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TOPIC HIGHLIGHT

2016 Inflammatory Bowel Disease: Global view

miRNAs as new molecular insights into inflammatory bowel disease: Crucial regulators in autoimmunity and inflammation

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Abstract

Inflammatory bowel disease (IBD) is characterized by chronic relapsing inflammatory disorders of the gastrointestinal tract, and includes two major phenotypes: ulcerative colitis and Crohn's disease. The pathogenesis of IBD is not fully understood as of yet. It is believed that IBD results from complicated interactions between environmental factors, genetic predisposition, and immune disorders. miRNAs are a class of small non-coding RNAs that can regulate gene expression by targeting the 3'-untranslated region of specific mRNAs for degradation or translational inhibition. miRNAs are considered to play crucial regulatory roles in many biologic processes, such as immune cellular differentiation, proliferation, and apoptosis, and maintenance of immune homeostasis. Recently, aberrant expression of miRNAs was revealed to play an important role in autoimmune diseases, including IBD. In this review, we discuss the current understanding of how miRNAs regulate autoimmunity and inflammation by affecting the differentiation, maturation, and function of various immune cells. In particular, we focus on describing specific miRNA expression profiles in tissues and peripheral blood that may be associated with the pathogenesis of IBD. In addition, we summarize the opportunities for utilizing miRNAs as new biomarkers and as potential therapeutic targets in IBD.

Key words: Autoimmunity; Immune system; Inflammation; Inflammatory bowel disease; miRNA

Core tip: Inflammatory bowel disease (IBD) is characterized by chronic relapsing inflammation in the gastrointestinal tract, but its pathogenesis remains unclear. Further understanding of the molecular mechanisms of IBD is helpful to find new therapeutic strategies. miRNAs play crucial regulatory roles in immune cellular differentiation and maturation, and maintaining immune homeostasis. Aberrant expression of miRNAs is present in IBD. Here, we summarize how miRNAs regulate autoimmunity and inflammation, and describe specific miRNA expression profiles in IBD. We also discuss the opportunities in utilizing miRNAs as new biomarkers and potential therapeutic targets in IBD.

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INTRODUCTION

Inflammatory bowel disease (IBD) comprises ulcerative colitis (UC) and Crohn's disease (CD). IBD is characterized by chronic relapsing inflammation in the gastrointestinal tract, and its incidence and prevalence are increasing[1]. The precise pathogenic mechanism of IBD remains unknown. Accumulated evidence suggests that IBD results from complicated interactions between environmental factors, genetic predisposition, and immune dysregulation. Of these, immune dysregulation is believed to play an important role in the pathogenesis of IBD[2]. Consequently, it is important to uncover the molecular mechanisms that regulate the immune responses in IBD.

miRNAs are a new class of small non-coding RNAs that regulate immune responses in physiologic and pathologic conditions[3]. miRNAs are considered to play significant roles in many biologic processes, including cellular proliferation, differentiation, maturation, and apoptosis[4]. In addition, miRNAs have been implicated in the pathogenesis of common human diseases, such as cardiovascular[5], neurologic[6], and hematologic diseases, cancer[7], and inflammatory and autoimmune diseases[8]. These research findings have led to new insights into IBD pathogenesis.

In this review, we summarize recent findings that miRNAs regulate autoimmunity and inflammation by affecting the differentiation, maturation, and function of various immune cells. We particularly focus on providing evidence of specific miRNA expression profiles in IBD pathogenesis. In addition, we also discuss the possibility for miRNAs as new biomarkers and potential therapeutic targets in IBD.

GENERAL OVERVIEW OF MIRNA

miRNAs are a new class of small (about 22 nucleotides), endogenous, non-coding single-stranded RNA molecules that can negatively regulate target gene expression at the post-transcriptional level[9]. The first miRNA, *lin-4*, was identified in 1993 in *Caenorhabditis elegans*[10]. The miRNA sequence database, miRBase, contains 35,828 mature miRNAs in 223 species at time of publication (http://www.mirbase.org/, Release 21, June 2014)[11].

