of over-expressed miRNAs.

Paraskevi, A *et al.* (2012)[42] have investigated a wide range of miRNAs and found that miRNA-16, miRNA-21, miRNA-28-5p, miRNA-151-5p, and miRNA-199a-5p were significantly overexpressed in UC and Crohn's disease patients compared to healthy volunteers. However, miRNA-155 was most highly expressed in UC, but not in Crohn's disease. Moreover, miRNA-155 was a potential candidate as biomarker to

distinguish UC and Crohn's disease[46]. On the contrary, Schaefer JS *et al.* (2015)[52] reported on another aberrant miRNA expression profile which indicated IBD. The authors investigated a panel of 89 miRNAs and found a signature of miRNAs which consisted of miRNA-19a, miRNA-21, miRNA-31, miRNA-101, miRNA-146a, and miRNA-375; this signature could serve as biomarkers to discriminate between UC and Crohn's disease. Viennois, E *et al.* (2017)[53] revealed that the signature of miRNAs (up-regulated miRNA-29b-3p, miRNA -122-5p, miRNA -192-5p, miRNA -194-5p, miRNA -375-3p, miRNA -150-5p, miRNA -146a-3p, and down-regulated miRNA-148a-3p and miRNA -199a-3p) had a high discriminatory ability for IBD, associated with Disease Activity Index, and exhibited good specificity for the presence of intestinal inflammation due to Crohn's disease. Identification of deferentially expressed miRNAs affecting autophagy activity, pro-inflammatory cytokine production, and gut repair suggests that this miRNA signature profile could serve as a new diagnostic tool for different types of IBD. Thus, numerous small miRNAs that are up- or down-regulated in IBD can be important in IBD. However, miRNA-155 appears to be a good biomarker for distinguishing UC from Crohn's disease. Perhaps, the determination of a signature (profile) for circulating or expressed miRNAs could be the most reliable diagnostic and predictive tool for IBD.

MIRNA SIGNATURE AS PREDICTOR OF DRUG RESPONSE IN IBD

In fact, in patients with IBD, clinical and histologic remissions do not accompany each other. There is evidence that impaired miRNA profile could be associated with clinical and histologic remission in patients treated with xenobiotic and biologically active anti-inflammatory drugs. Indeed, targeted treatment of UC and Crohn's disease appears to be crucial to identify possible modalities of further action for the drugs, including assays to assess efficacy and toxicity. Minacapelli, CD *et al.* (2019)[53] found that downregulated levels of miRNA-206 during clinically effective long-term mesalamine treatment of UC were associated with maintenance of anti-inflammatory A3 adenosine receptor expression in epithelial cells of the gut[53]. The authors concluded that miRNA-206 expression level can be used as a biological marker for prediction of positive therapeutic response to mesalamine treatment in UC. Perhaps, monitoring the immune status in IBD might be necessary when designing treatment regimens based on combination of conventional xenobiotic drugs (corticosteroids, mesalamine, *etc.*) and biological active drugs, including anti-TNF-α Abs/ blockers of soluble receptors for TNF-α, anti-IL-6 Abs, anti-IL-2 Abs, and anti-IL-8 Abs[54,55]. Additionally, an attractive alternative to control UC could be the choice of optimal treatment taking into consideration the personalized response of each patient with IBD after the initial drug is given. Notably, this approach could be especially intriguing in non-naïve patients treated with TNF-α Abs /antagonists and in IBD patients who are candidates for biological therapies other than TNF-α Abs (ustekinumab, vedolizumab and tofacitinib)[56]. In this context, the miRNA signature is, indeed, a great predictor of response towards treatment and a rational approach for designing personalized treatments[57]. However, there is still limited evidence regarding these assumptions and, therefore, large clinical trials are required in the future to better discern whether biomarker-guided therapy of IBD could be an effective approach for the clinical treatment of IBD as hoped.

CONCLUSIONS

In conclusion,miRNA profiles are dysregulated in patients at risk for IBD and with established diagnosis of UC and Crohn's disease. Determining an altered signature of miRNAs appears to be more preferable over single SNPs or up- and down-regulated RNAs for determining risk of susceptibility for IBD, diagnosis of the disease, transformation of UC/Crohn's disease into colon cancer, as well as predictive response to initial therapy. More clinical trials are also needed to evaluate the role of altered immune phenotype of miRNAs in IBD and in personalized treatment of IBD.

ABBREVIATIONS

3′ UTR: 3′ untranslated region
DGCR 8: DiGeorge syndrome critical region 8 protein
DIP1: ubiquitin protein ligase 1
GWAS: genome-wide association scans
IBD: inflammatory bowel disease
IL: interleukin
mAbs: monoclonal antibodies
mRNA: micro ribonucleic acid
MyD8: Myeloid differentiation primary response 88 protein
NF-kB: nuclear factor kappa beta
RISC: RNA-silencing complex
SNPs: single-nucleotide polymorphisms
Stat: Signal transducer and activator of transcription
TNF-α: tumor necrosis factor α

UC: ulcerative colitis
UCC: associated colorectal carcinoma

COMPETING INTERESTS

Authors have no competing interests.

AUTHORS' CONTRIBUTIONS

Alexander E Berezin: idea of the paper, selection and analysis of the findings, preparing manuscript, review and approvel of the paper.
Eugen Poplyonkin: preparing manuscript, searching and analysis of the raw data.

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