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EDITORIAL

MicroRNAs in inflammatory bowel disease - pathogenesis, diagnostics and therapeutics

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Abstract

The pathogenesis of inflammatory bowel disease (IBD) is complex and largely unknown. Until recently, research has focused on the study of protein regulators in inflammation to reveal the cellular and molecular networks in the pathogenesis of IBD. However, in the last few years, new and promising insights have been generated from studies describing an association between an altered expression of a specific class of non-coding RNAs, called microRNAs (miRs or miRNAs) and IBD. The short (approximately 22 nucleotides), endogenous, single-stranded RNAs are evolutionary conserved in animals and plants, and regulate specific target mRNAs at the post-transcriptional level. MiRNAs are involved in several biological processes, including development, cell differentiation, proliferation and apoptosis. Furthermore, it is estimated that miRNAs may be responsible for regulating the expression of nearly one-third of the genes in the human genome. Thus, miRNA deregulation often results in an impaired cellular function, and a disturbance of downstream gene regulation and signaling cascades, suggesting their implication in disease etiology. Despite the identification of more than 1900 mature human miRNAs, very little is known about their biological functions and functional targets. Recent studies have identified dysregulated miRNAs in tissue samples of IBD patients and have demonstrated similar differences in circulating miRNAs in the serum of IBD patients. Thus, there is great promise that miRNAs will aid in the early diagnosis of IBD, and in the development of personalized therapies. Here, we provide a short review of the current state-of-the-art of miRNAs in IBD pathogenesis, diagnostics and therapeutics.

Key words: Biomarker; Crohn's disease; Diagnostics; Inflammatory bowel disease; MicroRNA; Therapeutics; Ulcerative colitis

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INTRODUCTION

Inflammatory bowel disease (IBD), whose incidence is

increasing[1], comprises a number of intestinal chronic relapsing inflammatory disorders[2-4], among which ulcerative colitis (UC)[5] and Crohn's disease (CD)[6] are the two main entities. The pathogenesis of IBD remains largely unknown[7,8], but involves a complex interaction between genetic, environmental, and immunological factors[9,10]. In this context, research on microRNAs (miRs or miRNAs) is a promising new research, providing novel insights into the pathogenesis of IBD, biomarker identification, and treatment. Since their discovery and initial characterization in 1993[11,12], the number of miRNA sequences deposited in the miRBase database (Sanger Database) has grown continuously[13]. Numerous investigations have uncovered the key roles of miRNAs in several physiological networks[14-18]. Given their ability to target mRNAs and their predicted regulation of the expression of nearly one-third of all human transcripts, miRNAs have been linked to critical processes underlying development and tissue homoeostasis. Thus, dysregulation of miRNAs is implicated in the pathogenesis of several human diseases[18-26], including gastrointestinal disorders, such as cancer and inflammation[27-29]. Actually, loss of intestinal miRNAs in mouse models has been shown to impair differentiation of intestinal cells and epithelial barrier function, resulting in inflammation[30].

The discovery and role of miRNAs in IBD, particularly their role in cell signaling, seems to offer a new way of understanding this chronic disease and gives rise to new diagnostic tools and potential therapeutic strategies. Thus, it is possible that some miRNAs could serve as biomarkers for IBD, aiding early diagnosis, and lead to the development of personalized therapies.

Here we provide a short review of the current research in miRNAs in IBD; including pathogenesis, diagnostics and therapeutics.

MiRNA BIOGENESIS

MiRNAs are a recently discovered class of short (18-24 nucleotides in length), endogenous, non-coding single-stranded RNAs that regulate gene expression by controlling the stability and translation of protein-coding mRNAs[26,31,32]. A number of biological processes are regulated by miRNAs, including cell differentiation, proliferation, apoptosis, and cell cycle control[30,33,34]. Long primary miRNA transcripts (pri-miRNA) are initially transcribed by RNA polymerase Ⅱ or Ⅲ in the nucleus, and are then cleaved to precursor hairpin (pre-miRNA) by the microprocessor complex, Drosha and DiGeorge syndrome critical region gene 8[35-37]. Next, the pre-miRNAs are exported into the cytoplasm and further cleaved to mature miRNAs by the RNase Ⅲ endonuclease, Dicer, in a complex with a trans-activator RNA binding protein[38-40]. One RNA strand from the mature miRNA is incorporated into the RNA-induced silencing complex, and guides this complex to the 3' untranslated regions of "target" mRNA sequences, which in mammalian cells induces target mRNA degradation and suppresses protein expression[31,32,41-44].

