MicroRNA Biomarkers in IBD

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Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC). These are chronic autoimmune diseases of unknown etiology affecting the gastrointestinal tract. The IBD population includes a heterogeneous group of patients with varying disease courses requiring personalized treatment protocols. The complexity of the disease often delays the diagnosis and the initiation of appropriate treatments. In a subset of patients, IBD leads to colitis-associated cancer (CAC). MicroRNAs are single-stranded regulatory noncoding RNAs of 18 to 22 nucleotides with putative roles in the pathogenesis of IBD and colorectal cancer. They have been explored as biomarkers and therapeutic targets. Both tissue-derived and circulating microRNAs have emerged as promising biomarkers in the differential diagnosis and in the prognosis of disease severity of IBD as well as predictive biomarkers in drug resistance. In addition, knowledge of the cellular localization of differentially expressed microRNAs is a prerequisite for deciphering the biological role of these important epigenetic regulators and the cellular localization may even contribute to an alternative repertoire of biomarkers.

biomarkers | circulating miRNA | colitis-associated cancer (CAC) | Crohn's disease (CD) | inflammatory bowel disease (IBD) | microRNA (miRNA) | ulcerative colitis (UC)

1. Introduction

Inflammatory bowel disease (IBD) refers to Crohn's disease (CD) and ulcerative colitis (UC). In UC, inflammation generally includes the rectum and extends towards the coecum and remains confined to the colon. In contrast, in CD, inflammation can involve any part of the gastrointestinal tract (GI) from the oral cavity to the anus. Both CD and UC are associated with multiple pathogenic factors such as environmental changes, the array of susceptibility gene variants, qualitatively and quantitatively abnormal gut microbiota and broadly dysregulated immune response [1]. Although CD and UC have some common pathological and clinical characteristics, they have several different attributes that imply that they are two distinct disease subtypes. In CD, fissuring ulceration and sub-mucosal fibrosis can be observed along with granulomatous inflammation. In UC, the inflammatory process always involves the rectum [2] and general histological findings include crypt distortion, infiltration of lymphocytes and granulocytes and chronic inflammation, usually confined to the lamina propria [3]. The diagnosis of IBD is usually established by a collective assessment of clinical presentation and endoscopic, histopathological, radiographic and laboratory findings. A definitive diagnosis of IBD cannot be made without detailed endoscopic and histologic assessment [4]. However, a subset of IBD cases cannot be classified as either CD or UC but are categorized as IBD unclassified

(IBDU). Molecular biomarkers may support differential diagnosis of IBDU cases into CD or UC, or even be helpful in determining if IBDU represents a unique IBD diagnostic entity.

IBD starts developing at a younger age, including in infants [5], and is often characterized by a considerable diagnostic and therapeutic challenge because of the disease's clinical features and associated complications. The prevalence of IBD in the Western world is projected to be up to 0.5% of the overall population [6]. In Denmark, where one of the highest annual incidence rates of IBD in Europe is seen, the incidence has been increasing over the last three decades [7]. In 2013, the incidence was 9.1 per 100,000 persons and 18.6 per 100,000 persons for CD and UC, respectively [8]. Since the turn of the 21st century, IBD has become a global disease with accelerating incidence rates also in developing countries whose societies have adopted a western diet and lifestyle. Although the incidence rate has become steady in western countries, the burden remains high, as prevalence exceeds 0.3%. The chronical inflammatory condition in the affected colon of IBD patients has been linked to development of neoplastic lesions in the colon. Several studies have shown a higher incidence of colorectal cancer (CRC) in IBD patients [9][10][11]. No biomarkers exist for the identification of IBD patients at risk of developing colitis-associated cancer (CAC), strongly advocating for more translational research in this field.

In this review, we give an overview of microRNAs (miRNAs) as candidate biomarkers in the IBD diagnostic assessment. Changes in miRNA levels are associated with disease development and can be measured both within the diseased tissue and in the circulation by a variety of molecular methods. MiRNAs have been found to be well conserved in archived tissue specimens, enabling retrospective analyses of clinical sample cohorts.