miRNA genes are located either within intronic sequences of protein-coding genes, within intronic or exonic regions of non-coding RNAs, or within intergenic regions[12]. The biogenesis of miRNAs includes two parts: one is transcription in the nucleus, and the other is generation of mature miRNAs in the cytoplasm. First, miRNA is transcribed from the genome by RNA polymerase Ⅱ or Ⅲ to generate primary miRNA[13,14]. The primary miRNA is then cleaved by RNase Ⅲ-type enzyme Drosha to produce a pre-miRNA of approximately 70 nucleotides with a stem-loop structure in the nucleus[15]. Next, the pre-miRNA is exported to the cytoplasm by Exportin 5[16]. Once in the cytoplasm, the pre-miRNA is cleaved by Dicer in cooperation with protein partners, into an approximately 22-nucleotide miRNA duplex[17]. Then, one strand is selected as a functional miRNA, while the passenger strand is degraded. The functional miRNA is loaded into the RNA-induced silencing complex and acts as a guide strand that recognizes the target mRNA by complementary sequences[18]. Full complementarity occurs in plants, resulting in target mRNA degradation. However, incomplete complementary binding occurs in humans, and this leads to mRNA destabilization and translational inhibition[12].

MIRNAS AND THE INNATE IMMUNE SYSTEM

The innate immune system forms the first line of host defense, which is non-specific, and responds to pathogens in a generic way. It is comprised of tissue barriers, immune cells, and immune molecules. The tissue barriers include mechanical (epithelial) barriers, chemical barriers such as antimicrobial peptides, and biologic barriers (commensal flora). The innate immune cells include monocytes/macrophages, dendritic cells (DCs), neutrophils, natural killer (NK) cells, NK T cells, mast cells, eosinophils, and basophils. These cells perform phagocytosis, antigen presentation, and activation of the adaptive immune responses[19]. miRNAs regulate autoimmunity and inflammation by affecting the differentiation, maturation, and function

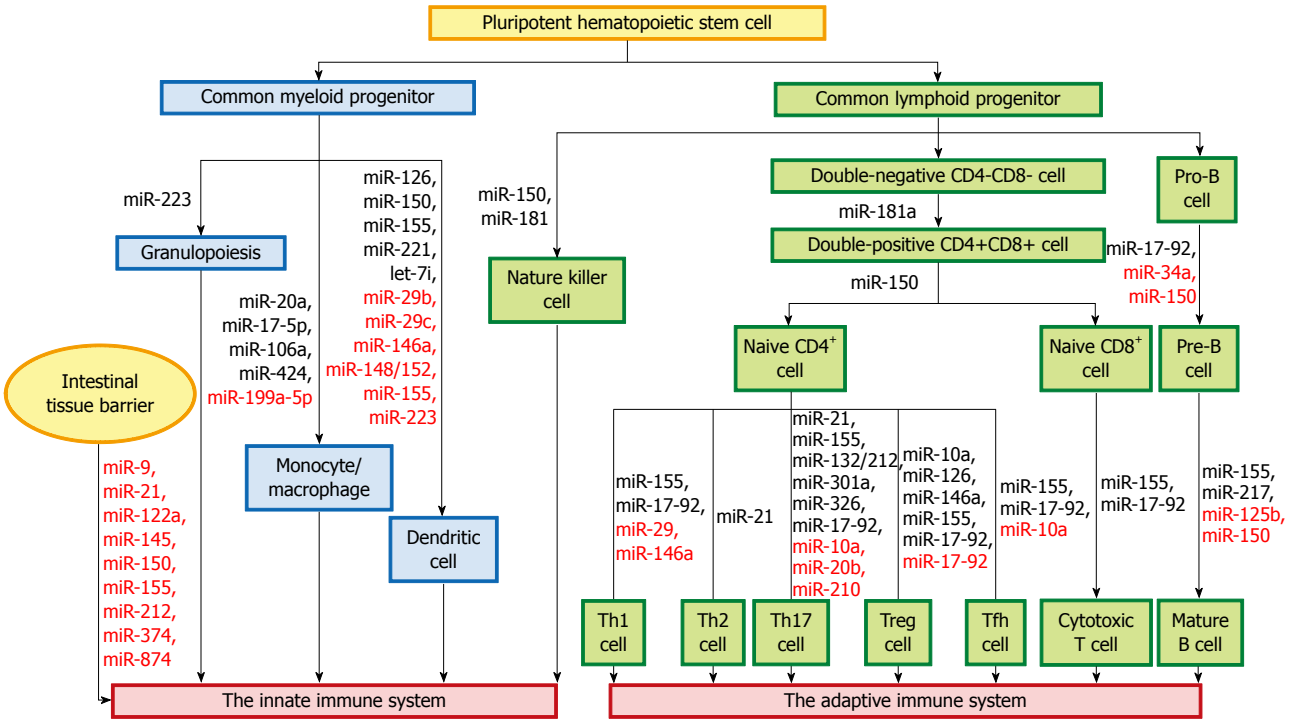

Figure 1 miRNAs and the immune system. miRNAs regulate autoimmunity and inflammation by affecting the differentiation, maturation, and function of various immune cells. The miRNAs in black letters are positive regulators in maintaining the differentiation and function of immune cells, while those in red letters act as negative regulators of these processes.

