Review

Role of microRNAs in the Pathophysiology of Ulcerative Colitis

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Abstract: Ulcerative colitis (UC) is an intractable disorder characterized by a chronic inflammation of the colon. Studies have identified UC as a multifactorial disorder affected by both genetic and environmental factors; however, the precise mechanism remains unclear. Recent advances in the field of microRNA (miRNA) research have identified an association between this small non-coding RNA in the pathophysiology of UC and altered miRNA expression profiles in patients with UC. Nevertheless, the roles of individual miRNAs are uncertain due to heterogeneity in both research samples and clinical backgrounds. In this review, we focus on miRNA expression in colonic mucosa where inflammation occurs in UC and discuss the potential roles of individual miRNAs in disease development, outlining the pathophysiology of UC.

Keywords: ulcerative colitis; inflammatory bowel disease; microRNA

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1. Introduction

Ulcerative colitis (UC) is a major type of inflammatory bowel disease (IBD), characterized by chronic inflammation of the colon and rectum. Inflammation confined to the mucosa is distributed continuously from the rectum to the proximal colon in UC and causes bloody stools, diarrhea, and abdominal pain [1]. Studies have demonstrated that the etiology of UC is based on complicated interactions among intestinal microbiota, dietary components, and host immune systems in genetically susceptible patients. However, the precise mechanisms underlying this pathology remain unclear [2]. Although there is currently no cure for UC, several new immunomodulatory drugs have been developed in recent decades. Furthermore, recent progress in genome-wide association studies (GWAS) has led to the identification of disease-associated loci, highlighting the mechanistic pathways involved in the development of UC, such as epithelial barrier, innate mucosal defense, and adaptive immune cell regulation [3]. However, the association risk with individual susceptibility loci is small and GWAS signals are often located in non-coding regions of the genome, suggesting that protein-coding genes alone cannot explain the disease mechanism. As a result, subsequent research has investigated the role of non-coding RNA, including microRNA in the pathophysiology of UC.

MicroRNAs (miRNAs) are a group of small (~22 nucleotides) non-coding RNAs that confer post-transcriptional regulation of target gene expression. Each miRNA can target hundreds of gene transcripts. Over 60% of human protein-coding genes harbor predicted miRNA target sites [4] that participate in the regulation of various biological processes, including cell proliferation, differentiation, apoptosis, and signal transduction [5]. As a result, miRNAs are implicated in a variety of diseases, including cancer, neurological diseases, cardiovascular diseases, and autoimmune diseases, such as IBD [6,7]. Dysregulated miRNA expression profiles have been reported in the saliva, peripheral blood, and intestinal mucosa of patients with UC compared to healthy individuals and patients with Crohn's disease (CD), another type of IBD [8,9]. In this review, we will specifically focus on the expression of miRNAs in the colonic mucosa, where inflammation occurs in UC, and discuss their potential contribution to disease pathophysiology.

2. Overview of miRNA

The first miRNA was discovered in 1993 as a critical regulator of developmental timing events in the nematode *Caenorhabditis elegans* [10]. Since then, over 2000 mature miRNAs have been identified in humans [11]. The mechanisms of miRNA biogenesis and miRNA-mediated gene regulation have been described in recent excellent reviews [5,12]; therefore, we will only briefly overview these mechanisms (Figure 1). miRNA genes located throughout the genome are first transcribed by RNA polymerase II or III to produce primary transcripts (pri-miRNAs). Pri-miRNAs are processed into precursor miRNAs (pre-miRNAs) in the nucleus via the actions of the microprocessor complex, consisting of the RNase III enzyme Drosha and the protein DiGeorge syndrome critical region 8 (DGCR8). Pre-miRNAs are exported to the cytoplasm by exportin 5 and further processed by the RNase III enzyme Dicer and TAR RNA binding protein (TRBP) to produce mature miRNAs. The mature miRNA provides 5p and 3p strands, which are derived from the 5' and 3' arms of the pre-miRNA hairpin, respectively. One strand is loaded into the RNA-induced silencing complexes (RISCs) with Argonaute (AGO) protein and silences target mRNA expression through mRNA cleavage, translational repression, or de-adenylation. This gene silencing process requires a complementary sequence in the 3'-untranslated region (3'-UTRs) of the target mRNA that can bind to the "seed" sequence (2–8 nt at the 5'-end) of miRNA. Although the effect of each miRNA is generally subtle, one miRNA can target hundreds of mRNAs, and multiple miRNAs cooperatively regulate the same gene [12]. This combinational targeting strategy of miRNAs enables them to regulate important cellular processes, including cell proliferation, apoptosis, differentiation, and signal transduction. These cellular changes and subsequent environmental changes can, in turn, regulate miRNA expression at multiple steps of biogenesis [7].

