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REVIEW ARTICLE

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MiRNAs and inflammatory bowel disease: An interesting new story

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Abstract

Inflammatory bowel disease (IBD), as a chronic and recurrent inflammatory disorder, is caused by a dysregulated and aberrant immune response to exposed environmental factors in genetically susceptible individuals. Despite huge efforts in determining the molecular pathogenesis of IBD, an increasing worldwide incidence of IBD has been reported. MicroRNAs (miRNAs) are a set of noncoding RNA molecules that are about 22 nucleotides long, and these molecules are involved in the regulation of the gene expression. By clarifying the important role of miRNAs in a number of diseases, their role was also considered in IBD; numerous studies have been performed on this topic. In this review, we attempt to summarize a number of studies and discuss some of the recent developments in the roles of miRNAs in the pathophysiology, diagnosis, and treatment of IBD.

KEYWORDS

apoptosis, autophagy, inflammatory bowel disease, inflammation, microRNA

1 | INTRODUCTION

MicroRNAs (miRNAs) are a bunch of noncoding RNA molecules that are about 22 nucleotides long, and these molecules are involved in the regulation of gene expression. MiRNAs were first identified in 1993 in nematodes, and thousands of these short RNA molecules have been identified in eukaryotes to date (Lee, Feinbaum, & Ambros, 1993). MiRNAs are complement certain sequences in messenger RNA (mRNA) molecules and regulate the activity of mRNA molecules through the destabilization or inhibition of translation. MiRNAs are made up of precursors with a length of about 70 nucleotides (these are known as PRE-miR); there are complementary sequences in the building of the precursors that produce a bobby-pin loop structure. These precursor molecules are broken down by certain endonucleases and double-stranded miRNA molecules, with a length of about 22 nucleotides, are produced. One of the miRNA strands processed is connected to its complementary sequence in the target mRNA building, which results in the destruction of mRNAs or the inhibition of the translation process (P. K. Singh, Singh, & Chauhan, 2013). The expression of miRNAs is regulated by various mechanisms, including DNA methylation, DNA deacetylation, and keratin modification (Majidinia et al., 2017). For example, certain studies

have shown that impaired miR-21 locus methylation increases the level of miR-21 in leukocytes and bowel inflammatory tissues (Adams et al., 2014). By clarifying the important role of miRNAs in a number of diseases, their role has also been considered in inflammatory bowel disease (IBD) and numerous studies have been performed in this regard (Ardekani & Naeini, 2010; Majidinia & Yousefi, 2017; Majidinia, Mihanfar, et al., 2016; Mohammadzadeh, Baradaran, Valizadeh, Yousefi, & Zakeri-Milani, 2014). IBD is a type of idiopathic inflammation that is divided into two major categories of chronic bowel disorders: Crohn's disease and ulcer colitis. Evidence suggests that the onset of IBD is caused by an inadequate immune response to intestinal germs in people susceptible to genetic damage (De Souza & Fiocchi, 2016). This disease is associated with a range of factors, ranging from trace elements and fatty acids to antioxidants, hormones, and so on; each of these associations is a separate study area (Badalzadeh et al., 2015; Matsunaga et al., 2008; Mohammadi, Qujeq, Taheri, & Hajian-Tilaki, 2017; Saliani et al., 2013; Shamran et al., 2017; Tehrani, Karimian, Parsian, Majidinia & Yousefi, 2018 Jan; H. Wang, Chao, et al., 2016; H. Wang, Zhang, et al., 2016; R. Wang, Gu, et al., 2016; Y. Wang, Liang, et al., 2016; Yousefi, Ahmadi, Ghorbanihaghjo, Faghfoori & irannejad, 2014). Certain studies have shown that miRNAs play an important role in mechanisms such as Th17-dependent inflammation and the autophagy involved in IBD pathophysiology. Certain other studies examine miRNAs as diagnostic tools for detecting IBD and differentiating its subtypes from each other (Schaefer et al., 2015). A number of studies have also introduced some of the specific miRNAs as therapeutic targets for the treatment of IBD (Cheng et al., 2015; Table 1).

This review article attempts to review a number of these studies and summarize some of the recent developments in the role of miRNAs in the pathophysiology, diagnosis, and treatment of IBD; these studies provide a brief overview of this interesting new advancement (Figures 1,2).

2 | ROLE OF miRNAs IN IBD PATHOGENESIS

2.1 | A brief description of IBD pathophysiology

IBD is a complex disease with many pertinent factors. Among the most significant factors, genetic predisposition, intestinal microbes, and host immune system have attracted the most attention (Kaser, Zeissig, & Blumberg, 2009). Bowel microbes, including microorganisms that live in the intestines, have created the bowel immune system. Intestinal germs provide some of the body's required compositions and contribute toward regulating energy metabolism (Podolsky, 1991). The interactions of the host and the bowel germs can be beneficial or harmful to both parties and cause inflammation of the intestine. Observations in patients with IBD and animal models indicate the role of bacteria in inflammation; in other words, the presence of bowel bacteria is necessary for inflammation (Annaházi & Molnár, 2014; Kaser et al., 2009; Podolsky, 1991). Intestine epithelium is a barrier between intestinal germs and the lymphoid tissue associated with the gastrointestinal system, which plays an essential role in the formation of mucosal immune response (Podolsky, 1991). The healthy mucus barrier is dependent on intracellular tight junctions that contribute to blocking the space between the adjacent cells (Kaser et al., 2009). In IBD, the barrier between adjacent epithelial cells is destroyed, the permeability of this space (para cellular space) increases, and the regulation of tight junctions is disrupted (Kaser et al., 2009). These disorders may arise due to mucosal barrier dysfunction or as a result of inflammation (Hanauer, 2006). The defense against invading bacteria is observed on two specific types of epithelial cells that include Goblet cells and Paneth cells (Hanauer, 2006). Goblet cells regulate mucus production, the factors contributing to epithelial repair, and the regulation of inflammation. Paneth cells secrete antimicrobial peptides such as α-defensin (Ho, Pothoulakis, & Wai Koon, 2013; Pastorelli, De Salvo, Mercado, Vecchi, & Pizarro, 2013).

The bowel mucosa covers the epithelium surface; as a result, contact between bacteria and epithelial cells is limited (Vermeire, Van Assche, & Rutgeerts, 2004). The regeneration and repair of the epithelium play a pivotal role in controlling and eliminating the inflammatory response to injury. In IBD, inflammatory response often results in epithelial damage that causes erosion, ulcers, and the loss of production of defensin (Vermeire et al., 2004). As a result, the bowel germs can be increased and the inflammatory response is strengthened. The intestinal lamina propria, which is located below the intestinal epithelium, is composed of a set of immune cells that balances the need for the immunological tolerance of luminal microbes, defense against pathogens, and the entry of excessive luminal microbes (Hanauer, 2006; Kaser et al., 2009; Podolsky, 1991). The characteristic of active intestinal inflammation involves the penetration of intrinsic immune cells (neutrophil, macrophage, and natural killer [NK] cells) and dendritic cells into the lamina propria (Hanauer, 2006; Kaser et al., 2009; Podolsky, 1991).