of various immune cells (Figure 1).

miRNAs and intestinal tissue barriers

The intestinal mucosa forms a barrier that separates luminal contents from the interstitium. Tissue barriers include tight junctions (TJs), adherens junctions, and desmosomes, which regulate the paracellular permeability of epithelial layers across the apical/basolateral axis[20]. The main protein complexes of TJs are composed of transmembrane proteins such as claudins, occludin and junctional adhesion molecules[21]. Disruption of the intestinal barrier has been shown to be an important pathogenic mechanism contributing to the development of intestinal inflammation[22,23]. McKenna *et al*[24] reported that miRNAs are important for maintaining the function of intestinal barriers.

miR-21, which is overexpressed in chronic UC, induces the degradation of Ras homolog gene family member (Rho)B mRNA and leads to an increase in intestinal epithelial permeability due to the loss of TJ proteins and ultrastructural changes[25]. miR-150 is significantly elevated in colon tissue in dextran-sulfate-sodium-induced murine experimental colitis and active UC patients. Overexpression of miR-150 results in intestinal epithelial disruption through targeting of c-Myb[26]. Both occludin and claudin-1 have been demonstrated to be involved in miR-874-induced intestinal barrier dysfunction by targeting the 3′-untranslated region of aquaporin 3[27]. miR-9 and miR-374 directly target the 3′-untranslated region of claudin-14 mRNA, leading to claudin-14 mRNA translational repression and decay, in a cooperative manner[28]. miR-145 impairs TJ function by repressing junctional adhesion molecule-1 expression[29]. miR-212 impairs the intestinal epithelial barrier by downregulating zonula occludens-1 protein expression, which is another major component of TJs[30].

Tumor necrosis factor (TNF)-α is an essential mediator of inflammation in the gut. Anti-TNF-α therapy induces remission in patients with severe active CD[31], UC[32], and refractory celiac disease[33]. TNF-α-induced upregulation of miR-122a mediates the degradation of occludin mRNA in enterocytes and influences their permeability[34]. TNF-α-induced miR-155 overexpression inhibits synthesis of zonula occludens-1 by downregulating RhoA expression[35].

miRNAs and monocytes/macrophages

Monocyte/macrophage differentiation is an essential branch of hematopoiesis, which is under the control of a complex network of regulatory factors[36]. During monocytopoiesis, the transcription factor acute myeloid leukemia (AML)1 is upregulated, while miRNAs-17-5p/20a/106a are downregulated. Monocytopoiesis is regulated by a circuitry comprising sequential miRNAs-17-5p/20a/106a, AML1, and monocyte colony-stimulating factor receptor, whereby miRNAs-17-5p/20a/106a act as a master gene complex that negatively regulates AML1 expression[37]. The transcription factor PU.1 upregulates miR-424 expression, and this induces monocyte differentiation *via* miR-424-dependent translational inhibition of nuclear factor (NF)I-A. This result indicates an important role of miR-424 and its target NFI-A in

controlling monocyte/macrophage differentiation[38]. miR-199a-5p targets the activin A receptor type 1B gene, leading to decreased expression of CCAAT/enhancer binding protein α, and eventually, inhibits monocyte/macrophage differentiation[36].

miRNAs and DCs

DCs serve as the most potent antigen-presenting cells, responsible for primary immune responses. Accumulating evidence highlights the importance of specific miRNAs in DC development, antigen-presentation capacity, and cytokine release[39]. miR-146a[40], miR-155[41], and let-7i[42] are involved in the maturation and functional state of DCs, while miR-148/152[43] and miR-223[44] are involved in their antigen-presentation capacity. miR-150 is required for the cross-presentation capacity of Langerhans cells (skin-resident DCs)[45]. In addition, miR-29b, miR-29c[46], miR-126[47], miR-146a[40,48], miR-155, and miR-221[49] have been shown to regulate DC apoptosis and cytokine production.