Figure 1. miRNA biogenesis and the mechanism of gene regulation. DGCR8, DiGeorge syndrome critical region 8; TRBP, TAR RNA binding protein; AGO2, Argonaute2; RISC, RNA-induced silencing complexes.

3. miRNA Profile in UC

Since first being reported in 2008 [13], an increasing number of studies have identified dysregulated miRNA expression profiles in the saliva, peripheral blood, and colonic mucosa of patients with UC [14]. These studies, especially those focusing on body fluids, were partially motivated by the potential usefulness of miRNAs as biomarkers for the diagnosis of disease or the monitoring of disease activity in UC. However, it should be noted that the miRNA profiles in the colon are different from those in body fluids [15]. In addition, heterogeneous comparators, including healthy individuals, patients with CD, and other types of intestinal disorders included in these studies make it difficult to interpret the significance of dysregulated miRNAs in the pathophysiology of UC. Therefore, in this review, we focus on miRNAs whose expression is altered in the colonic mucosa of patients with UC compared to healthy individuals. Table 1 shows a list of miRNAs whose colonic expression was consistently elevated or reduced in adult patients with UC compared to healthy individuals in more than two studies. Although these miRNAs are candidates for the “key miRNAs” involved in disease development, it should be kept in mind that their expression in UC may be affected by heterogeneous clinical background, which includes disease duration, medical treatment, and disease activity. Further investigations are necessary to clarify these associations.

Table 1. miRNAs with altered expression in colonic mucosa of patients with UC compared to healthy individuals.

miRNA	Expression	Inflammation on Samples	Detection Method
miR-16	Elevated	Inflamed [13,16,17]	Microarray [13,16], PCR [17]
miR-21	Elevated	Inflamed [13,16,18–22], Uninflamed [13], Unspecified [9,23–25]	Microarray [13,16,18,19,23], PCR [9,13,20–22,24,25]
miR-29a/b	Elevated	Inflamed [13,16,26,27], Uninflamed [13,26]	Microarray [13,16,27], PCR [13,26]
miR-31	Elevated	Inflamed [26,28], Unspecified [9,29]	smRNA-Seq [29], PCR [9,26,28,29]
miR-125b	Elevated	Inflamed [18,30,31], Uninflamed [18]	Microarray [18], PCR [18,30,31]
miR-126	Elevated	Inflamed [13,16,21,22,26], Uninflamed [13,26]	Microarray [13,16], PCR [13,21,22,26]
miR-142	Elevated	Inflamed [16,20,32]	Microarray [16,32], PCR [20,32]
miR-146a/b	Elevated	Inflamed [16,20,33], Unspecified [23,25,29]	smRNA-Seq [29], Microarray [16,23], PCR [20,25,29,33]
miR-155	Elevated	Inflamed [16,19,30,33]	Microarray [16,19], PCR [16,30,33]
miR-223	Elevated	Inflamed [22,26,27,30,31], Uninflamed [30], Unspecified [23]	Microarray [23,27], PCR [22,26,30,31]
miR-192	Reduced	Inflamed [13,20,27]	Microarray [13,27], PCR [13,20]
miR-200a/b/c	Reduced	Inflamed [16,20,27]	Microarray [16,27], PCR [20,27]
miR-378	Reduced	Inflamed [16,27], Unspecified [23]	Microarray [16,23,27]

smRNA-Seq, small RNA-sequencing.

4. miRNAs in the Pathophysiology of UC

Intestinal homeostasis is maintained on a single layer of epithelial cells, which separates potentially harmful luminal antigens, such as dietary components and microbiota, from mucosal immune cells. The mucus produced by goblet cells overlying the epithelium provides additional protection against the invasion of these antigens. The breakdown of these epithelial barrier systems and the subsequent activation of mucosal immune cells are critical steps in the disruption of intestinal homeostasis and disease development in UC.