Increasing the number and the activation of these cells in the intestinal mucus increases the local level of tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interferon-γ (TNF-α), and the cytokines of the Th17-IL23 pathway (De Souza & Fiocchi, 2016). Initial immunity response to intestinal microbes is highly regulated. This regulation determines tolerance creation or defensive inflammatory response. Any disruption in the interaction between these responses can lead to the development of IBD (De Souza & Fiocchi, 2016).

Detection of germs by epithelial cells, dendritic cells, and macrophages is dependent on identifying a pattern in them. Identifying these patterns, which is necessary for immune response, is the responsibility of toll-like receptors or the nucleotide oligomerization domain 2 (NOD2), which many studies have been dealing in relation to IBD (Elia, Tolentino, Bernardazzi, & de Souza, 2015; Geremia, Biancheri, Allan, Corazza, & Di Sabatino, 2014; Strober, Asano, Fuss, Kitani, & Watanabe, 2014). Dendritic cells express antigens to trap T cells, which include CD4+ in the secondary lymphoid organs where factors, such as the types of antigen-expressing cells and cytokines

TABLE 1 The role of miRNAs in inflammatory bowel disease

MiRNAs	Targets	Functions	References
Tight junctions and intestinal mucus barrier			
MiR-191a and miR-212	ZO-1	Weaken tight junctions	Tang et al. (2015) and L. Wang et al. (2017)
MiR-675	Cadherin E and ZO-1	Destructs tight junctions	Zou et al. (2016)
MiR-874	Aquaporin 3	Weakens the intestinal barrier	Su et al. (2016), W. Zhang et al. (2011), X. Zhi et al. (2014)
MiR-122a	Zonulin	Decreases EGFR level and targeting EGFR signaling pathways Increases the intestine permeability	A. Zhang, Wang, et al. (2017) and B. Zhang, Tian, et al. (2017)
MiR-21	PTEN/PI3K/Akt signaling	Exerts destructive effect on intestinal barrier Regulates permeability of tight junctions	C. Zhang, Xi, et al. (2015), L. Zhang, Ke, et al. (2015), and L. Zhang, Shen, et al. (2015)
MiR-150	C-myc	Disrupts the intestinal barrier	Bian et al. (2011)
MiR-34C	PLNCRNA1	Disrupts the intestinal barrier	He et al. (2017)
MiR-200b	TNF-α	Inhibits destructive effects on tight junctions Decreases the expression of interleukin Reinforces the bowel barrier	Shen et al. (2016) and L. Wang et al. (2017)
MiR-93	PTK6 Claudin3	Inhibits destructive effects on tight junctions Enhancing tight junctions	Haines et al. (2016)
Immune cells			
MiR-20	NOD2	Inhibits the inflammation process in IBD patients	Pierdomenico et al. (2015)
MiR-143 and miR-150	PIP2, TAK1, and NOD2	Applies inhibitory effect on the inflammation process	Prakhar et al. (2015)
MiR-10a	Th1/Th17 immune response	Inhibits the activation of dendritic cells as well as the Th1/Th17 immune response Is associated with Th17 and Th1 cells and dendritic cells Undermines the inflammatory response of Th17 and Th1 cells in IBD patients	W. Wu et al. (2014)
MiR-141	CXCL12β	Regulates colonic leukocytic trafficking	Huang et al. (2013)
MiR-21	MIP2, TNF-α	Intensifying colitis	Shi et al. (2013)
MiR-26a/26b	MIP2	Decreases colitis	Kwon et al. (2015)
MiR-155	SHIP1	Associates with signaling pathway contributed to the pathogenesis of IBD	Z.-J. Lu et al. (2017)
MiR-124	AhR receptors	Increases inflammation	Zhao et al. (2016)
MiR-223	Th17/IL23 signaling	Plays a very significant function in the pathogenesis of IBD	R. Wang et al. (2016)
Apoptosis and autophagy			
MiR-665	XBP1	Enhances apoptosis and exacerbates colitis in IBD	M. Li et al. (2017)
MiR-130A, miR-30c, miR-106b, miR-93, and miR-143–3P	ATG16L1	Involve in the pathogenesis of IBD	Brest et al. (2011), C. Lu et al. (2014), Nguyen et al. (2014), and Zhai et al. (2014)

Note. AhR: aryl hydrocarbon receptors; EGFR: epidermal growth factor-receptor; IBD: inflammatory bowel disease; MIP2: macrophage inflammatory protein 2; NOD2: nucleotide oligomerization domain 2; PI3K: phosphoinositide 3-kinase; PTK6: protein tyrosine kinase 6; TNF: tumor necrosis factor; XBP1: X-box binding protein 1.

(like IL-10), regulate transforming the growth factor and the distinction of TCD4+ cells (Geremia et al., 2014). Enterotropic molecules facilitate the entry of lymphocytes from the bloodstream to the bowel. Then, these activated TCD4+ cells enter the lamina propria and there they perform their activating actions (Geremia et al., 2014; Kaser et al., 2009).

In patients with intestinal inflammation, several events happen and lead to an increased contact between bacteria and epithelial

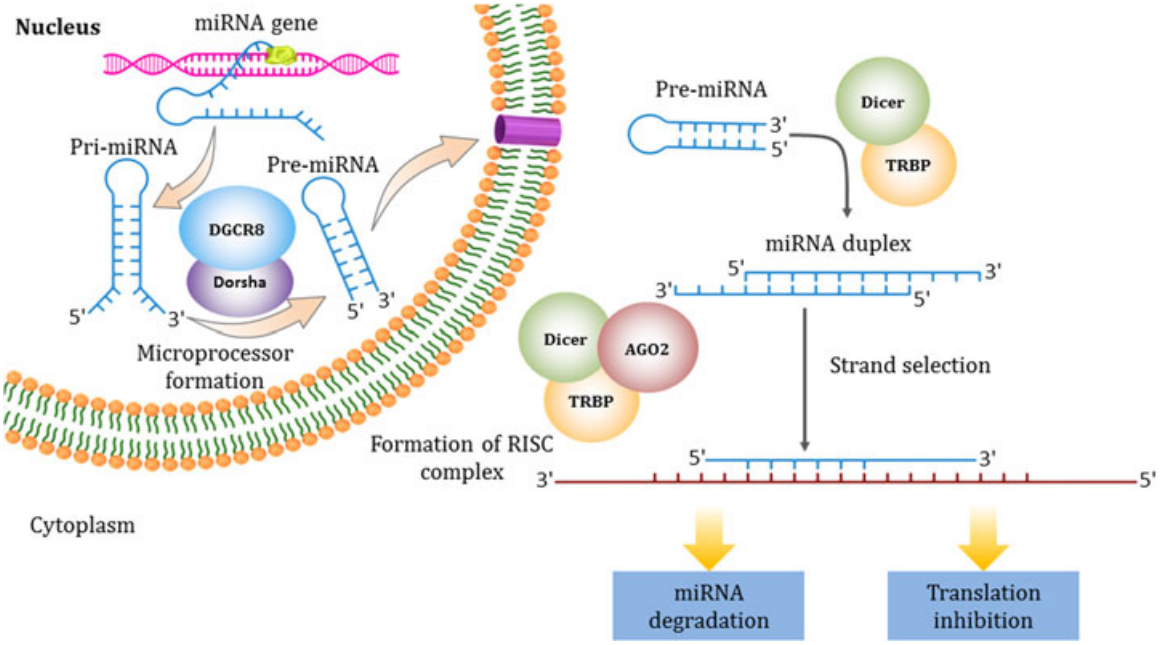

FIGURE 1 MiRNAs structure and biogenesis. miRNA: microRNA [Color figure can be viewed at wileyonlinelibrary.com]