2. MicroRNA—An Introduction

MiRNAs play a central role in the regulation of several immune-mediated disorders including IBD [12][13][14]. MiRNAs are a group of small noncoding RNAs, approximately 18–22 nucleotides [15] which are found conserved across species. Their discovery was first described first in 1993 in Caenorhabditis elegans [16]. MiRNAs are transcribed as primary transcripts by RNA polymerase, processed into a precursor miRNA by the RNase III enzyme, Drosha, and exported from the nucleus to the cytoplasm. The precursor miRNA is cleaved by the RNase III enzyme, Dicer, into its mature form, which becomes stably incorporated into an RNA induced silencing complex (RISC). The miRNA guides the binding of the RNA-induced silencing complex to complementary sequences in the 3′-untranslated regions (UTR) of target mRNA molecules, resulting in either mRNA degradation or translational inhibition [17]. During stages of miRNA biogenesis, several factors can influence the development of the mature miRNA. These include regulation of transcription, cleavage of the stem loop structures by Drosha and Dicer enzymes, and editing as well as regulation of miRNA turnover. Each of these mechanisms acts as part of a signaling network that modulates gene expression in response to cellular or environmental changes.

MiRNA expression has been shown to be of importance in a wide variety of human diseases such as cancer, autoimmune, cardiovascular, and neurodegenerative diseases [18][19][20][21][22][23][24]. The miRNAs not only circulate in the human peripheral blood in a stable form, they are also present in other body fluids such as urine, saliva, milk, cerebrospinal fluid, and feces [25][26][27][28]. The miRNAs are engaged in disease origin and development, and some

are pathology-specific [29], thus, changes in miRNA expression profiles have been addressed for applications in early detection as well as prognostics, diagnostic classification and drug response prediction.

3. MiRNAs in IBD

In IBD, miRNAs have been found to be involved in pathogenesis and have been identified as both diagnostic biomarkers and therapeutic targets [30]. Most of the recent research in the IBD field has measured levels of circulating miRNAs in body fluids such as blood or feces, and in homogenized tissue biopsies using techniques like microarray profiling, RT-qPCR, and NGS [31][32][33][34]. Studies have also performed tissue miRNA expression analysis using in situ hybridization (ISH) methods [35][36][37]. ISH methods for expression analyses of miRNAs can determine the cellular origin of miRNA expression and can offer insight into the biology of the disease mechanisms involved. Local expression levels of miRNAs can greatly vary from those of circulating miRNAs, e.g., due to contribution of miRNAs from circulating cells. Esquela-Kerscher and Slack [38] proposed that tumor cells release miRNAs into the neighboring microenvironment and enter circulation during angiogenesis. Some studies suggest that this likely occurs through exosomal release from cells [39][40]. Changes in the levels of circulating miRNA may occur due to other inflammatory reactions or the host immune response rather than only due to the intrinsic changes within the lesion [41]. Thus, as discussed further below, it is not surprising that miRNAs analyzed in tissue biopsies poorly correlate with those found in the circulation [42]

There is an increasing interest in exploring epigenetic mechanisms in common diseases, with notable progress in characterizing the contribution of miRNAs [43]. In their 2008 study, Wu et al. found that miRNAs regulate colonic epithelial cell-derived chemokine expression and were the first to relate miRNAs to IBD [44]. The field of miRNA research has grown rapidly after their discovery in human disease biology including in IBD [43]. We have listed a series of IBD-related miRNA studies from recent years in Table 1, with a focus on sample type and quantitative method. MiR-21, miR-155, and miR-31 have repeatedly been identified and seem to be the most studied miRNAs related to IBD [45][46][47][48]. MiR-21 is possibly the most intriguing miRNA involved in IBD, with associations between miR-21 and IBD being replicated in several studies, as well as functional relevance reported in mouse models of IBD [49][50]. Each miRNA can potentially target hundreds of mRNAs resulting in mRNA destabilization and/or inhibition of translation, however, restricted to a specific cellular context, the number of relevant targetable transcripts is probably quite low.