The importance of miRNAs in epithelial barrier function has been previously reported in intestinal epithelial cell (IEC)-specific Dicer1 knock-out (KO) mice, which lack

all miRNAs in IECs [34]. Increased epithelial permeability and the development of spontaneous intestinal inflammation in these mice suggest a critical role for miRNAs in IEC biology and maintenance of epithelial barrier integrity. Similarly, selective Dicer1 or Drosha deletion in immune cells implicates miRNAs in regulating immune cell functions. Bone marrow-derived macrophages from Dicer1 KO mice produce decreased levels of pro-inflammatory cytokines compared to control mice upon stimulation with Toll-like receptors (TLRs) [35]. Dicer1-deficient T cells preferentially produce interferon gamma (IFN- γ) [36], while Drosha deficiency impairs the suppressive ability of regulatory T cells (Tregs) and induces spontaneous inflammatory disease in mice [37]. These findings collectively indicate the importance of miRNAs in maintaining intestinal homeostasis and suggest their potential roles in the pathophysiology of UC. In the following sections, we will discuss the potential contribution of UC-associated miRNAs to the disruption of intestinal homeostasis and disease development.

4.1. Mucus Barrier

Dysfunction of the mucus barrier has been reported in patients with UC, even in those with endoscopic remission [38–40]. Spontaneous colitis in mice lacking Muc2, a primary structural component of mucus, demonstrates the vital importance of mucus in intestinal homeostasis and suggests that mucus dysfunction can be a cause of, and not just a consequence, of colonic inflammation [41]. Deteriorated experimental colitis in Muc5ac-deficient mice further confirmed the importance of mucus in maintaining epithelial barrier integrity [42]. Although the mechanism of mucus dysfunction is unclear, goblet cell depletion, a pathological hallmark of UC, implies the impaired differentiation of goblet cells, the main producer of mucus, in UC [43]. Indeed, mice lacking the transcriptional factor Spdef responsible for goblet cell differentiation have a defect in the mucus barrier and subsequently develop spontaneous colitis [38]. Interestingly, miR-125b, which is upregulated in the colonic mucosa of patients with UC [18] targets Spdef and is reported to decrease mucus secretion in a mouse model of allergic airway inflammation by inhibiting goblet cell differentiation [44]. Therefore, upregulated miR-125b may contribute to the development of colitis in UC by suppressing SPDEF expression, thereby inhibiting goblet cell differentiation. On the other hand, several miRNAs may be able to directly modulate mucus expression (Table S1). These miRNAs include miR-16, which suppresses MUC5AC expression in nasal epithelial cells by directly targeting IKK β and thereby suppressing NF- κ B activity [45]. The overexpression of miR-31 targets IL-13 receptor α 1 (IL13RA1) [46] and suppresses IL-13-induced MUC5AC expression in nasal epithelial cells [47], while miR-155 suppresses LPS-induced MUC5AC expression by targeting SOCS1 [48]. MiR-378, whose expression is downregulated in UC, reduces MUC5AC expression in bronchial epithelial cells by directly targeting TNF (TNF- α). Collectively, these data suggest a strong association between miRNAs and the mucosal barrier system in UC.

4.2. Epithelial Permeability

The cell-to-cell junction between IECs is maintained by tight junction proteins (TJPs) and provides physical protection against invading luminal antigens. The altered expression of TJPs, such as a decreased expression of barrier-forming claudins and occludin and an increased expression of pore-forming claudin-2, has been reported in the colonic mucosa of patients with UC [49] and is implicated in increased paracellular permeability in symptomatic patients with UC [50,51]. In contrast to the breakdown of the mucus barrier, increased intestinal epithelial permeability is not accompanied by spontaneous colitis in genetically modulated mice with impaired TJP expression [52,53]. This suggests that the “leakiness” of the IEC monolayer alone may be insufficient for the onset of UC. A variety of miRNAs overexpressed in UC, such as miR-21, miR-31 [54], miR-142 [32], miR-155 [55], and miR-223 [56] are involved in the regulation of TJPs [57] (Table S1). MiR-21 downregulates the expression of tight junction protein 1 (TJP1) and occludin and increases epithelial permeability in vitro [24]. Increased miR-31-5p targets activin A receptor like type 1 (ACVRL1)