cells, such as the mucous membrane disorder, disorder in tight junctions, increased intestinal permeability, and an increase in the binding of bacteria to epithelial cells (Kaser et al., 2009). In IBD, intrinsic immune cells produce a high level of TNF-α and IL23, IL-12, IL-6, IL-1, and other chemokines (Kaser et al., 2009). These cells increase the level of TCD4+ cells, especially preinflammatory subtypes, which also secrete a high level of chemokines. Increasing these compounds increases the number of leukocytes. Successive cycles of inflammation, therefore, occur (Kaser et al., 2009). Studies have shown that miRNAs play a substantial role in a number of the events mentioned; these are discussed below. Interestingly, the role of these small magic molecules has been increasingly detected in the pathogenesis of IBD every day.

2.2 | MiRNAs, tight junctions, and intestinal mucus barrier

As mentioned above, disruption of tight junctions and intestinal mucosal membranes is one of the most important factors that can lead to IBD. In recent years, it has been shown that a number of miRNAs, including

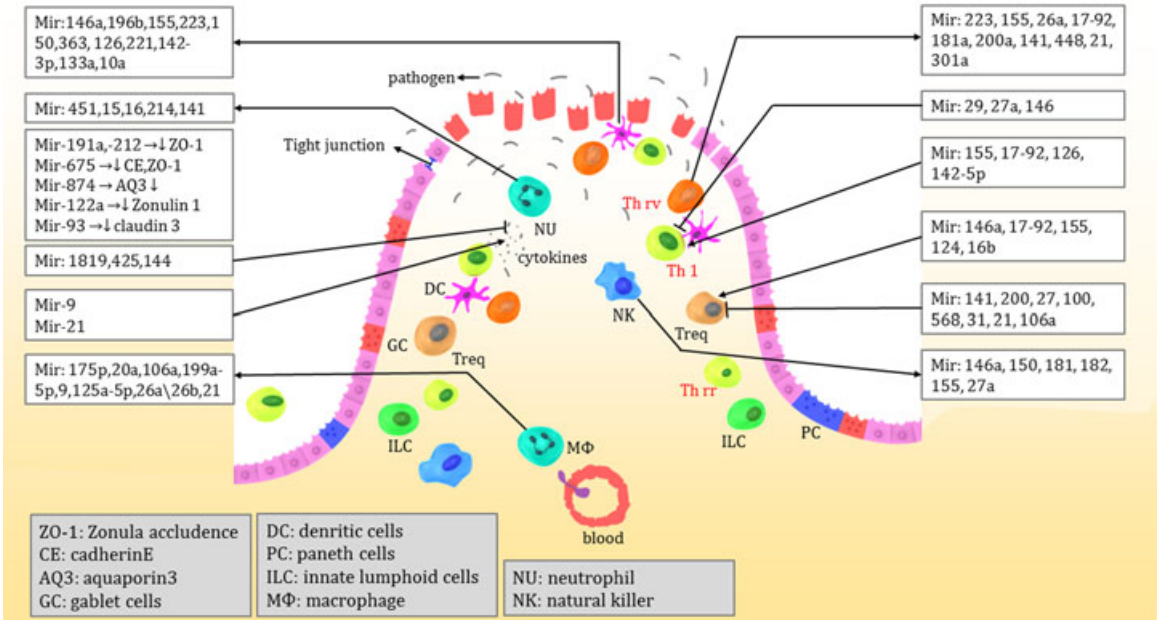

FIGURE 2 The roles of miRNAs in regulating intestinal epithelial tight junction and IBD. IBD: inflammatory bowel disease; miRNA: microRNA [Color figure can be viewed at wileyonlinelibrary.com]

miR-21, miR-34C, miR-191a, miR-200b, miR-93, miR-150, miR-874, miR-122a, miR-675, and so on, contribute toward enhancing or weakening the intestinal barrier, and it is expected that this number, through the conducting of more studies, will increase in the coming years (Heidary et al., 2015; Tang et al., 2015; L. Wang, Zhang, Chen, Wu, & Kuang, 2017; Zou et al., 2016). MiRNAs usually apply their influence by affecting the expression of the key protein genes of the tight junctions; one of these proteins is zonula occludens 1 (ZO-1). Studies have shown that miR-191a and miR-212 weaken tight junctions, although ZO-1 gene expression reduction (Tang et al., 2015; Wang et al., 2017), and miR-675 also have a destructive effect on the intestinal barrier through the destabilization of the MRNA of cadherin E and ZO-1 (Zou et al., 2016). TNF-α, which destroys tight junctions by increasing the expression of IL-8, increases the expression of miR-191a; thus, it is likely that the miRNAs are involved in inflammatory effects caused by TNF-α (Shen et al., 2016). On the other hand, it has been shown that miR-200b prevents the destructive effects of TNF-α on tight junctions by decreasing the expression of interleukin and this somehow reinforces the bowel barrier (Shen et al., 2016; Wang et al., 2017; 26, 28).

MiR-874 and miR-122a also have destructive effects on the intestinal barrier. MiR-874 weakens the intestinal barrier by reducing the level of aquaporin 3, which is one of the important proteins for the integration of the intestinal barrier (Su et al., 2016; W. Zhang, Xu, Chen, Xu, & Xu, 2011; X. Zhi et al., 2014). MiR-122a also increases zonulin levels by decreasing the epidermal growth factor-receptor (EGFR) level and targeting the EGFR signaling pathways (A. Zhang, Wang, et al., 2017; B. Zhang, Tian, et al., 2017). Zonulin is one of the proteins present in tight junctions, which are known as intestinal permeability indicators; thus, miR-122a increases intestinal permeability by increasing the level of zonulin; in this way, miR-122a exerts its destructive effect on the intestinal barrier.