ABBERANT EXPRESSION OF MiRNAS IN INFLAMMATORY BOWEL DISEASE

In 2008, Wu *et al*[45] were the first to report miRNA expression in colonic mucosa samples from IBD patients. They identified 11 miRNAs that were differentially expressed in active UC *vs* controls (Table 1)[45] and demonstrated an inverse relationship between macrophage inflammatory peptide-2α (previously shown to be implicated in IBD[46]) and miR-192. Similarly, Bian *et al*[47] found miR-150 to be significantly upregulated in inflamed colonic mucosa of UC patients, as compared to controls (Table 1), and they established an inverse correlation between miR-150 and its target, *c-Myb*[48], a proto-oncogene that is involved in apoptosis. Consequently, these two studies have exposed new and important insights into the pathogenesis of IBD.

In 2010, three studies[49-51] identified altered miRNA expression in IBD tissue but without concomitant functional analyses. In a cohort of 12 controls and 12 active UC patients, Takagi *et al*[49] reported miR-21 and miR-155 to be significantly upregulated in inflamed colonic UC tissue (Table 1). In a second study, Wu *et al*[50] assayed the expression of 467 miRNAs in patients with sigmoid CD and in patients with active terminal ileal CD. They found five miRNAs to be associated with active sigmoid CD, and four miRNAs were significantly increased in active ileal CD, as compared to control tissues (Table 1)[50]. These reports were followed by a similar study by Fasseu *et al*[51] evaluating the expression of more than 300 miRNAs in colonic tissue samples of UC and CD patients using quantitative real-time polymerase chain reaction analysis. Several miRNAs were differentially expressed in accordance with disease type, but with a large number in common to both groups (Table 1). They identified a set of eight miRNAs (miR-26a, miR-29a, miR-29b, miR-30c, miR-126*, miR-127-3p, miR-196a, and miR-324-3p) defining quiescent IBD *vs* controls, and a distinct subset of 15 miRNAs that could differentiate between quiescent UC and CD (n = 16) (Table 1)[51]. These three studies illustrate the potential use of miRNAs as biomarkers and the possibilities of developing miRNA profile-based diagnostic tools.

Other recent studies have focused on certain specific miRNAs and their association with target genes. Hence, Pekow *et al*[52] reported an inverse correlation of the tumor suppressors miR-143 and miR-145 with their target genes, *IRS-1* (miR-145), and *K-RAS*, *API-5* and *MEK-2* (miR-143). Similarly, Nguyen *et al*[53] demonstrated decreased levels of miR-7 in inflamed CD colonic tissue, where expression of its target, CD98, was upregulated compared with control tissue. Dysregulation of CD98 interferes with the natural proliferation and differentiation of enterocytes. These two studies[52,53] not only provided new information on the pathophysiology of the well known, but poorly understood, inflammation-driven neoplastic progress in the colonic mucosa of UC, but also provided targets for future therapeutic interventions.

Some studies have focused on single miRNAs and their relation to single-nucleotide polymorphisms (SNPs). Brest *et al*[54] found increased expression of miR-196 re-

Table 1 Overview of dysregulated miRNAs reported to date in tissues from inflammatory bowel disease patients

