

MicroRNAs: New therapeutic targets for intestinal barrier dysfunction

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Author contributions: Fan XM conceived the topic and revised the paper; Zhang L reviewed the literature and wrote the paper; Cheng J reviewed the literature.

Supported by Grant for Key Clinical Discipline Construction of Shanghai Municipality, China, No. ZK2012B20; and Phase II Outstanding Young Medical Personnel Training Fund of Jinshan District Health Systems, Shanghai, China, No. JWKJ-RCYQ-201207

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Received: October 28, 2013 Revised: December 9, 2013

Accepted: January 14, 2014

Published online: May 21, 2014

Abstract

Defects in intestinal barrier function characterized by an increase in intestinal permeability contribute to intestinal inflammation. Growing evidence has shown that an increase in intestinal permeability has a pathogenic role in diseases such as inflammatory bowel disease (IBD) and celiac disease, and functional bowel disorders such as irritable bowel syndrome. Therefore, clarification of the inflammatory responses, the defense pathway and the corresponding regulatory system is essential and may lead to the development of new therapies. MicroRNAs (miRNAs) are small (19-22 nt) noncoding RNA molecules that regulate genes at the post-transcriptional level by base-pairing to specific messenger RNAs for degradation to repress translation. Recent studies suggested that miRNAs are important in the immune response and mediate a critical role in multiple immune response-related disorders. Based on these discoveries, attention has been focused on understanding the role of miRNAs in regulating intestinal

barrier dysfunction, especially in IBD. Here, we provide a review of the most recent state-of-the-art research on miRNAs in intestinal barrier dysfunction.

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Key words: MicroRNAs; Intestinal barrier dysfunction; Inflammatory bowel disease; Celiac disease; Therapeutic target

Core tip: This article summarizes the latest findings on the important roles of microRNAs (miRNAs) in regulating inflammation and autoimmune disorders in inflammatory bowel disease (IBD). Insight into miRNAs-21 as a novel biomarker is also provided, which shows that miRNAs-21 is a potential diagnostic and therapeutic target for IBD.

Zhang L, Cheng J, Fan XM. MicroRNAs: New therapeutic targets for intestinal barrier dysfunction. *World J Gastroenterol* 2014; 20(19): 5818-5825 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i19/5818.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i19.5818>

INTRODUCTION

The intestinal barrier plays an important role in absorbing nutrients and secreting waste^[1]. In addition to its abilities to support paracellular transport, the intestinal barrier can also prevent luminal microbes and their products reaching the internal milieu. Tight junctions and their associated proteins, including claudins, occludin, and zonula occludens, are the most adhesive apical junctional complexes and act as a structural and functional barrier against paracellular permeation of luminal substances^[2-4]. Break-down or disruption of the epithelial barrier is thought to be an essential determinant in the predisposition to

intestinal inflammation and a number of inflammatory disorders, such as Crohn's disease^[5], ulcerative colitis^[6,7], celiac disease^[8], and a series of infectious diarrheal syndromes^[9,10]. The phenomenon of intestinal tight junction (TJ) barrier disruption has previously been reported, but the intracellular mechanism is still poorly understood. Of the essential factors relating to this issue, two are most critical. The first is to identify the early signaling event which triggers the immune response and inflammatory cascade which will help us to understand induction of the disease, and the second is to identify the regulatory system which will lead to the discovery of the therapeutic target. MicroRNAs (miRNAs), which are small noncoding RNAs, were recently discovered to have a promising role in the treatment of immune-related diseases^[11,12]. By regulating the degradation of mRNAs at the post-transcriptional level, miRNAs can affect various signaling pathways, and may be good candidates for the treatment of immune-related diseases. More recently, investigations have focused on the role of miRNAs in intestinal-related diseases. These studies may not only provide novel insights into understanding the pathological and physiological process of intestinal barrier dysfunction, especially in inflammatory bowel disease (IBD), but have also suggested the therapeutic role played by miRNAs. The major purpose of this review was to examine current research on the role of miRNAs in the regulation of intestinal barrier function and their therapeutic potential.

miRNA BIOGENESIS AND FUNCTION

MiRNAs, non-coding small endogenous RNAs of 19-22 nucleotides in length, were first identified in *C. elegans* by Lee *et al.*^[13] in a study on the function of gene *lin-14* as a sequence-specific regulator of gene expression^[14]. MiRNAs which are encoded by eukaryotic nuclear DNA can target the 3' untranslated region (3'UTR) of specific mRNAs, usually resulting in gene downregulation *via* translational repression or target degradation^[15]. More than 1500 miRNAs have been found to be encoded in the human genome and over 60% of human genes are targeted by miRNAs^[16-18]. miRNAs play an important role in many different types of human cells^[19].