MiR-21 is one of the most important miRNAs involved in IBD and several studies have confirmed its key role in the pathogenesis of IBD (C. Zhang, Xi, et al., 2015; L. Zhang, Ke, et al., 2015; L. Zhang, Shen, Cheng, & Fan, 2015). The effect of miR-21 on tight junctions is a destructive effect as some studies have shown that it regulates the permeability of tight junctions through the PTEN/PI3K/Akt signaling pathway and miR-21 increase is associated with the weakening of the tight junctions (C. Zhang, Xi, et al., 2015; L. Zhang, Ke, et al., 2015; L. Zhang, Shen, et al., 2015). MiR-34C and miR-150 have a destructive effect on the intestinal barrier. Certain studies have shown that the expression of miR-150 increases in the colon tissue of patients with ulcerative colitis as well as the intestinal tissue of mice with dextran sulfate sodium (DSS)-induced colitis (Bian et al., 2011). It is likely that miR-150 disrupts the intestinal barrier by reducing the amount of C-myc, which is a transcription factor (Bian et al., 2011). MiR-34C likely disrupts the intestinal barrier by diminishing the protective effects of PLNCRNA1, which is a noncoding long RNA (T. Chen, Xue, Lin, & Huang, 2017). MiR-01A is also one of miRNAs that weakens the intestinal barrier and enhances the inflammation process. In addition, this miRNA is associated with tumorigenicity in IBD patients (He et al., 2017). In addition to the aforementioned miR-200b, miR-93 is likely to have protective effects on tight junctions as some studies have shown that miR-93 reduces the expression of the protein tyrosine kinase 6 (PTK6), which disrupts the performance of tight junctions by reducing the expression of one of the important proteins of the tight junctions called claudin 3, thereby enhancing tight junctions (Haines, Beard, Eitner, Chen, & Wu, 2016).

2.3 | MiRNAs, immune cells, and immunological events

The connection between miRNAs and immunological interactions occurring in IBD is one of the most interesting research areas that have been overlooked in recent years. MiRNAs affect almost all the immune cells and the immunological events that occur in certain inflammatory and autoimmune diseases, including IBD, which, addressing all the aspects of these effects, require another overview article. In this paper, we have attempted to only present a brief overview of the latest findings.

2.3.1 | Nucleotide oligomerization domains, toll-like receptors, and miRNAs

As previously stated, the identification of germs by epithelial cells, dendritic cells, and macrophages is necessary for the initiation of immune response and is dependent on identifying a pattern in them (Xavier & Podolsky, 2007). MiRNAs affect toll-like receptors and nucleotide oligomerization domains (NOD), which are responsible for identifying these patterns (Fabbri et al., 2012). Toll-like receptors and their associated signaling pathways play an important role in the pathogenesis of IBD (Xavier & Podolsky, 2007). Studies have shown that a number of miRNAs, including miR-146a, miR-155, and miR-132, are associated with toll-like receptors and their associated signaling pathway (Y. Chen et al., 2016; Hajivalili et al., 2016; Nahid, Satoh, & Chan, 2011). Alike toll-like receptors, the family of NODs, in particular NOD2, are associated with IBD (Ogura et al., 2001). NOD2 acts as a cytosolic receptor and, as previously mentioned, identifies specific peptide patterns on the cell wall of the bacteria and triggers the inflammation process (Ogura et al., 2001). Certain miRNAs are associated with NOD2 and its signaling pathway. As shown, miR-20 inhibits the inflammation process in IBD patients by decreasing the expression of NOD2 (Pierdomenico et al., 2015), miR-143, and miR-150 by targeting phosphatidylinositol 4,5-bisphosphate (PIP2) and transforming growth factor β-activated kinase 1 (TAK1), which are the mediators of the NOD2 signaling pathway, and applying their inhibitory effect on the inflammation process (Prakhar et al., 2015). MiR-122, miR-29, miR-146a, miR-495, miR-512, miR-671, and miR-192 are the other miRNAs that are associated with NOD2 and are involved in the pathogenesis of IBD, especially Crohn's disease (Brain et al., 2013; Y. Chen et al., 2013; Chuang, Chuang, Zhai, Wu, & Kwon, 2013; Ghorpade, Sinha, Holla, Singh, & Balaji, 2013).

2.3.2 | MiRNAs and dendritic cells

Dendritic cells are one of the most important antigen-presenting cells that play a very important role in early immune responses

(Banchereau & Steinman, 1998). Several studies have been conducted on the relationship between miRNAs and dendritic cells, and a number of miRNAs have been identified, which are associated with dendritic cells (Montecalvo et al., 2012). The effects of miRNAs on dendritic cells are further restricted to the maturation of these cells, the ability of these cells to present antigens, apoptosis, and release some cytokines (Montecalvo et al., 2012). MiR-146a, mir-146b, miR-155, miR-223, miR-150, miR-126, and miR-221 are among the most important miRNAs associated with dendritic cells (Karrich et al., 2013; C. Lu et al., 2011; Q.-S. Mi et al., 2013; Q. S. Mi, Xu, Qi, Shi, & Zhou, 2012; Park, Huang, Lu, Cairo, & Zhou, 2015; Sineh Sepehr et al., 2014). MiR-363, miR-142-3p, and miR-133a are also miRNAs whose association with dendritic cells has been identified in studies of 1 or 2 years (Gao, Han, & Fan, 2016; Pan et al., 2017; H. Wang, Chao, et al., 2016; H. Wang, Zhang, et al., 2016; R. Wang, Gu, et al., 2016; Y. Wang, Liang, et al., 2016). MiR-10a is also one of the few miRNAs whose association with dendritic cells has been specifically investigated in the intestinal tissue of IBD patients, and it has been shown that this miRNA inhibits the activation of dendritic cells as well as the Th1/Th17 immune response (W. Wu et al., 2014).

2.3.3 | MiRNAs and NK cells

The accumulation of immune cells in the intestinal lamina propria is a precondition for IBD (Ginsburg, Dambrauskas, Ault, & Falchuk, 1983). NK cells are among the most important of these immune cells (Cerwenka & Lanier, 2016). These cells have cytotoxic activities as well as lytic activities, and they are important in defending against infections as well as in destroying cancerous cells (Jahanban-Esfahlan, Guardia, Ahmadi, & Yousefi, 2017). Studies have shown that some of the miRNAs, including miR-146a, miR-150, miR-181, and miR-182, are the most important of these miRNAs. MiR-150 plays a role in the maturation and function of NK cells, and the lack of this miRNA inhibits the lytic activity and stimulates the cytotoxic activity of NK cells (Bezman, Chakraborty, Bender, & Lanier, 2011; N. Kim et al., 2014). MiR-146a targets the STAT1 signaling pathway, thereby disrupting function of NK cells (Xu, Han, Hou, Zhang, & Zhang, 2017), miR-182 enhances cytotoxic activity of NK cells (Abdelrahman et al., 2016), and miR-181 also plays a role in differentiation of NK cells (Cichocki et al., 2011). MiR-155 and miR-27a-5P are other miRNAs that their relations have been identified with NK cells (Sullivan et al., 2013; C. Zhang, Xi, et al., 2015; L. Zhang, Ke, et al., 2015; L. Zhang, Shen, et al., 2015). Studies have shown that miR-155 regulates the activation of NK cells by regulating the protein level of the signaling pathways of phosphoinositide 3-kinase (PI3K), the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and calcineurin (Sullivan et al., 2013). As NK cells lacking miR-155 are more readily activated (Sullivan et al., 2013), certain studies also have indicated an inverse relationship between miR-155 and the cytotoxic activity of NK cells (C. Zhang, Xi, et al., 2015; L. Zhang, Ke, et al., 2015; L. Zhang, Shen, et al., 2015). The migration of NK cells in physiological and pathological conditions is regulated by the expression of specific receptors known as chemokine receptors. One of these receptors is the CXC chemokine receptor (CXCR1); miR-27a-5P imposes an inhibitory effect on the migration of NK cells by targeting these receptors (Regis et al., 2017). Studies have shown that the transforming growth factor β1 (TGF-β1), an anti-inflammatory cytokine, increases the level of miR-27a-5P (Regis et al., 2017).