and may indirectly reduce the expression of TJP1 and occludin by inhibiting colonocyte differentiation through ACVRL1 and bone morphogenetic protein-9 (BMP9) interactions [58]. Enhanced epithelial permeability in BMP9-stimulated human colonic IECs [58] implies that the overexpression of miR-31-5p may contribute to the breakdown of the epithelial barrier in UC. MiR-142-5p directly targets and suppresses the expression of claudin-1 and increases the permeability of the thyroid monolayer in vitro [59]. In addition, miR-142-5p potentially targets transcripts encoding other TJPs, including claudin-8, occludin, and TJP1 [57]. Similarly, miR-155-5p targets the transcript of claudin-1 and potentially targets claudin-8 and occludin [60]. Interleukin (IL)-23-induced miR-223 increases epithelial permeability in colonic epithelial cells, at least in part, by directly targeting claudin-8 [56]. Collectively, these data suggest that UC-associated miRNAs have a detrimental effect on the maintenance of epithelial barrier integrity and the development of colitis (Figure 2).

Figure 2. Potential roles of UC-associated miRNAs in epithelial barrier disruption. TJP1, tight junction protein 1.

4.3. Innate Immune Cells

Intestinal lamina propria underlying the IEC monolayer is the largest reservoir of innate immune cells, including dendritic cells (DCs) and macrophages, in the human body. These cells recognize pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs), including TLRs, nucleotide binding, and oligomerization domain (NOD)-like receptors (NLRs). Stimulated PRRs subsequently activate downstream signaling cascades, including NF- κ B and mitogen-activated protein kinase (MAPK), and promote the production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-alpha, IL-6, IL-12, and IL-23 [1,61]. This prompt response through PRRs is indispensable for innate immune cells to function as the first line of defense against luminal antigens, but also requires negative feedback regulation to prevent excessive immune reactions and terminate inflammation. The aberrant and prolonged activation of innate immune cells causes sustained colonic inflammation, as found in mice with macrophage-restricted IL-10 receptor deficiency [62], which induce persistent macrophage activation due to lack of anti-inflammatory regulation through IL-10 receptors and is implicated in the development

of UC. Indeed, the efficacy of antibodies against innate immune cytokines, including TNF- α and IL-12/23p40 subunits, has already been established in the treatment of UC [1]. Several miRNAs, including miR-21, miR-146a, and miR-155, are involved in the negative feedback regulation of the innate immune response [63] (Table S2). TLR4 stimulation with lipopolysaccharide (LPS) induces miR-21 expression in macrophages, which in turn suppresses LPS-mediated production of pro-inflammatory cytokines from macrophages by directly targeting TLR4 and phosphatase and tensin homolog (PTEN), thereby inhibiting the TLR4-NF κ B signaling pathway [64,65]. Upregulated miR-21 also promotes the production of anti-inflammatory cytokine IL-10 from macrophages by silencing programmed cell death 4 (PDCD4) [65]. The expression of miR-146a is directly induced by NF- κ B binding to its promoter [66]. In turn, increased miR-146a negatively regulates TLR signaling by targeting interleukin-1 receptor-associated kinase 1 (IRAK-1) and TNF receptor associated factor 6 (TRAF6), resulting in a reduced production of IL-1 β , IL-6, and TNF- α in bacteria-infected macrophages [67]. MiR-146a also targets receptor interacting serine/threonine kinase 2 (RIPK2), an NLR signaling intermediate, and limits the production of Th17-driving cytokines, such as IL-1 β , IL-6, and IL-23, from intestinal DCs and macrophages in a mouse model of experimental colitis [68]. The induction of miR-155 is dependent on c-Jun N-terminal kinase (JNK) [69]. Induced miR-155 targets transforming growth factor β -activated protein kinase 1 (TAK1)-binding protein 2 (TAB2) and suppresses IL-1 β production in monocyte-derived DCs stimulated with LPS [70]. On the other hand, miR-155 targets suppressor of cytokine signaling 1 (SOCS1) and Src homology 2 domain-containing inositol-5-phosphatase 1 (SHIP1) and promotes the production of IL-6 and IL-23 from bone marrow-derived DCs stimulated with LPS [71], suggesting that miR-155 exerts bidirectional roles in the regulation of the innate immune response. Similarly, TLR stimulation downregulates the expression of miR-223, which targets ras homolog gene family member B, RhoB, in macrophages [72]. The downregulation of miR-223 increases RhoB expression, which leads to the activation of NF- κ B and MAPK signaling, and promotes TNF- α , IL-6, and IL-1 β production from macrophages upon LPS stimulation [72]. In addition, miR-233 targets NLRP3, an intracellular NLR forming a multiprotein inflammasome complex [73], and suppresses the production of IL-1 β and IL-18 in macrophages by limiting inflammasome activation [74,75].