RNA polymerase II (*Pol II*) is associated with the miRNA promoter and induces primary miRNAs (pre-miRNAs) to be transcribed in the nucleus^[20,21]. These pre-miRNAs have a capped structure and a poly(A) tail^[20,22]. After being transported to the cytoplasm, the pre-miRNAs are further processed by the RNase III endonuclease, Dicer, in a complex with a trans-activator RNA binding protein into a double-stranded mature miRNA^[23-25]. One strand of the mature miRNA is then incorporated into the RNA-induced silencing complex (RISC) and leads this complex to the untranslated region (3'UTR) of specific mRNAs, which causes repression of the corresponding protein^[26-29]. In this way, miRNAs are thought to be fine-tune regulators in gene expression and disease control.

A number of biological processes are regulated by

miRNAs, such as cell proliferation, apoptosis, differentiation, migration and cell cycle control^[30-33]. miRNAs have also been reported to be involved in human diseases, including tumors^[34-41], immune dysregulation^[42-44], cardiovascular diseases^[45-48], metabolic syndrome^[49,50] and others^[51].

EXPRESSION OF miRNAs IN INTESTINAL EPITHELIAL CELLS

In 2008, Wu *et al.*^[52] first reported miR-192 which was detected in the epithelial cells of colonic mucosa samples from healthy individuals, but not in patients with active UC using immunohistochemistry and *in situ* hybridization. These authors also found 11 differentially expressed miRNAs in active UC *vs* healthy samples and confirmed an inverse relationship between macrophage inflammatory peptide-2 α (*MIP-2 α* , previously shown to be involved in IBD^[53]) and miR-192. Similarly, Bian *et al.*^[54] demonstrated that miR-150 was significantly increased in the epithelial cells of colonic mucosa in UC patients compared with controls, and suggested an inverse correlation between miR-150 and its target, *c-Myb*^[55], a proto-oncogene involved in apoptosis. Consequently, these two pioneer studies have provided new insight into the pathogenesis of intestinal barrier dysfunction. A summary of the expression of miRNAs in IBD is shown in Figure 1.

ROLE OF miRNAs IN REGULATION OF TIGHT JUNCTION PROTEINS

Occludin and claudins are important transmembrane TJ proteins localized at the TJ strands and function in the TJ barrier^[56-58]. Ye *et al.*^[59] demonstrated that miR-122a plays a central role in the regulation of intestinal TJ permeability by degrading the protein occludin. The regulation of claudins by miRNAs was reported in breast cancer^[60,61] and HIV-associated neurological disorders^[62], but not in the intestinal TJ barrier. Further studies on the relationship between claudins and miRNAs in the intestinal TJ barrier system are required. Zonula occludens 1 (*ZO-1*) is another major component of the TJ barrier which regulates intestinal permeability^[63]. Tang *et al.*^[64] found miR-212 overexpression in colon biopsy samples from patients with alcoholic liver disease and in Caco-2 cells (a human intestinal epithelial cell line) treated with ethanol. Alcohol can induce miR-212 overexpression and leads to gut leakiness by down-regulating *ZO-1* translation.

miRNAs AND INFLAMMATION

Many groups have demonstrated that miRNAs play pivotal roles in both adaptive and innate immunity^[65]. miRNAs regulate the development of various immune cells as well as their immunological functions. miRNAs are also essential in B- and T-cell functions. A deficiency