2.3.4 | MiRNAs and neutrophils

Undoubtedly, neutrophils are one of the most important cells involved in the inflammation process (Jones, Robb, Perretti, & Rossi, 2016). These cells, also called polymorphonuclear cells (PMNs), are present in blood circulation (Jones et al., 2016). The following tissue damage, infections, or inflammation of these cells go to the damage site through a process called chemotaxis, where they perform their phagocytosis and antimicrobial activities (Majidinia & Yousefi, 2016). Studies have shown that some of the miRNAs affect chemotaxis and neutrophil migration. The chemotaxis process is affected by a number of cytokines including IL-8; the miR-155, by strengthening the PI3K/Akt signaling pathway, increases the level of IL-8 and, subsequently, increases the migration of neutrophils and enhances the inflammation process (Bhattacharyya et al., 2011). On the other hand, miR-451 has an inhibitory effect on the chemotaxis process by targeting the P38-mitogen-activated protein kinase (MAPK), which is a key enzyme for neutrophil migration (Eckert, Sharief, & Jones, 2009; Murata et al., 2014). In addition, there are other miRNAs that are associated with neutrophils; miR-142-3P contributes to the maturity and the differentiation of neutrophils (Fan et al., 2014); miR-15, miR-16, and miR-214 enhance the process of inflammation by decreasing the level of A2A receptors in the neutrophils that are involved in the control of inflammation (Heyn et al., 2012). MiR-141 also disrupts the migration process of immune cells and has been suggested for use in the treatment of Crohn's disease (Huang et al., 2013).

2.3.5 | MiRNAs, macrophages, and monocytes

Macrophages are very important for immune response (Mahida, 2000). These cells are produced from monocytes in the tissues of the body (Mahida, 2000). The activation of macrophages is carried out through two paths: Classical and alternative (Mahida, 2000). The macrophages activated through the classical path are called M1 macrophages; these macrophages have preinflammatory properties (Mahida, 2000). Macrophages that are activated in the alternative pathway, called M2, have anti-inflammatory properties (Banerjee et al., 2013). MiRNAs affect all of these events—from the construction and the differentiation of monocytes to the activation of macrophages (Y. Wei & Schober, 2016). AML1 is a transcription factor that increases during the production process of monocytes (monocytopoiesis) and plays an important role in this process. MiR-17-5P, miR-20a, and miR-106a weaken the process of the production of monocytes by targeting AML1 (Roy, 2016). MiR-424 contributes to the differentiation of monocytes and enhances the process of differentiation, whereas miR-199a-5p has an inhibitory effect

on the differentiation of monocytes (Lin et al., 2014; Roy, 2016). MiRNAs also affect the inflammatory activity of macrophages as miR-9 contributes to strengthening, and miR-125a-5p contributes to weakening the inflammatory response of macrophages (Carson IV et al., 2017; Melton, Lei, Gelfond, & Shireman, 2016; Yousefi et al., 2012). Certain studies on mice with DSS-induced colitis have shown that miR-21 increases the level of the macrophage inflammatory protein 2 (MIP2) and TNF-α, thereby intensifying colitis (Shi et al., 2013); this occurs while miR-26a/26b decreases the expression of MIP2 (Kwon et al., 2015).

2.3.6 | MiRNAs and T cells

T cells play a very important role in the pathogenesis of IBD (Neurath, 2014). T cells are generated from lymphoid precursors and are divided into two groups of TCD4+ and TCD8+ lymphocytes, or the same cytotoxic T, in which the role of TCD+ cells have been further emphasized in the pathogenesis of IBD (Neurath, 2014). As previously mentioned, the characteristic of active intestinal inflammation takes place due to the accumulation of immune cells, including TCD4+ cells in the bowel lamina propria. The TCD4+ precursors (naive CD4+ cells) are differentiated into two categories of T cells: Effector CD4+ T cells and regulatory T cells (Geremia et al., 2014). The effector T cells include Th1, Th2, Th17, and Tfh. The nTreg, iTreg, Tr1, and Th3 cells are also from the regulatory T cells (Geremia et al., 2014). Each of these two T cell groups secretes cytokines that are very important. The effector T cells are involved in defending against pathogens (Geremia et al., 2014).

The activity of these cells is regulated by regulatory T cells, and there is a balance between the function of these two categories of T cells (Larmonier, Shehab, Ghishan, & Kiela, 2015). One of the events that can cause IBD is the collapse of this balance. In fact, the excessive activity of effector T cells or a disturbance in the differentiation and immunosuppressive activities of regulatory T cells can lead to IBD (Larmonier et al., 2015; J. Zhu & Paul, 2008). MiRNAs contribute to all of the aforementioned cases from the formation and the differentiation of TCD4+ cells to the function of these cells. MiR-181a, miR-150, and miR-21 are involved in the maturity, function, and activation of naive CD4+ cells, as studies have shown (Ghisi et al., 2011; G. Li et al., 2012; Smigielska-Czepiel et al., 2013).