miRNAs are also involved in macrophage polarization, a process by which macrophages adopt distinct functional phenotypes in response to signals from the microenvironment (Figure 3) [76]. Classically activated (M1) macrophages have a pro-inflammatory phenotype, whereas alternatively activated (M2) macrophages have an anti-inflammatory phenotype and are involved in tissue repair [77]. MiR-125b and miR-155 drive M1 polarization by directly targeting interferon regulatory factor 4 (Irf4) and IL13RA1, respectively [78,79]. MiR-146a drives M2 polarization, at least in part, by modulating the expression of Notch1 and inhibin β A subunit of activin A (INHBA) [80,81]. MiR-223 is required for peroxisome proliferator-activated receptor γ (PPAR γ)-dependent M2 macrophage activation by targeting nuclear factor of activated T cells 5 (Nfat5) and Ras p21 protein activator 1 (Rasa1) in mice [82]. Collectively, miRNAs play a crucial role in regulating innate immune responses by targeting PRR signaling molecules at multiple levels of cascades and directly modulating the functions of innate immune cells.

Figure 3. Potential roles of UC-associated miRNAs in aberrant mucosal immune response. MiRNAs with suppressive function are highlighted in blue. M1, M1 macrophage; M2, M2 macrophage; DC, dendritic cell; Th, helper T cell; CCR6, chemokine receptor 6; CXCR4, C-X-C motif chemokine receptor 4; S1P1, sphingosine-1-phosphate receptor 1.

4.4. Adaptive Immune Cells

Antigen presentation and cytokine production by activated innate immune cells induce the maturation and development of T cells within inductive sites, such as gut-associated lymphoid tissue (GALT) and mesenteric lymph nodes. Aberrant T cell activation and preferential differentiation towards pathogenic phenotypes on these inductive sites are strongly implicated in the development of UC [73]. Although UC is thought to be a type 2 helper T (Th2) cell-driven disease, studies have demonstrated the involvement of other T cell lineages, including Th1, Th9, Th17, and Tregs, in disease progression [73].

miRNAs are involved in the regulation of adaptive immune responses by modulating T cell differentiation and function (Table S3, Figure 3). These miRNAs include miR-21, which increases in response to IL-13, a major cytokine upregulated in the colonic mucosa of patients with UC [83]. MiR-21 promotes Th2 differentiation, at least in part, by directly targeting the transcript of IL-12p35 and modulating IL-12 production from DCs [84,85]. At the same time, it suppresses the apoptosis of activated T cells, at least in part, by targeting TNF alpha-induced protein 8-like protein 2 (Tnfaip8l2) [86,87]. MiR-31 promotes Th1 differentiation by targeting hypoxia inducible factor 1 subunit alpha inhibitor (HIF1AN), mitogen-activated protein kinase kinase kinase 14 (MAP3K14), and SH2 domain containing 1A (SH2D1A) [88], while it negatively regulates peripherally derived Tregs by targeting Gprc5a [89]. MiR-155 contributes to the attenuation of Th2 cell responses in vitro, at least in

part, by targeting c-Maf, a potent trans-activator of the IL-4 promoter [90,91], while it skews T cell differentiation towards Th17 lineage mainly by a cell-intrinsic mechanism, promoting autoimmune encephalomyelitis in a rodent model of multiple sclerosis [71]. Wang et al. also demonstrated the Th9- and Th17-driving effects of miR-155 by targeting c-Maf in murine splenocytes and found an ameliorated wound healing in miR-155-deficient mice using a skin wound mouse model [92]. Forkhead box P3 (Foxp3)-induced miR-155 promotes the proliferative ability of thymic and peripheral Tregs by preventing SOCS1-dependent suppression of IL-2 receptor signaling [93]. These data suggest that the overexpression of miR-21 and miR-155 may enhance colonic inflammation in UC by driving pro-inflammatory T cell differentiation and enhancing adaptive immune responses.