MiRNAs regulate important cellular functions such as cell differentiation and proliferation and signal transduction and apoptosis and exhibit highly specific regulated patterns of gene expression [15]. In autoimmune diseases, miRNAs can act through interference with inflammatory signaling pathways, such as the nuclear transcription factor kappa B (NF-κB) pathway, IL23/IL23R pathway, and IL-6/STAT3 pathway[51][52][53][54][55]. Studying the RhoB pathway of cell adhesion in UC mucosa and cultured colon cancer cells, Yang et al. [36] examined the role of miR-21 in regulation of intestinal epithelial barrier function and found that miR-21 induced the degradation of RhoB mRNA, reduction in RhoB protein, causing loss of tight junctions in intestinal epithelial cells. Tian et al. showed miR-31 to be highly expressed in tissues from IBD patients, and miR-31 reduced the inflammatory response in the Dextran Sodium Sulphate (DSS)-induced colitis mouse model (see below), by preventing the expression of

inflammatory cytokine receptors such as IL7R and IL17RA and signaling proteins such as GP130 [56]. Another study based on the DSS model showed that miR-155 directly binds to SHIP-1 mRNA and causes a significant decrease in SHIP-1 levels, which regulate cell membrane trafficking, and thereby contribute to the pathogenesis of colitis [57]. Taken together, these examples indicate the complexity of how miRNAs may act through signaling pathways in the biological settings of IBD.

Studies of circulating miRNAs have shown that miRNAs are potential candidates as biomarkers for diagnosing IBD and various other diseases [58][59][60][61][62]. The high stability of miRNAs in the body fluids and the ability to obtain rapid and accurate quantitative estimates are some merits of using circulating miRNAs as biomarkers in IBD [28]. MiRNAs are not only interesting tools for diagnosis, but also for potential future therapeutic applications by miRNA mimics or miRNA antagonists [63][64].

Table 1. A summary of studies on microRNA research in inflammatory bowel disease (IBD). CD: Crohn's disease, UC: Ulcerative colitis, HC: Healthy controls, RT-qPCR: Quantitative real time polymerase chain reaction, Biopsy: colon tissue biopsy, ISH: In situ hybridization, QISH: Quantitative in-situ hybridization, PBMC: Peripheral blood mononuclear cells, DSS: Dextran sodium sulphate, AOM: Azoxymethane, TNF: Tumor necrosis factor alpha.

#	MiRNAs	Disease Subtype	Sample Type	Techniques Used	Outcome	Reference
1	miR-16, miR-29a, miR-199a-5p, miR-363-3p, miR-340, miR-532-3p, miRplus-1271, miR-140-3p, miR-127-3p, miR-196b, miR-877, miR-150	CD, UD, HC	Serum, Biopsy	RT-qPCR, Microarray	Mixed outcomes	[42]

2	miR-223-3p, miR-31-5p	CD, HC	Biopsy	Nano string	Mir-223-3p expression showed age and sex effects and miR-31-5p expression was driven by location	[45]
3	miR-29b	CD	Fibroblasts	RT-qPCR	MCL-1 is modulated in CD fibrosis by miR-29b via IL-6 and IL-8	[65]
4	miR-141, miR-200a, miR-200b, miR-200c	UC, CD	Biopsy	RT-qPCR	All investigated miRNAs were significantly down regulated in CD, and 3 of them were downregulated in UC in comparison to the normal or the least affected mucosa.	[66]
5	miR-141	UC, HC	Biopsy	Microarray, RT-qPCR	MiR-141 plays a role in the bowel inflammation of individuals with active UC via down regulation of CXCL5 expression.	[67]
6	miR-124	UC, HC	Biopsy	RT-qPCR	MiR-124 regulates the expression of STAT3. Reduced levels of miR-124 in colon tissues of children with active UC appear to increase expression and activity of STAT3.	[68]

7	miR-19b	CD, HC	Biopsy, Cell culture	RT-qPCR, ISH	MiR-19b suppresses the inflammation and prevents the pathogenesis of CD.	[69]
8	miR-590-5p	CD, HC	Human and mice tissues	RT-qPCR	Decreased miR-590-5p levels in CD.	[70]
9	miR-122	CD, HC	Biopsy	RT-qPCR, Sequencing	Significant increase of miR-122 expression in cells treated with 5′-AZA.	[71]
10	miR-10a	CD, UC, HC	Biopsy	RT-qPCR	Dendritic cell activation and Th1/Th17 cell immune responses were inhibited via miR-10a in IBD.	[72]
11	miR-192	CD, UC, HC	Biopsy	RT-qPCR, Microarray, ISH	MiR-192 with decreased expression in active UC.	[44]
12	miR-15a	CD, UC, HC	Biopsy, Cell cultures	RT-qPCR	MiR-15a negatively regulates epithelial junctions through Cdc42 in Caco-2 cells	[73]
13	miR-146a, miR-155	CD	Biopsy	RT-qPCR	MiR-146a and -155 shows increased duodenal expression in pediatric CD.	[74]