2.3.7 | MiRNAs and effector T cells

Naïve CD4+ cells can be differentiated into effector T cells or regulatory T cells (Sakaguchi, Yamaguchi, Nomura, & Ono, 2008). Th1, Th2, Th17, and Tfh are the effector T cells that differentiate on the basis of certain cytokines from naïve CD4+ cells; by producing a number of cytokines, they help activate other immune cells and play a very important role in the inflammation process (Sakaguchi et al., 2008). Th1 cells are differentiated from CD4+ naive cells by the IL-12 and the STAT4 signaling pathway. Th1 cells contribute to defense against intracellular pathogens, including germs and protozoa; these cells enhance the activity of macrophages in addition to increasing the cytotoxic T cells (L. Zhou, Chong, & Littman, 2009). IFN-γ is the main cytokine effector of Th1 cells and these cells apply their effects by producing this. Unlike Th1 cells, Th2 cells are more involved in defense against extracellular pathogens; these cells are differentiated by the IL4 and the signaling pathways STAT6 and GATA3 from naïve CD4+ cells; their most important produced cytokines are the same IL4 (L. Zhou et al., 2009). The Th1 and the Th2 cells are closely interconnected as the IFN-γ released from the Th1 cells can control the differentiation and the function of the Th2 cells by inhibiting IL4 secretion. The relation of both of these cells has been shown with IBD. Furthermore, it has become clear that Th1 cells show closer association to Crohn's disease and Th2 cells are more associated to ulcerative colitis (Larmonier et al., 2015; J. Zhu & Paul, 2008). The association of miRNAs with these cells is also remarkable and various studies have shown that miRNAs play a role in the differentiation and the cytokine production ability of this cell, as shown by the fact that miR-155 strengthens the differentiation of Th1 cells from naïve CD4 + cells, while it undermines the differentiation of Th2 cells. It has also been shown that the lack of miR-155 causes resistance to colitis in mice (J. Li et al., 2014; U. P. Singh et al., 2014; C. Zhang, Zhao, et al., 2014; J. Zhang, Cheng, et al., 2014). Recently, it has also been shown that miR-155 affects the inflammation process by targeting the SH-2 containing inositol 5′ polyphosphatase 1 (SHIP1) protein and its associated signaling pathway, and it likely contributes to the pathogenesis of IBD (Z.-J. Lu et al., 2017). MiR-17-92 and miR-126 also belong to miRNAs that stimulate Th1 cell differentiation by increasing IFN-γ production (Cui et al., 2016; Jiang et al., 2011). MiR-142-5P also enhances the differentiation of Th1 cells (Talebi et al., 2017). Certain miRNAs also inhibit the differentiation of Th1 cells. MiR-29 and miR-27a are from this category (Ma et al., 2011; Min et al., 2012; Steiner et al., 2011). MiR-146a also inhibits the differentiation and the proliferation of Th1 cells by stopping the cell cycle in the G1 phase and targeting the STAT4 signaling pathway (Möhnle et al., 2015; W.-J. Yang, Ma, Li, Su, & Liu, 2017). Reducing this miRNA can enhance the inflammation process (Hu, He, Li, Chen, & Xie, 2017).

MiRNAs also affect the cytokine production ability of T cells. Studies have shown that miR-181a and miR-425 reduce the production of IFN-γ and IL-2, while miR-9 enhances the production of these cytokines (Nakagawa et al., 2017; Sang et al., 2015; Thiele, Wittmann, Jäck, & Pahl, 2012). MiR-144 also has an inhibitory effect on IFN-γ and TNF-α production, while miR-21 increases the production of these cytokines and contributes to the formation of colitis in mice (Ando et al., 2013; D. Li et al., 2015; L. Y. Liu, Schaub, Sirota, & Butte, 2011). In addition, Th17 cells play a very active role in the inflammation process and the development of IBD. These cells secrete a very important inflammatory cytokine called IL-17 and play a key role in the recruitment of neutrophils and macrophages in the inflammatory and infected tissues (Abraham & Cho, 2009). Significant evidence suggests that Th17 cells interfere with the pathogenesis of many inflammatory and autoimmune diseases, including IBD (Abraham & Cho, 2009). In addition to IL-17, these cells also produce other cytokines, including IL-21 and IL-22.

IL-21, which is produced by the IL-6-STAT3 signaling pathway, amplifies the differentiation of Th17 cells (Dong, 2008; Troncone, Marafini, Pallone, & Monteleone, 2013). The role of Th17 cells in IBD has been well studied, and it has been shown that IL-17 levels increase in the intestinal tissue of patients with IBD (Globig et al., 2014). The relation of miRNAs with Th17 cells is undeniable, and numerous studies have shown the impact of miRNAs on the differentiation and the function of the Th17 cells. A number of these studies have shown that a number of miRNAs, such as miR-20b, miR-10a, miR-18a, miR-210, miR-106a, miR-363-3p, miR-18b, miR-27a, and miR-15b, have an inhibitory effects on the process of differentiation of Th17 cells (Ahmadian-Elmi et al., 2016; Kaestle et al., 2017; R. Liu et al., 2017; Montoya et al., 2017; Takahashi et al., 2012; H. Wang et al., 2014; E. Zhu et al., 2014), while the miR-223, miR-155, miR-26a, miR-17–92 cluster, miR-181a, miR-200a, miR-141, miR-448, and miR-21 strengthen the process of differentiating Th17 cells (Honardoost, Kiani-Esfahani, Ghaedi, Etemadifar, & Salehi, 2014; Ifergan, Chen, Zhang, & Miller, 2016; S.-Q. Liu, Jiang, Li, Zhang, & Li, 2014; Mele et al., 2015; Naghavian et al., 2015; R. Wu et al., 2017; A. Zhang, Wang, et al., 2017; B. Zhang, Tian, et al., 2017). MiR-301a is another miRNA that has been shown to have a positive effect on the differentiation of Th17 cells as well as the production of IL-17 and TNF-α, which is a key cytokine in the development of IBD; this miRNA is likely to increase the inflammation of the intestine in mice in this manner (He et al., 2015). MiR-155, in addition to differentiating, affects the ability to produce cytokines of Th17 cells. It is likely that this miRNA will increase the ability of Th17 cells to produce cytokines by inhibiting a DNA-binding protein called Jarid, which inhibits the expression of cytokines genes (Escobar et al., 2014). MiR-10a is also associated with Th17 and Th1 cells in addition to dendritic cells, and undermines the inflammatory response of Th17 and Th1 cells in IBD patients (W. Wu et al., 2014). Certain miRNAs perform their actions by targeting the aryl hydrocarbon receptors (AhR). The importance of these receptors in preventing IBD is well-documented. These receptors are very important in suppressing immune response and preventing inflammation, and one of their important actions is to weaken the function of Th17 cells (P. Wei et al., 2014). MiR-212/132 cluster exerts its stimulatory effect on the differentiation and the function of Th17 cells through the inhibition of these receptors (Chinen et al., 2015; Nakahama et al., 2013); miR-124 also increases inflammation in Crohn's disease by inhibiting these receptors (Zhao et al., 2016). Certain microRNAs also affect the Th17-/IL23-signaling pathway, which is very important for IBD. MiR-223 is associated with this signaling pathway, and IL23, with the aid of this miRNA, reduces the level of one of the major intestinal barrier proteins called claudin-8; therefore, it seems that miR-223 plays a very significant function in the pathogenesis of IBD (H. Wang, Chao, et al., 2016; H. Wang, Zhang, et al., 2016; R. Wang, Gu, et al., 2016; Y. Wang, Liang, et al., 2016).