miRNAs and NK cells

NK cells are cytotoxic lymphocytes that play a vital role in host defense against infection, and they mediate antitumor responses. Recent advances have demonstrated that miRNAs are crucial in NK cell biology[50]. For instance, miR-150 and miR-181 regulate NK cell development[51,52]. Mice lacking miR-150 are defective in generating mature NK cells. On the contrary, transgenic mice with a gain-of-function miR-150 have enhanced NK cell development[51]. miR-181 promotes NK cell development by targeting Nemo-like kinase, which is a inhibitor of Notch signaling[52].

miRNAs and other kind of innate immune cells

Invariant NK T cells are a separate subset of T lymphocytes with innate effector functions. A Dicer-dependent miRNA pathway is important in the regulation of invariant NK T cell differentiation, function, and homeostasis[53]. The normal granulocytic differentiation requires the zinc finger protein growth factor independent-1, which is a transcription inhibitor that regulates the expression of miR-21 and miR-196b during myelopoiesis[54]. In addition, miR-223 plays a crucial role in the regulation of granulocyte differentiation and function, and mediates inflammatory responses[55,56].

miRNAs and activation of the innate immune system

Pattern recognition receptors are critical for the recognition of microorganisms and the induction of immune and inflammatory responses[57]. The families of these proteins include the membrane-bound Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors, and retinoic acid-inducible gene-I-like receptors[58]. Pattern recognition receptors promote downstream signaling cascades. Emerging evidence indicates that miRNAs regulate these processes.

TLRs: miR-146a expression can be induced through exposure to TLR ligands, such as lipopolysaccharide, peptidoglycan, and flagellin, and this induction is controlled by NF-κB. Mice lacking miR-146a are more likely to develop autoimmune diseases, tumorigenesis, and myeloid cell proliferation. miR-146 targets TNF-receptor-associated factor 6 and interleukin (IL)-1-receptor-associated kinase 1, which are key elements of the myeloid differentiation factor 88 pathway, and form a negative feedback mechanism in TLR signaling[59-61]. miR-155 expression is also induced by TLR signaling[61,62]. Unlike miR-146a, miR-155 promotes the immune response. Mice deficient in miR-155 are highly resistant to experimental autoimmune encephalomyelitis[63].

NOD-like receptors: Of this family of proteins, NOD2 functions as an intracellular sensor that contributes to inflammation and immune defense. It has been identified as the strongest single genetic locus in determining susceptibility in CD[64]. A miRs-NOD interaction has been implicated in IBD. These miRNAs include miR-29[65], miR-122[66], miR-146a[67], and miR-192[68]. For example, polymorphisms in NOD2 impair miR-29 expression in DCs, and this results in exaggerated IL-23-induced inflammation[65]. miR-122 targeting of NOD2 has a crucial role in the damage of intestinal epithelial cells induced by lipopolysaccharide[66].

MIRNAS AND THE ADAPTIVE IMMUNE SYSTEM

The adaptive immune system mainly consists of two different lymphocytes (T and B cells), and is highly pathogen specific. The appropriate development and function of these two immune cells are essential when distinguishing foreign from resident antigens. Current studies have indicated that miRNAs play important roles in maintaining the differentiation and function of T and B cells[69].

miRNAs and T-cell regulation

Increasing evidence shows that some specific miRNAs participate in the regulation of crucial immune functions. These immuno-miRs play significant roles in T-cell development, maturation, activation, differentiation, and aging[70]. For example, miR-150[71] and miR-181a[72] are involved in T-cell development, while miR-21[73] and miR-17-92 cluster[74,75] participate in T-cell activation.

miRNAs and T-helper 1/2 cell differentiation

miRNAs have significant effects on T helper (Th) cell

differentiation. Naïve T cells can differentiate into Th1, Th2, or Th17 cells after activation[76]. Th1 cells have been associated with the pathogenesis of CD, while Th2 cells have been implicated in UC[19]. miR-155 promotes Th1 differentiation by targeting interferon (IFN)-γ receptor α chain[77]. In contrast, $CD4^+$ T cells deficient in miR-155 display a bias towards Th2 differentiation, which is partly due to increased expression of the Th2-associated transcription factor c-Maf[41,78]. miR-17-92 cluster promotes Th1 differentiation. The function of miR-19b is mediated through phosphatase and tensin homolog, while miR-17 targets transforming growth factor (TGF)-β receptor Ⅱ and cAMP-responsive element-binding protein 1[79]. miR-29 regulates Th cell differentiation by directly targeting T-box transcription factor T-bet and eomesodermin to suppress IFN-γ production[80]. miR-146a may be a potent inhibitor of Th1 differentiation by targeting protein kinase Cε[81]. miR-21 promotes Th2 differentiation[82].