14	miR-146b-5p	CD, UC, HC	Serum	RT-qPCR	Higher expression of serum miR-146b-5p in patients with CD and UC than in HC.	[75]
15	miR-425	CD, UC, HC	Biopsy, PBMC	RT-qPCR	Increased expression of miR-425 in IBD.	[76]
16	miR-301a	IBD	PBMC, Biopsy	RT-qPCR	MiR-301a promotes intestinal mucosal inflammation via induction of IL-17a and TNF in IBD.	[77]
17	miR-125b, miR-155, miR-223 and miR-138	UC	Biopsy	RT-qPCR, Microarray	Differential expression of miR-223, miR-125b, miR-138, and miR-155 in the inflamed mucosa compared to non-inflamed mucosa and controls.	[48]
18	miR-16, miR-21, miR-155, and miR-223	CD, UC, HC	Serum, Feces	RT-qPCR	Differential expression of miR-16, miR-155, miR-21, and miR-223 in IBD.	[46]
19	miR-21	UC, HC	Biopsy	RT-qPCR, ISH	Over expression of miR-21 in UC.	[36]

20	miR-133a	IBD	Mice Tissue	RT-qPCR	MiR-133a-UCP2 pathway participates in IBD by altering downstream inflammation, oxidative stress, and markers of energy metabolism.	[78]
21	miR-20b, miR-98, miR-125b-1, let-7e	CD, UC, HC	Biopsy	RT-qPCR, Microarray	MiR-20b, miR-98, miR-125b-1, and let-7e are deregulated in patients with UC.	[79]
22	miR-155	CD, HC	PBMC	RT-qPCR, Transfection	MiR-155 regulates IL-10-producing CD24 CD27+ B Cells.	[80]
23	miR-21, miR-126	CD, UC, HC	Biopsy	RT-qPCR, qISH	Endothelial expression of miR-126 are increased in UC. MiR-21 is expressed in subsets of monocytes/macrophages and T cells.	[35]
24	miR-31	CD, UC, HC	Cell culture, Biopsy	RT-qPCR, ISH, Transfection	Expression of miR-31-3p in human colonic epithelial cells.	[81]
25	miR-21, miR-155	UC, HC	Biopsy	RT-qPCR	MiR-21 and miR-155 was highly expressed in UC.	[82]
26	miR-15	UC, HC, IBS	Biopsy	RT-qPCR	MiR-15 activates NF-κB Pathway in UC.	[83]

27	miR-143, miR-145	UC, HC	Biopsy	RT-qPCR, ISH	MiR-143 and miR-145 are down regulated in UC.	[84]
28	miR-206	UC, HC	Cell culture, Biopsy	RT-qPCR,	MiR-206 as a biomarker for response to mesalamine treatment in UC.	[85]
29	miR-193a-3p	UC, HC	Cell culture, Biopsy	RT-qPCR, ISH	MiR-193a-3p reduces intestinal inflammation in response to microbiota.	[86]
30	miR-19a	UC, HC	Biopsy, mice tissue	RT-qPCR	Reduced expression of miR-19a in human colon tissue with UC and in DSS-treated mice colitis.	[87]
31	miR-21-5p	UC, HC	Sera, rat tissue	RT-qPCR, Transfection	MiR-21-5p was down regulated in the sera and colon tissue of UC compared with healthy people and the control group.	[88]
32	miR-200b	CD, HC	Biopsy, Serum. Cell culture	RT-qPCR	MiR-200b is involved in intestinal fibrosis of CD.	[89]
33	miR-155	Colitis	Mice tissue, cell culture	RT-qPCR, Transfection	MiR-155 promotes the pathogenesis of experimental colitis by	[57]