2.3.8 | MiRNAs and regulatory T cells

Regulatory T cells are another group of TCD4+ cells that regulate the activity of T cells and play an important role in immune tolerance (De Souza & Fiocchi, 2016). The efficacy of most regulatory T cells is related to the expression of a transcription factor called the fork head box protein P3 (FOXP3); the lack of this factor has deleterious effects. In addition to FOXP3, the disorder in other regulatory T cell genes, including CD25 and IL-10, is also associated with IBD. Regulatory T cells are divided into two major categories (De Souza & Fiocchi, 2016; Kaser et al., 2009). The first group constitutes Treg cells that originate from thymus. The second group constitutes iTreg cells that are generated under the influence of IL-2 and TGF in the peripheral tissues of the naive CD4+ cells (Geremia et al., 2014; Kaser et al., 2009). These two sets of regulatory T cells reinforce each other's function. In the case of IBD, the role of the iTreg cells is further discussed; iTreg cells are divided into two subgroups: The TrL cells whose main characteristic is the lack of FOXP3 and the production of large amounts of IL-10, and the Th3 cells that, in addition to expressing FOXP3, produce significant amounts of TGFβ, which is an anti-inflammatory cytokine (Geremia et al., 2014). It has been shown that TrL and Th3 contribute toward protecting against experimental colitis in mice; therefore, the disorder in the differentiation and function of Treg cells is likely to play a very important role in the pathogenesis of IBD (Larmonier et al., 2015; J. Zhu & Paul, 2008). MiRNAs also regulate the differentiation and the function of regulatory T cells, and many studies point to the association of miRNAs with these cells. Two of these miRNAs are miR-141 and miR-200 (these were previously mentioned). These miRNAs, in addition to enhancing the differentiation of Th17 cells, also inhibit the differentiation of Treg cells (Naghavian et al., 2015). Furthermore, miR-27 is associated with the differentiation of the function of Treg cells, and increasing its expression disrupts the differentiation and the function of Treg cells and, consequently, impairs immune tolerance (Naghavian et al., 2015). Studies have shown that miR-100, miR-568, miR-31, miR-21, and miR-106b also inhibit the differentiation and the function of regulatory T cells (W. Li et al., 2013; Negi et al., 2015; C. Zhang, Xi, et al., 2015; L. Zhang, Ke, et al., 2015; L. Zhang, Shen, et al., 2015; Q. Zhou, Haupt, et al., 2015; S. Zhou, Dong, et al., 2015). By targeting one of the FOXP3 coregulator called EOS, miR-17 can disrupt the function of Treg cells (H.-Y. Yang et al., 2016). Certain miRNAs also stimulate the differentiation and the function of Treg cells, including miR-17–92, miR-146a, miR-155, miR-124, and miR-16b/16 (de Kouchkovsky et al., 2013; Heyn et al., 2016; Yin et al., 2017; C. Zhang, Zhao, et al., 2014; J. Zhang, Cheng, et al., 2014). The interesting point is, however, the fact that some of these miRNAs have a stimulating effect on the differentiation and the function of Th17 cells, as previously mentioned. In addition, miR-99a, in collaboration with miR-150, also supports the differentiation of Treg cells (Warth et al., 2015).

2.4 | Apoptosis, autophagy, and IBD. What is the role of miRNAs?

2.4.1 | MiRNAs and apoptosis

Apoptosis or programmed cell death is a physiological and essential process for the body (Nunes, Bernardazzi, & de Souza, 2014). For example, in cases where the DNA of the cell has been damaged by

certain damaging factors and the restorative processes cannot resolve the damage, the cell will eliminate itself through the apoptosis process as the prolongation of such a cell's life could lead to severe anomalies such as cancer (Nunes et al., 2014). Apoptosis begins with the reception of a signal of death. Cells start to die after receiving the signal, which ultimately leads to the activation of enzymes called caspase, and eventually cell death (Wyllie, 2010). The association of apoptosis has been studied with IBD, and it has been shown that the apoptosis of the epithelial bowel cells increases in patients with IBD (Wyllie, 2010). In addition, it has been determined that some antiapoptotic proteins, including X-box binding protein 1 (XBP1), have protective effects against intestinal inflammation in mice (Portt, Norman, Clapp, Greenwood, & Greenwood, 2011). The relationship between miRNAs and apoptosis have been identified as a large range of studies that have shown that some of these small magic molecules, including miR-150, miR-351, miR-133a, miR-491, and miR-199b, contribute to apoptosis enhancement (Favreau, McGlauflin, Duarte, & Sathyanarayana, 2015; Hanisch et al., 2017; Ji et al., 2013; Sato et al., 2016), while some other miRNAs have inhibitory effects on apoptosis. The miR-365, miR-590, and miR-17–92 cluster are as the same miRNAs (Hamada, Masamune, Miura, Satoh, & Shimosegawa, 2014; G. Huang, Nishimoto, Zhou, Hughes, & Kleinerman, 2012; Shaffiey, Cross, & Sathyanarayana, 2013). A number of miRNAs also affect apoptosis by targeting the XBP1 protein; studies have shown that miR-214 has an inhibitory effect on XBP1 and a stimulating effect on miR-148a (Cho et al., 2016; Duan et al., 2012; Duan et al., 2015). MiR-665 is one of the few miRNAs whose effect has been investigated on apoptosis, specifically in IBD patients, and it has been determined that this miRNA, by inhibiting XBP1, enhances apoptosis and exacerbates colitis in IBD (M. Li, Zhang, et al., 2017; P. Li, Shen, et al., 2017).

2.4.2 | miRNAs and autophagy

Autophagy, like apoptosis, is a physiological process, in which cells pack their unnecessary components in membranes; the membrane then merges with lysosomes and forms autophagosomes; lysosomal enzymes destroy the unnecessary components of the cell (Nunes et al., 2014). Autophagy is a process that greatly helps in saving cellular energy by eliminating unnecessary components; this condition is more important in certain conditions, such as those in which food shortages exist or while dealing with pathogens (Nunes et al., 2014). Studies have shown that some of the effective genes in autophagy, including ATG16L1 and IRGM, are associated with IBD, especially Crohn's disease (Kabat et al., 2016; X. C. Lu et al., 2013; Moon et al., 2012; Nguyen et al., 2014; Nunes et al., 2014; Pugazhendhi, Baskaran, Santhanam, & Ramakrishna, 2017). ATG16L1, as an adaptor protein, is constitute an ATG5-binding region and coiled-coil domain (CCD; for self-dimerization), in N- and amino terminal, respectively (Mizushima et al., 2003). This protein also contains 7 tryptophan-aspartic acid (WD40)-repeat domains (Kuma, Mizushima, Ishihara, & Ohsumi, 2002; Mizushima et al., 2003). Nine genetic variants of ATG16L1 (rs13412102, rs12471449, rs6431660, rs1441090, rs2289472, rs2241880, rs2241879, rs3792106, and rs4663396) are reported to be associated with Crohn's (Glas et al., 2008). Since there is a strong correlation between rs3792106 variant and women with Crohn's are more susceptible to surgery, this genetic variant is believed to be linked to sex differences (L. Y. Liu, Schaub, et al., 2011; Y. Liu, Wang, et al., 2011). The most frequency, as well as strongest association with Crohn's disease, is belonged to the variants rs2241879 and rs2241880 (Glas et al., 2008). The precise functions of the other mentioned ATG16L1 variants are still unknown in other contexts (Ishibashi et al., 2011). In addition to ATG16L1, a more recently discovered isoform of this protein, ATG16L2, was also reported to be associated with Crohn's (Ishibashi et al., 2011). ATG16L2 contains two alternative splicing isoforms (α and β) and forms tetrameric complexes with ATG5 and ATG12 (Ishibashi et al., 2011). ATG16L1 and L2 have nonexclusive function in the in the process of autophagy because ATG16L1 is unable to compensate for the function of ATG16L1 in autophagosome formation (S.-K. Yang et al., 2013). The strong association of the rs2241880 SNP with Crohn's disease is frequently reported in independent European disease populations (Barrett et al., 2008; Lacher et al., 2009; Prescott et al., 2007). However, there is no significant association in the Japanese, Chinese, and Brazilian populations, and conflicting data are reported in two Italian studies (Baptista et al., 2008; Latiano et al., 2008; Perricone et al., 2008; Yamazaki et al., 2007; H.-F. Zhang et al., 2009; J. Zhi et al., 2008). Similarly, multiple IRGM risk polymorphisms are also reported to be associated with Crohn's disease and replicated in independent cohorts of North America, North Europe, and New Zealand (Brest et al., 2010). MiR-106b, miR-93, and miR-143-3P are also other miRNAs whose inhibitory effects have been identified on the ATG16L1 gene (C. Lu et al., 2014; Zhai et al., 2014). MiR-196 is also related to IRGM (Brest et al., 2011).