miRNAs and Th17 cell differentiation

Th17 cells, a new subset of Th cells capable of producing IL-17, play a vital role in the formation of several autoimmune-mediated inflammatory diseases, including IBD[83,84]. Current studies demonstrate that miR-21[85], miR-155[63], miR-301a[86], miR-326[87], miR-17-92 cluster[88], and miR-132/212 cluster[89] act as positive regulators of Th17 differentiation. For example, miR-155 enhances the development of inflammatory T cells (Th1 and Th17 cells), and facilitates Th17 cell formation through cytokines produced by DCs[63]. miR-10a[90], miR-20b[91], and miR-210[92] act as negative regulators of Th17 differentiation. Deletion of miR-210 promotes Th17 differentiation under hypoxic conditions[92].

miRNAs and regulatory T cells

Regulatory T (Treg) cells are another subset of $CD4^+$ T cells that can suppress activity of effector T cells and maintain self-tolerance[76,90]. Treg cells can be classified into two populations, naturally-occurring Treg (nTreg) cells that are generated in the thymus, and inducible Treg (iTreg) cells that arise from naïve $CD4^+$ precursors in the periphery[90]. miRNAs play pivotal roles in the regulation of both Treg cell development and function[93,94]. miR-10a is highly expressed in nTreg cells and can be induced by retinoic acid and TGF-β in iTreg cells[90]. Repression of miR-10a *in vitro* results in reduced forkhead box (Fox)p3 expression levels, while ablation of miR-10a does not affect the phenotype or number of nTreg cells[93]. miR-155-deficient mice display a marked reduction in the number of Treg cells. Additionally, miR-155 maintains homeostasis of Treg cells by targeting suppressor of cytokine signaling 1 *via* the IL-2 signaling pathway[95]. miR-146a is important for maintaining suppressive function of Treg cells. Treg cells deficient in miR-146a lead to immunologic intolerance by targeting signal transducer and activator of transcription-1[96]. Silencing of miR-126 can influence the expression of Foxp3 on Treg cells and impair their suppressive function *via* the PI3K/Akt pathway[97]. miR-17-92 cluster is also involved in Treg cell function. Mice with Treg-specific loss of miR-17-92 cluster develop an exacerbated form of experimental autoimmune encephalomyelitis and fail to achieve clinical remission[74]. However, there are conflicting results. For instance, the study from Jiang *et al*[79] showed that miR-17-92 cluster prevents Treg cell differentiation and promotes Th1 responses.

miRNAs and follicular helper T cells

Follicular helper T (Tfh) cells are a novel subset of $CD4^+$ T cells that can provide help to B cells, and they are important for germinal center formation[98]. Several studies have demonstrated that miRNAs are crucial for Tfh cell differentiation and function[99,100]. Mice with T-cell-specific loss of miR-17-92 cluster exhibit severely compromised Tfh cell differentiation, germinal center formation, and antibody responses. On the contrary, T-cell-specific miR-17-92 cluster transgenic mice spontaneously accumulate Tfh cells[99]. miR-10a attenuates phenotypic conversion of iTreg cells to Tfh cells by simultaneously targeting Bcl-6, a transcription factor critical for Tfh cell differentiation[101], along with the corepressor Ncor2[90]. Moreover, miR-155 has been reported to promote Tfh cell development[102].

miRNAs and $CD8^+$ T cells

$CD8^+$ T cells or cytotoxic T lymphocytes can devastate various intracellular pathogens and malignancies[103]. Dicer is required for $CD8^+$ T-cell survival and accumulation, but not required for the early steps in $CD8^+$ T-cell activation[104,105]. Dicer and miRNAs such as miR-139 and miR-150 also participate in controlling the cytolytic program, as well as other programs of effector cytotoxic T lymphocyte differentiation[106]. miR-155 is demanded for effector $CD8^+$ T-cell responses to viral and intracellular bacterial infection and cancer. miR-155 has the potential to be a target for immunotherapy for infectious diseases and cancer[103,107,108]. miR-17-92 cluster has dynamic regulation of $CD8^+$ T cells differentiating from naïve to effector and memory states[75,109].