In contrast to miR-21 and miR-155, several UC-associated miRNAs function as negative regulators of adaptive immune responses. These miRNAs include miR-29 and miR-146a, whose expression is increased in UC. The NOD2-mediated upregulation of miR-29 suppresses IL-23 production in dendritic cells by targeting IL-12p40 directly and IL-23p19 indirectly, and thereby inhibits Th17 differentiation [94]. In addition, miR-29 directly targets T-bet (Tbx21) and eomesodermin (Eomes), transcriptional factors responsible for Th1 differentiation, and reduces IFN- γ production in T cells [95]. MiR-146a limits the production of Th17-driving cytokines from innate immune cells, restricts colonic IL-17, and attenuates colonic inflammation in a mouse model of experimental colitis [68]. Similarly, miR-146a prevents Th17 differentiation in a rodent model of multiple sclerosis by reducing the production of IL-6 and IL-21 from auto-reactive T cells [96]. MiR-146a also ensures the regulatory T (Treg) cell-mediated control of Th1 responses, at least in part, by targeting signal transducer and activator transcription 1 (Stat1) [97]. These findings suggest that the overexpression of miR-29 and miR-146a in UC function as negative regulators of activated pro-inflammatory Th1 and Th17 responses in the inflamed colon.

B cells are another type of adaptive immune cells that have a multitude of functions, including antibody production, antigen presentation, and cytokine production. B cells also exhibit immunosuppressive functions through diverse regulatory mechanisms [98]. This subset of B cells, known as regulatory B cells (Bregs), contributes to the regulation of intestinal inflammation and is thus implicated in the pathophysiology of UC [99–101]. Several miRNAs, including miR-21 and miR-146a, have been implicated in regulating the differentiation and function of Bregs. MiR-21 works as a negative regulator of Bregs by directly or indirectly targeting IL-10. Thus, the silencing of miR-21 ameliorates experimental autoimmune encephalomyelitis (EAE) in mice by promoting the differentiation of IL-10-producing Bregs [102]. MiR-146a-deficient mice show reduced expression of kidney injury molecule-1 (Kim1), a critical factor for maintaining Breg functions [103], in B cells, as well as showing a decreased number of IL-10-producing Bregs in the spleen [104]. The development of an autoimmune-mediated glomerulonephritis in miR-146a-deficient mice [104] implies a vital role of this miRNA in regulating the adaptive immune system by promoting Breg differentiation. Further study is needed to determine the role of miRNAs in the pathophysiology of UC by regulating the differentiation and function of Bregs.

4.5. Intestinal T Cell Homing

Selective T cell homing to the colon plays a critical role in the development of colitis in UC [1]. This process relies on the interaction between $\alpha 4\beta 7$, a cell adhesion molecule expressed on T cells, and MAdCAM-1, expressed on endothelial cells with the support of chemokine receptors, including G-protein-coupled receptor 15 (GPR15) and chemokine receptor 6 (CCR6) [105], and sphingosine-1-phosphate receptor 1 (S1P1) [106]. Antibodies against $\alpha 4\beta 7$ integrin [107], MAdCAM-1 [108] and S1P modulators [109,110] are effective treatments for patients with UC. The relationship between dysregulated miRNAs and intestinal T cell homing in UC remains unclear. However, a number of reports have demonstrated that several miRNAs regulate the expression of cell adhesion molecules and chemokine receptors in mice. For example, miR-21 directly targets and suppresses CCR7 expression in activated naïve T cells [111]. A lack of miR-155 expression was found

to reduce the expression of CCR5, C-X-C motif chemokine receptor 4 (CXCR4), and S1P1 receptor on T cells, as well as alleviating intestinal inflammation, in a mouse model of acute graft-versus-host disease (GVHD) [112,113]. Park et al. reported that exosomes, nano-sized lipid bilayer bioparticles, secreted from gut-tropic T cells, are enriched with miRNAs targeting NK2 homeobox 3 (NKX2-3), a transcription factor responsible for MAdCAM-1 expression, thereby inhibiting intestinal T cell homing [114]. Therefore, the impact of dysregulated miRNAs on intestinal T cell homing in UC should be a critical focus in future studies.