3 | miRNA AS DIAGNOSTIC INDICATORS OF IBD

IBD diagnosis has always been a serious challenge. Many studies have been conducted to find an appropriate, noninvasive, and low-cost diagnostic marker, and a number of laboratory markers have been introduced to diagnose IBD (Moein, Qujeq, Tabari, Kashifard, & Hajian-tilaki, 2017). Meanwhile, the measurement of some proteins, including calprotectin, in the stool sample have had promising results as it has been shown that the measurement of stool calprotectin has shown significant sensitivity and specificity in the diagnosis of IBD, and even has a remarkable advantage over traditional inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR; Moein et al., 2017). Nevertheless, colonoscopy and histopathologic studies are still known as the golden standard methods for the diagnosis of IBD, which has led to miRNAs being considered as the IBD diagnostic markers in recent years (Moein et al., 2017). Many studies have been performed in this area; it has been determined that a significant level of change in the IBD occurs, and all these findings are beyond the reach of this discussion. It requires a different review article.

In this study, therefore, only a brief overview of the latest findings is provided; we will try to focus more on the miRNAs whose sensitivity and specificity are identified for the diagnosis of IBD. Among these miRNAs, miR-31 has been introduced as a potentially useful marker in identifying IBD in recent years. In addition, it has also been shown that this miRNA is associated with Crohn's disease and can distinguish colonlike and ileumlike Crohn's disease phenotypes from one another (Sheikh et al., 2017; C. Zhang, Zhao, et al., 2014; J. Zhang, Cheng, et al., 2014). Another study has shown that the combination of 11 different miRNAs including miR-16, miR-20a, miR-21, miR-30e, miR-93, miR-106a, miR-140, miR-192, miR-195, miR-484, and let7b miRNAs has a sensitivity of between 70% and 83% and specificity between 75% and 100% for the diagnosis of Crohn's disease (Zahm et al., 2011). MiRNAs may also be useful in the differential diagnosis of IBD subtypes. MiR-24 is as the same miRNAs, with a sensitivity of 83.3% and a specificity of 85.7% for the differentiation of ulcerative colitis from colonlike Crohn's disease (Zahm et al., 2014). In addition to miR-24, it has been shown that miR-21 and miR-126 can also be useful markers in this regard (Thorlacius-Ussing, Schnack Nielsen, Andersen, Holmstrøm, & Pedersen, 2017).

Measuring miR-16b in plasma has also been proposed to diagnose Crohn's disease, and it has been shown that the area below the ROC curve of this miRNA is 65% for distinguishing between the patients of Crohn's disease and healthy subjects (Jensen et al., 2015). MiR-223 is another miRNA that has been described as an IBD diagnostic biomarker; this miRNA is also associated with disease activity and reflects the disease activity in both Crohn's disease and ulcer colitis well—even better than traditional inflammatory markers such as CRP and ESR (H. Wang, Chao, et al., 2016; H. Wang, Zhang, et al., 2016; R. Wang, Gu, et al., 2016; Y. Wang, Liang, et al., 2016). As previously stated, many studies have examined miRNAs as IBD diagnostic indicators; further progress is being made in this area and new miRNAs are being added to the list of miRNAs whose levels alter in the serum or the intestinal tissue of patients with IBD. What we have discussed in this study is a summary of the most interesting and recent findings in this field—a field which will attract more attention in the near future.

4 | MiRNAs AND IBD TREATMENT: THE TRUTH OR MYTH

The use of miRNAs in the treatment of human disease has been considered a new and interesting field of research in recent years (W.-X. Chen, Ren, & Shi, 2014). In the pathogenesis section, the involvement of miRNAs was described in many events involved in the pathogenesis of IBD. According to what has been mentioned, perhaps it is not too far-fetched to imagine the inhibition of miRNAs that stimulate the pathogenesis of IBD with the antagonists of miRNAs called antagomir or the enhancement of inhibitory effects of miRNAs that inhibit the pathogenesis of IBD with RNAs mimic, which are efficient in the treatment of IBD (W.-X. Chen et al., 2014). Although promising results have been obtained from the effectiveness of antagomirs and RNA mimic in the treatment of some human diseases, the efficacy of these compounds has not yet been exhaustively studied in IBD treatment (Janssen et al., 2013; M. Li, Zhang, et al., 2017; P. Li, Shen, et al., 2017). However, a few studies have shown promising results. One of these studies has shown that miR-210 mimic has an inhibitory effect on the differentiation of Th17 cells—the importance of which was previously stated in the pathogenesis of IBD (H. Wang et al., 2014). In addition, recent studies have shown that certain compounds, such as phenolic compounds and nicotine, apply their protective effects against bowel inflammation by targeting some miRNAs, such as miR-126, miR-124, and miR145 (Kim, Banerjee, Barnes, et al., 2017; Kim, Banerjee, Sirven, et al., 2017; Qin et al., 2017). The use of antagomir and mimic RNA for the treatment of IBD is likely to attract more attention in the near future, and their use may be an effective form of treatment of this complex and chronic disease.

5 | CONCLUSION

In this review, we discussed the critical function of various miRNAs the pathogenesis of IBD, and comprehensively listed miRNAs involved in dysregulation of tight junctions and intestinal mucus barrier, in the modulations of immune and inflammatory response in various cells including dendritic cells, macrophages, neutrophils, NK and T cells, regulation of apoptosis and autophagy. We also summarized some studies on the current understanding of the connection between miRNAs and diagnosis, as well as treatment of IBD. An increasing number of studies have been reported that patients with IBS present specific miRNA expression profiles, which may be involve in the initiation/ progression of inflammation. In spite of a long list of miRNAs contributed in the pathogenesis of the IBD, the precise role of most of miRNAs in IBD is still unknown, which need further investigations to validate the roles of miRNAs, as diagnostic and therapeutic modalities in IBD.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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