miRNAs and B cells

Ablation of Dicer in early B-cell progenitors leads to a formative block from the pro-B to pre-B transition[110]. miRNAs are also involved in B-cell development and function[110,111], including miR-34a[112], miR-150[113,114], and miR-17-92 cluster[115]. miR-125b inhibits B-cell differentiation in germinal centers[116]. In addition to regulating B-cell differentiation, miR-150[113], miR-155[78], and miR-217[111] regulate B-cell function, including the establishment of B-cell tolerance, as well as antigen-dependent and -independent antibody repertoire diversification.

Table 1 Aberrantly expressed miRNAs in inflammatory bowel disease

Sample type	Expression	miRNAs	Ref.
Ulcerative colitis *vs* healthy controls			
Mucosal tissues	Upregulated	miR-7, miR-16, miR-20b, miR-21, miR-23a, miR-24, miR-29a, miR-29b, miR-31, miR-125b-1*, miR-126, miR-126*, miR-127-3p, miR-135b, miR-146a, miR-150, miR-155, miR-195, miR-206, miR-223, miR-324-3p, miR-424, and let-7f	[25,26,117-122]
	Downregulated	miR-188-5p, miR-192, miR-200b, miR-215, miR-320a, miR-346, miR-375, and miR-422b; miR-124 (pediatric cases)	[117,119,123,124]
Peripheral blood	Upregulated	miR-16, miR-21, miR-28-5p, miR-103-2*, miR-151-5p, miR-155, miR-188-5p, miR-199a-5p, miR-340*, miR-362-3p, miR-378, miR-422a, miR-500, miR-501-5p, miR-532-3p, miR-769-5p, miR-874, and miRplus-E1271	[125-127]
	Downregulated	miR-505*	[126]
Crohn's disease *vs* healthy controls			
Mucosal tissues	Upregulated	miR-9, miR-21, miR-22, miR-26a, miR-29b, miR-29c, miR-30b, miR-31, miR-34c-5p, miR-106a, miR-106b, miR-126, miR-126*, miR-127-3p, miR-130a, miR-133b, miR-146a, miR-146b-5p, miR-150, miR-155, miR-181c, miR-196a, miR-196, miR-206, miR-324-3p, miR-375, and miR-424	[119,121,130,131]
	Downregulated	miR-7 and miR-141	[128,129]
Peripheral blood	Upregulated	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; miR-16, miR-20a, miR-21, miR-30e, miR-93, miR-106a, miR-140, miR-192, miR-195, miR-484, and let-7b (pediatric cases)	[125,133]

MIRNAS AND IBD

Abnormal miRNA expressions exist in some diseases, including IBD (Table 1). This offers a new way to improve our comprehension of the mechanism of this disease. Moreover, some specific miRNAs in IBD may serve as potential biomarkers for diagnosis, evaluation indicators of disease activity, or targets for treatment.

miRNAs in UC

miRNAs in mucosal tissues: In 2008, the first profiling study of altered expression of miRNAs in IBD patients was published[117]. Wu and colleagues[117] found a specific miRNA expression pattern: three miRNAs (miR-192, miR-375, and miR-422b) were markedly downregulated, whereas eight miRNAs (miR-16, miR-21, miR-23a, miR-24, miR-29a, miR-126, miR-195, and let-7f) were observably upregulated in active UC tissues. Furthermore, they found that miR-192 participated in the regulation of chemokine production in colonic epithelial cells. Since 2008, some new research in active UC and healthy controls has confirmed the upregulation of miR-21[25,118], miR-29a[119], and miR-126[120], and identified additional upregulated miRNAs, including miR-7, miR-29b, miR-126*, miR-127-3p, miR-135b, miR-223 and miR-324-3p[119], miR-31[119,121], miR-150[26], miR-155[118], miR-146a, miR-206, and miR-424[121], and miR-20b and miR-125b-1*[122]. In contrast, miR-188-5p, miR-215, miR-320a, miR-346[119], and miR-200b[123] were downregulated in colon tissues from active UC patients compared with healthy controls. miR-124 was markedly decreased in pediatric but not in adult UC tissues. Reduced levels of miR-124 in colon tissues appear to increase the expression and activity of signal transducer and activator of transcription-3, and this mediates the pathogenesis of UC in children[124].