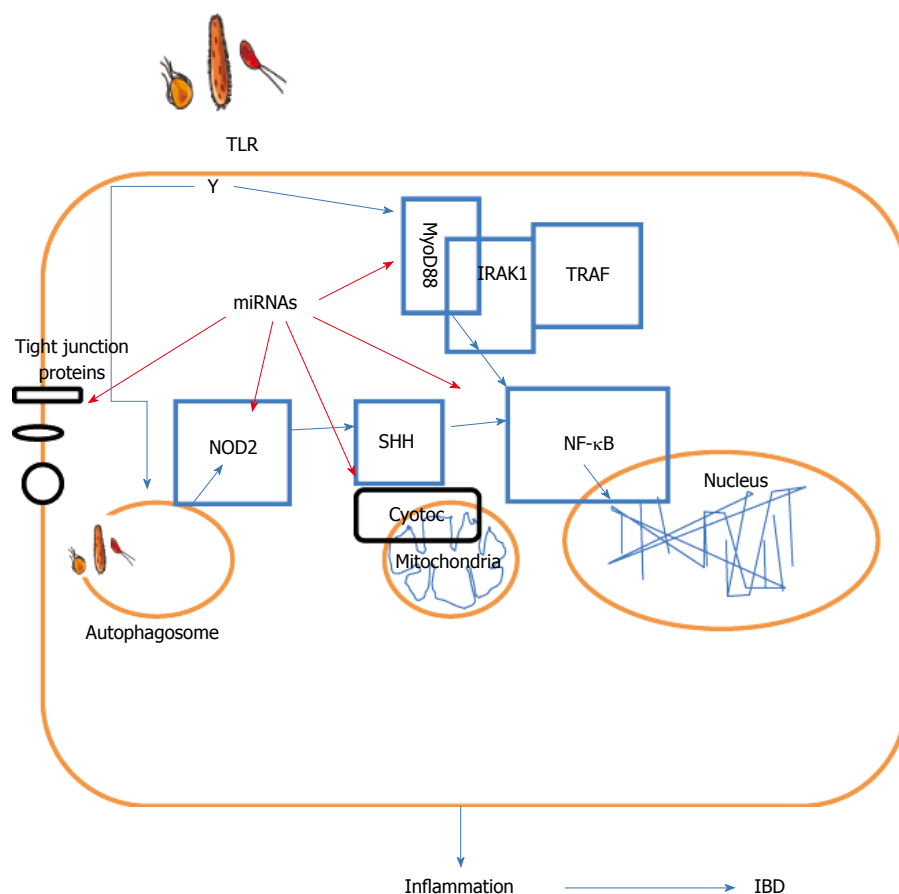


Figure 1 Summary of the role of microRNAs in inflammatory bowel disease. IBD: Inflammatory bowel disease. NF-κB: The nuclear factor NF-κB; TLR: Toll-like receptor; TRAF: TNF receptor-associated factor; NOD2: Nucleotide-binding oligomerization domain-containing protein 2.

in Dicer, the key enzyme in processing miRNAs, results in inhibition of T cell development^[65]. In addition, several miRNAs, including miR-155, miR-181a, miR-150 and the miR-17-92 cluster, are also involved in B- and T-cell regulation^[66]. Forced overexpression of miR-150 blocks B cell development^[67]. Innate immune responses provide the initial defense against pathogens. Pattern recognition receptors, such as Toll-like receptor (TLR), expressed on macrophages and dendritic cells (DCs), are regulated by miRNAs. miRNAs have also been shown to be important in regulation of the TLR signaling cascade^[68,69]. MiR-146a expression can be induced by exposure to TLR ligands, such as lipopolysaccharide (LPS), peptidoglycan, and flagellin^[70]. miR-146a then functions in a negative feedback mechanism in the TLR signaling cascade by decreasing the expression of TNF-receptor-associated factor-6 and IL-1 receptor associated kinase-1, two target genes of the TLR signaling cascade. Furthermore, loss of miR-155 in DCs impairs their antigen presenting capacity and costimulation activity. The target gene of miR-155 in DCs is *SOCS1* which negatively regulates antigen presenting capacity in DCs. Therefore, deregulation of *SOCS1* in the absence of miR-155 could account for impaired DC function^[71]. In macrophages, the downregulation of miR-125b is required to ensure that the correct inflammatory response is produced^[72]. The idea of miRNAs as regulators of

IBD provides new insight into the development of appropriate therapies.

miRNAs AND AUTOIMMUNE RESPONSE IN IBD

Several studies have reported that miRNAs are involved in autoimmune diseases (AIDs)^[42-44]. As miRNAs have been confirmed to play a role in immune cell development and have an impact on cell functions, it is reasonable to deduce that miRNAs are related to AIDs. Reports have shown that miRNAs take part in AIDs, such as rheumatoid arthritis^[73], systemic lupus erythematosus^[74], multiple sclerosis^[75], primary biliary cirrhosis^[76], inflammatory bowel disease^[52], idiopathic thrombocytopenic purpura^[77] and psoriasis^[78].

IBD, including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic gastrointestinal inflammatory disorder whose pathophysiology has been extensively studied over the past several years, but is still poorly understood.

Wu and colleagues^[52] studied mucosal tissues from healthy subjects and UC patients and found that miR-192 was predominantly expressed in the intestinal epithelial tissue of healthy subjects and was significantly decreased in UC patients. Furthermore, they also observed that the

inflammatory protein, *MIP-2*, was mainly expressed in UC patients and was decreased in healthy subjects. The expression of *MIP-2α* had an inverse relationship with miR-192. Besides miR-192, they also identified several other differentially expressed miRNAs between UC patients and healthy subjects. MiR-21 was increased in UC patients compared with healthy subjects. miR-375, miR-422b and miR-23a were increased in healthy subjects and all three miRNAs had a similar level of expression in inactive UC^[52]. A previous study also showed that *TGF-β* can induce miR-192^[79]. This suggests that miR-192 may be the master regulator in the process of inflammation. These findings indicate that miRNAs are involved in the pathogenesis of IBD.