4.6. Overall Effect of Individual miRNAs in the Development of Colitis

We have discussed the roles of UC-associated miRNAs in the regulation of the epithelial barrier and mucosal immunity and how the dysregulation of these miRNAs may affect intestinal homeostasis in patients with UC. These findings provide insights into the functional importance of individual miRNAs in the development of colitis, which was further confirmed in mouse models of experimental colitis resembling UC. Dextran sulfate sodium (DSS)-induced colitis is the most frequently used UC model, with many studies demonstrating the effect of specific miRNA deletion/inhibition or overexpression in the development of acute colitis (Table 2). Nevertheless, it should be noted that these results only show the overall impact of individual miRNAs in the acute phase of colitis. Further studies are needed to understand the cell-type-specific roles of miRNAs in different phases of colitis.

Table 2. Role of UC-associated miRNAs in dextran sodium sulfate (DSS)-induced acute colitis.

miRNA	Expression in UC	miRNA Modulation in Mice	Result (Degree of Colitis)
miR-16	Elevated	Inhibited	Ameliorated [115]
miR-21	Elevated	Deficient	Ameliorated [116]
miR-29a/b	Elevated	Deficient	Deteriorated [94]
miR-31	Elevated	Deficient	Deteriorated [117]
miR-126	Elevated	Deficient	Deteriorated [118]
miR-146a/b	Elevated	Deficient (miR-146a) Overexpressed (miR-146b)	Deteriorated [68] Ameliorated [119]
miR-155	Elevated	Deficient	Ameliorated [120]
miR-223	Elevated	Overexpressed	Ameliorated [75]
miR-200a/b/c	Reduced	Inhibited (miR-200c)	Ameliorated [121]

5. Potential of miRNAs as Therapeutic Targets in UC

There is a growing interest in the manipulation of miRNAs with antagonists or mimics for use as therapeutic targets in UC, similar to other fields of disease [122–124]. However, despite promising results from rodent models of IBD, clinical application of miRNA-based therapy has not yet been established in UC due to several limitations [125]. First, currently available data on miRNA expression profiles in patients with UC are heterogeneous in terms of clinical background. The potential impacts of a heterogeneous background, including disease activity, duration, and treatment contents, on miRNA expression should be noted when identifying a therapeutic target of miRNA. Second, previous reports have investigated colonic miRNA expression profiles in diseases endoscopically using biopsy specimens. Therefore, the cell-type specific expression of miRNAs is largely unknown. Investigating miRNA expression in a single cell-type specific manner is necessary to understand the impact of dysregulated miRNAs on the etiology of UC and to identify appropriate targets for therapeutic manipulation. Third, recent advances in technologies of drug delivery, such as lipid nanoparticles and dendrimer complexes with a targeting moi-

ety attached, have enabled miRNA-based treatment in clinical practice [126]. These include miR-16 mimic (MesomiR-1, EnGeneIC Ltd., Sydney, NSW, Australia) encapsulated in lipid vesicles for mesothelioma [127], cholesterol-conjugated miR-29 mimic (Remlarsen/MRG-201, miRagen Therapeutics Inc., Boulder, CO, USA) for scleroderma [128], and a locked nucleic acid-modified oligonucleotide inhibitor of miR-155 (Cobomarsen/MRG-106, miRagen Therapeutics Inc., Boulder, CO, USA) for cutaneous T cell lymphoma [129]. Despite these advances, tissue- or cell type-specific treatments remain technically challenging. Since individual miRNAs can target hundreds of transcripts, establishing a tissue/cell type-specific targeting technology is key to avoid potential toxicities and off-target effects. Successfully resolving these problems will carve a concrete path toward the development of novel miRNA-based therapeutics in UC, which would enhance intestinal epithelial barrier and/or modulate mucosal immune response. Antagonizing miR-21 and miR-155 might be of particular interest for clinical application considering their multifaceted roles in the pathophysiology of UC.

6. Conclusions

Recent progress in the field of miRNA research has provided strong evidence of the association between dysregulated miRNAs and the pathophysiology of UC. However, the role of individual miRNAs is not yet fully understood due to the heterogeneity of the data obtained from diverse tissues and cell types. In this review, we focused on miRNAs whose expression was altered in the colonic mucosa of patients with UC to specifically understand their role in the location of inflammation. We outlined the pathophysiology of UC and discussed the potential roles of miRNAs in each step of disease development. The findings presented in this review will serve as a guide for researchers who wish to determine the direction of their work in this field.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/immuno1040039/s1>, Table S1: Role of UC-associated miRNAs in intestinal epithelial permeability, Table S2: Role of UC-associated miRNAs in innate immunity, Table S3: Role of UC-associated miRNAs in adaptive immunity.

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