miRNAs in peripheral blood: Paraskevi and colleagues[125] found that six miRNAs (miR-16, miR-21, miR-28-5p, miR-151-5p, miR-155, and miR-199a-5p) were remarkably upregulated in blood from UC patients compared with healthy controls. miR-155 had the highest expression level of these six UC-associated miRNAs in peripheral blood. Wu and colleagues[126] found that compared with healthy controls, 12 miRNAs were significantly upregulated, and miRNA-505* was downregulated in blood from active UC patients. Peripheral blood miRNAs may distinguish active UC patients from healthy controls. As compared to active CD patients, ten miRNAs were markedly upregulated, and one miRNA was downregulated in blood from active UC patients[126]. Duttagupta *et al*[127] completed analyses of miRNA expressions from different hematologic fractions as noninvasive predictors for incidence of UC. They found that seven miRNAs derived from platelets (miR-188-5p, miR-378, miR-422a, miR-500, miR-501-5p, miR-769-5p, and miR-874) were upregulated. This study provides new platelet-derived miRNA biomarkers for clinical application and perception of the potential roles of these miRNAs in the pathogenesis of UC.

miRNAs in CD

miRNAs in mucosal tissues: Most studies of miRNA expression profiles in CD have concentrated on Crohn's colitis. Fasseu *et al*[119] found that 23 miRNAs (miR-9, miR-21, miR-22, miR-26a, miR-29b, miR-29c, miR-30b, miR-31, miR-34c-5p, miR-106a, miR-126, miR-126*, miR-127-3p, miR-130a, miR-133b, miR-146a, miR-146b-5p, miR-150, miR-155, miR-181c, miR-196a, miR-324-3p, and miR-375) were remarkably upregulated in colonic tissues from CD patients compared with healthy controls. Five of these miRNAs were specific for patients in

an active stage of CD (miR-9, miR-126, miR-130a, miR-181c, and miR-375), whereas the remaining 18 were also upregulated in colonic tissues from inactive CD patients. Huang and colleagues[128] identified that miR-141 was downregulated in inflamed colon tissues from active CD patients. miR-141 inhibited colonic chemokine CXC ligand 12β expression by directly targeting it and blocked colonic immune cell recruitment. Nguyen and colleagues[129] found that only miR-7 was downregulated in eight active colonic CD patients compared to six healthy controls. In addition, miR-206, miR-424[121], miR-106b[130] and miR-196[131] are also upregulated in active colonic CD.

However, is there any tissue-specific miRNA expression profile in the gastrointestinal tract? Wu and colleagues[132] examined miRNA expression patterns in tissues from different intestinal segments in active CD patients. Ten intestine-specific miRNAs (miR-19b, miR-22, miR-23a, miR-26a, miR-31, miR-126, miR-215, miR-320, miR-422b, and let-7d) were identified. Specifically, three of these (miR-22, miR-31, and miR-215) were markedly upregulated in the terminal ileum compared with colon tissue, while miR-19b was downregulated in the terminal ileum. Moreover, miR-23a, miR-26a, miR-126, miR-320, miR-422b, and let-7d showed colon-specific expression. In active colonic CD patients, three miRNAs (miR-23b, miR-106, and miR-191) were upregulated and two (miR-19b and miR-629) were downregulated compared to healthy controls. In active terminal ileal CD patients, four miRNAs (miR-16, miR-21, miR-223, and miR-594) were upregulated in terminal ileal tissues.

miRNAs in peripheral blood: Apart from assessing miRNA expressions in peripheral blood in UC, Paraskevi *et al*[125] examined miRNA expression patterns in peripheral blood samples from 128 patients with active CD and 162 healthy individuals. Eleven 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) were markedly upregulated in peripheral blood from CD patients as compared with healthy individuals. There were no significant differences in miRNA expressions in accordance with disease location and phenotype.