miRNAs AND MITOCHONRIAL STRESS IN IBD

Mitochondria are fundamental subcellular components that play a critical role in the maintenance of normal structure, function and survival of cells. Mitochondrial dysfunction is associated with metabolic diseases including insulin resistance, obesity, diabetes, and the cardiorenal metabolic syndrome^[80-83]. Growing evidence suggests that miRNAs provide another layer of regulation with regard to mitochondrial function. MiR-338 can modulate mitochondrial function by targeting cytochrome c oxidase IV (*COX IV*) mRNA^[84]. The miRNA-200 family is implicated in epithelial-to-mesenchymal transition which is accompanied by mitochondrial biogenesis and is involved in organ fibrosis and carcinoma progression^[85]. Nishi *et al*^[86] showed that miR-15b, miR-195 and miR-424 can down-regulate cellular ATP levels and affect mitochondrial integrity. In addition, miR-23a/b in hypertrophy acts in a compensatory mechanism to down-regulate mitochondrial glutaminase^[87]. More recently, Yuan *et al*^[88] suggested that prohibitin which can inhibit mitochondrial dysfunction may be a potential target in IBD. However, further studies are required to determine whether miRNAs can affect IBD by regulating mitochondrial function.

miRNAs AND AUTOPHAGY IN IBD

Autophagy is a unique cellular process of self-digestion, characterized by the engulfment of cytosolic macromolecules and organelles in a autophagosome, which are then transported to the lysosome for degradation^[89,90]. Autophagy helps to recycle and store nutrients for stress conditions^[89].

Recently, autophagy-related gene (*ATG*) *16L1* was reported to be involved in CD^[91,92]. *ATG 16L1* shares some sequence homology with yeast *Apg16L* and was originally identified in the protein complex *ATG5-ATG12*^[93]. In autophagy, *ATG16L* plays an important role in autophagosome formation and functions as an E3-like enzyme to mediate lipidation^[94]. Lu *et al*^[95] recently provided evidence to show that miR106b and

miR93 suppress autophagy-mediated removal of bacteria in epithelial cells by targeting *ATG16L1*. Furthermore, *NOD2*, an intracellular bacterial sensor of the nucleotide-binding and oligomerization domain (NOD)-like receptor family, can sense the presence of muramyl dipeptide, a component of the peptidoglycan cell wall from both Gram-positive and -negative bacteria. *NOD2* activation results in pro-inflammatory and anti-bacterial molecule production dependent on cell signaling pathways mediated by *RICK/RIP2*, *NF-κB* and *MAPKs*. More recently, Ghorpade *et al*^[96] found that miR-146a-mediated *NOD2-SHH* signaling regulated gut inflammation in a mouse model of IBD. In addition, Brest *et al*^[97] demonstrated that the miR-196 family of miRNAs downregulates the CD protective variant (*c.313C*) of the immunity-related GTPase family M protein 1 gene in CD patients. Consequently, the control of intracellular replication of CD-associated adherent invasive *E. coli* by autophagy was lost due to a decrease in *IRGM1*^[97]. By targeting the related gene, miRNAs may eventually contribute to the improvement of IBD.

NOVEL BIOMARKERES AND THERAPEUTIC TARGETS IN IBD

With regard to the involvement of miRNAs in the pathogenesis of IBD, it is vital to identify which miRNAs are consistently dysregulated in IBD and the target genes of the miRNAs. miR-21, the most investigated and well-described miRNA, also known as the “oncomiR”, has been shown to have potential clinical application^[98]. According to published data^[52,53,99,100], miR-21 is the only miRNA usually upregulated in inflamed tissue or serum in IBD patients. The expression of miR-21 is regulated by *NF-κB* which is a master gene in multiple immune diseases (including IBD)^[101]. Thus, miR-21 has the potential as a biomarker. Iborra *et al*^[102] recently conducted a study to establish the specific expression patterns of miRNAs in the serum and mucosa of IBD patients. They identified six and five differentially expressed miRNAs in the serum and mucosa of patients with active CD compared with those with inactive CD, respectively. Their study again suggested the utility of miRNAs as possible biomarkers. The actual role of miRNAs in IBD still need to be confirmed by functional studies, however, miRNAs have shown promise in the treatment of IBD.

CONCLUSION

Recently, increasing attention has been paid to the gene expression of miRNAs in IBD. Clinical trials have been carried out to test the therapeutic efficacy of miRNA-based therapies. “Miravirsen”, a specific inhibitor of miR-122, is now being evaluated in a phase II clinical trial^[103]. Furthermore, a recent review^[104] suggested the use of an miRNA inhibitor or synthetic miRNA targeting the *PI3K* and *Ras/MAPK* pathways in multiple my-

eloma (MM) treatment. MiR-29b is a promising target in MM treatment by multiple mechanisms, including the regulation of osteoclastic differentiation^[105] and epigenetic regulation of the cell cycle^[106,107]. Future studies will provide a basis for more clinical trials and shed light on miRNA-based therapies in IBD.

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