					repressing SHIP-1 expression.	
34	miR-31	IBD, CAC, CRC	Biopsy	RT-qPCR, Microarray, Transfection	MiR-31 expression levels as a marker for disease progression and to discriminate distinct pathological entities that co-exist in IBD.	[90]
35	miR-150	UC, HC	murine model	RT-qPCR	MiR-150 was elevated and c-Myb were down regulated in human colon with active UC compared to HC.	[91]
36	miR-122	CD	Cell culture	RT-qPCR, Transfection	MiR-122 reduces the expression of pro-inflammatory cytokines (TNF and IFN-γ) and promotes the release of anti-inflammatory cytokines (IL-4 and IL-10).	[92]
37	miR-141	CD	Murine models, Biopsy	Microarray, RT-qPCR	MiR-141 regulates colonic leukocytic trafficking by targeting CXCL12β during murine colitis and human CD.	[93]
38	miR-7	CD, HC	Cell culture,	Transfection, RT-qPCR	MiR-7 modulates CD98 expression during	[94]

			Biopsy		intestinal epithelial cell differentiation.	
39	miR-146b	IBD	IL-10 deficient mouse	Microarray, Transfection, DSS induced colitis in vivo	MiR-146b improves intestinal injury in mouse colitis.	[95]
40	miR-21	IBD	IL-10 deficient mouse, Biopsy	DSS-induced Experimental Colitis, RT-qPCR, ISH	MiR-21 is overexpressed in intestinal inflammation and tissue injury.	[96]
41	miR-215	UC, CAC	Biopsy	Nano string	MiR-215 discriminates patients who progressed to neoplasia as early as 5 years prior to the diagnosis of neoplasia	[97]
42	miR-449a	HC, CAC	DSS animal model biopsy	RT-qPCR, ISH	MiR-449a expression decreased gradually during the progression of CAC	[98]
43	miR-135a	CAC	DSS mouse model biopsy	ISH, RT-qPCR	MiR-135a in colonic cells were suppressed and up-regulating miR-135a inhibited apoptosis and inflammation of colonic epithelial cells	[99]

44	miR-146a, miR-155, miR-122	CD, UC, HC	Biopsy	RT-qPCR	Altered expression of all three miRNAs in colonic mucosa of children with IBD	[46]
45	miR-146a, miR-335, miR-26b and miR-124	CD, UC, CRC	Genome-wide expression profiles	Bioinformatics	MiR-146a, miR-335, miR-26b and miR-124 were identified in CD, UC, and CRC samples	[100]
46	miR-155	CAC, HC	AOM and DSS mouse model biopsy	Microarray, RT-qPCR	MiR-155 is upregulated in and relates to CAC	[101]

To study the pathogenesis and intricacy of IBD, the advancement of a variety of animal models has provided important information. The most extensively used mouse model of colitis utilizes DSS, a so-called chemical colitogen with anticoagulant properties, to stimulate epithelial damage. The DSS colitis model is simple and easy to administer. Acute and persistent colitis is achieved by altering the concentration of DSS and the frequency of administration [102]. A genetically engineered in vivo model that has been widely used to examine IBD etiology is the interleukin-10 (IL-10)-deficient mouse model [103]. IL-10 is an anti-inflammatory cytokine. Mutated IL-10 signaling systems shows early and aggressive expansion of systemic inflammation in IBD. IL-10 knockout mice develop spontaneous colitis and CAC [104]. Nata et al. [95] performed miRNA microarray profiling on IL-10-deficient mice and identified that several miRNAs were upregulated, including miR-146b that, through further studies, was found to contribute to increased intestinal inflammation by upregulating NF-κB. Shi et al. [96] showed that knockout of miR-21 in mice improved the survival rate in DSS-induced fatal colitis via protecting against inflammation and tissue injury. Hence, it was suggested that impaired expression of miR-21 in gut may block the onset or progression of IBD. Other animal models used in IBD research include genetically engineered mice, congenic mouse strains, chemically induced models, and cell-transfer models [105]. Most of the studies investigating miRNA

expression in IBD have used high-throughput methods such as a microarray combined with RT-qPCR as a validation method for prioritized miRNAs.

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