Zahm *et al*[133] examined serum samples from 46 pediatric CD patients and 32 healthy controls by means of a low-density microarray and quantitative reverse transcriptase (qRT) PCR. They found 11 miRNAs (miR-16, miR-20a, miR-21, miR-30e, miR-93, miR-106a, miR-140, miR-192, miR-195, miR-484, and let-7b) that were CD-associated circulating miRNAs. Receiver operating characteristic analyses indicated that these CD-associated miRNAs had promising diagnostic value, with sensitivities of 70%-83% and specificities of 75%-100%. These results demonstrate that circulating miRNAs may be used as novel noninvasive biomarkers in CD.

miRNAs in IBD at different stages

Iborra and colleagues[134] assessed miRNA expression patterns in serum and tissue samples from nine patients with active UC, nine with inactive UC, nine with active CD, and nine with inactive CD, and serum from 33 healthy subjects. They found that two miRNAs (miR-548a-3p and miR-650) were higher, and three (miR-196b, miR-489, and miR-630) were lower in the mucosa of active UC patients compared with inactive UC patients. There were no differences in serum miRNA expression profiles in patients with active UC compared with inactive UC. However, there were differences in serum miRNA expressions between active and inactive CD patients; two serum miRNAs (miR-188-5p and miR-877) were increased, and four serum miRNAs (miR-18a, miR-128, miR-140-5p, and miR-145) were decreased in patients with active CD. Furthermore, four miRNAs (miR-18a*, miR-140-3p, miR-629*, and let-7b) were higher, and three miRNAs (miR-328, miR-422a, and miR-855-5p) were lower in the mucosa of active CD patients compared with inactive CD patients. These results indicate that there are specific miRNA expression patterns associated with different stages of IBD. Further prospective cohort studies in large samples are necessary to validate these findings.

miRNAs as therapy in IBD

miRNA-related therapeutic applications may represent a new and fascinating field in IBD treatment. miRNA-related therapy is based on antisense technology and gene therapy; thus, it involves either miRNA antagonists or miRNA mimics.

miRNA antagonists: miRNA antagonists include anti-miRNA oligonucleotides (AMOs), miRNA sponges, and miRNA masks.

AMOs: AMOs are synthetic anti-miRNA oligonucleotides with reverse complementary sequences to their target miRNAs, which suppress miRNA functions. It is believed that AMOs have a promising future in therapeutic applications. Chemical modifications of AMOs can improve their stability and binding affinity. Common modifications include addition of different 2′-ribose modifications to AMOs (2′-O-methyl and 2′-O-methoxyethyl) and 2′,4′-methylene bridge-locked nucleic acid (LNA). LNA-modified AMOs create high-affinity binding to target mRNAs[135,136]. A study by Janssen *et al*[137] demonstrated that miravirsen, an LNA-anti-miR-122, is designed to target and inhibit miR-122, and this can reduce viral RNA levels in patients with chronic hepatitis C virus infection. This result proves the possibility of miRNA agents in clinical practice.

miRNA sponges: miRNA sponge technology utilizes plasmid or viral vectors to achieve loss-of-function of miRNAs. The strong promoters can be applied in miRNA sponge vectors for generating high-level expression of the competitive inhibitor transcripts for either transient or long-term inhibition of miRNA function. Considering the merit of sharing a common seed sequence by members of a miRNA family, this technology provides a strong approach for coinstantaneous inhibition of multiple miRNAs of interest with a single inhibitor[138].

miRNA mimicry/replacement therapy: In order to restore miRNA activity, miRNA mimics (synthetic oligonucleotides) and miRNA expression gene vectors are used. MRX34 is a double-stranded miRNA mimic of the naturally occurring miR-34a loaded in liposomal nanoparticles to reestablish its tumor suppressor function. MRX34 was the first miRNA mimic introduced into clinical study for primary as well as metastatic liver cancer in 2013[139,140]. Many miRNAs are down-regulated in UC and CD. For example, miR-192, miR-375, miR-422b[117], miR-188-5p, miR-215, miR-320a, miR-346[119], and miR-200b[123] are decreased in UC, and miR-19b and miR-629[132] are decreased in Crohn's colitis tissues. Theoretically, replenishing these decreased miRNAs by miRNA mimics may provide therapeutic restoration of physiologic functions lost in IBD.

CONCLUSION

In this review, we described the roles of miRNAs as crucial regulators of inflammatory responses and autoimmune disorders, particularly focusing on miRNAs affecting the differentiation, maturation, and function of various immune cells. We also summarized some studies on the current understanding of the connection between miRNAs and IBD. Accumulating evidence suggests that specific miRNA expression profiles exist in IBD, and these miRNAs contribute to the development of inflammation. The definite functions of most miRNAs in IBD have not yet been clarified. Further studies are necessary to validate whether miRNAs could be used to diagnose IBD, distinguish IBD subtypes, and determine the disease activity or location.

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