miRNAs	Sample type	Population (*n*)	Approach	Reference
miRs-192, 375, 422b, **16, 21, 23a, 24, 29a, 126, 195,** and **let-7f**	Sigmoid colon biopsies	Active UC (*n* = 15) *vs* healthy controls (*n* = 15)	Microarray and qRT-PCR	Wu *et al*[45]
miR-**21** and miR-**155**	Sigmoid colon biopsies	Active UC (*n* = 12) *vs* healthy controls (*n* = 12)	Microarray and qRT-PCR	Takagi *et al*[49]
miRs-19b, 629, **23b, 106a,** and **191**	Sigmoid colon biopsies	Active CD (*n* = 5) *vs* healthy controls (*n* = 13)	Microarray and qRT-PCR	Wu *et al*[50]
miRs-**16, 21, 223,** and **594**	Terminal ileum biopsies	Active CD (*n* = 6) *vs* healthy controls (*n* = 13)	Microarray and qRT-PCR	Wu *et al*[50]
miRs-188-5p, 215, 320a, 346, **7, 31, 135b, 223, 29a, 29b, 126*, 127-3p**, and **324-3p**	Colon biopsies	Active UC (*n* = 8) *vs* healthy controls (*n* = 8)	qRT-PCR	Fasseu *et al*[51]
miRs-188-5p, 215, 320a, 346, **196a, 29a, 29b, 126*, 127-3p**, and **324-3p**	Colon biopsies	Inactive UC (*n* = 8) *vs* healthy controls (*n* = 8)	qRT-PCR	Fasseu *et al*[51]
miRs-**9, 126, 130a, 181c, 375, 26a, 29b, 30b, 34c-5p, 126*, 127-3p, 133b, 155, 196a, 324-3p, 21, 22, 29c, 31, 106a, 146a, 146b-3p**, and **150**	Colon biopsies	Active CD (*n* = 8) *vs* healthy controls (*n* = 8)	qRT-PCR	Fasseu *et al*[51]
miRs-**9*, 30a*, 30c, 223, 26a, 29b, 30b, 34c-5p, 126*, 127-3p, 133b, 155, 196a, 324-3p, 21, 22, 29c, 31, 106a, 146a, 146b-3p,** and **150**	Colon biopsies	Inactive CD (*n* = 8) *vs* healthy controls (*n* = 8)	qRT-PCR	Fasseu *et al*[51]
miRs-150, 196b, 199a-3p, 199b-5p, 223, and 320a	Colon biopsies	Inactive UC (*n* = 8) *vs* Inactive CD (*n* = 8)	qRT-PCR	Fasseu *et al*[51]
miR-7	Colon biopsies	Active CD (*n* = 8) *vs* healthy controls (*n* = 6)	qRT-PCR	Nguyen *et al*[53]
miR-**150**	Colon biopsies	Active UC (*n* = 5) *vs* healthy controls (*n* = 4)	qRT-PCR	Bian *et al*[47]
miR-**196**	Colon biopsies	Active CD (*n* = 83) *vs* healthy controls (*n* = 67)	qRT-PCR and ISH	Brest *et al*[54]
miR-143 and miR-145	Colon biopsies	Active UC (*n* = 8) *vs* healthy controls (*n* = 8)	qRT-PCR	Pekow *et al*[52]

Both downregulated miRNAs (miRs) and upregulated (bold characters) are shown. CD: Crohn's disease; ISH: *In situ* hybridization; UC: Ulcerative colitis; qRT-PCR: Quantitative real-time polymerase chain reaction.

stricted to intestinal epithelial cells within inflamed CD as compared to controls. They showed that miR-196 binds to, and correlates with, a decreased expression of the immunity-related GTPase M (*IRGM*) protective variant (c.313C) during inflammatory conditions, but not with the *IRGM* c.313C>T polymorphism, $IRGM^T$, which is strongly associated with CD in European populations[55]. In a similar study, Zwiers *et al*[56] found that the mutation (rs10889677 C>A) in the *IL-23R* gene, associated with IBD, results in loss of its binding sites for let-7e and let-7f miRNAs, leading to sustained *IL-23R* expression *in vitro*, which contribute to the chronicity of IBD. Thus, these studies indicate that single SNPs located at miRNA-binding sites are likely to affect the expression of their targets and that they might contribute to the pathogenesis of IBD.

In a semi-invasive approach and with diagnostic intentions, few studies have used whole blood instead of colonic tissue. As a proof of concept, Wu *et al*[57] performed a microarray-based study on whole blood from IBD patients and found a panel of differentially expressed miRNAs (Table 2) that enabled them to distinguish active IBD subtypes from each other and from controls. In a similar study by Zahm *et al*[58], higher concentrations of 11 miRNAs (Table 2) were found in the sera of pediatric CD patients *vs* controls. Receiver operating characteristic analyses resulted in a diagnostic sensitivity above 80% for CD[58]. Recently, Paraskevi *et al*[59] identified that 11 circulating miRNAs that were differentially expressed in blood samples from active CD *vs* controls, and identified a set of six miRNAs that were significantly elevated in active UC *vs* healthy controls (Table 2). Similarly, Duttagupta *et al*[60] found seven circulating miRNAs that were differentially expressed in UC patients *vs* controls (Table 2).

Although these studies are preliminary, they demonstrate the possibilities of developing a much-needed semi-invasive test based on differentially expressed peripheral blood miRNAs.

FUTURE USE IN DISEASE DIAGNOSTICS AND THERAPEUTICS

The studies described above have significantly increased our knowledge regarding the pathogenesis of IBD and have demonstrated the usefulness of miRNAs, not only as potential biomarkers, but also as latent targets for therapeutic interventions. However, a range of obvious challenges lie ahead, especially as identification of new miRNAs is an ongoing process. In 2008, Wu *et al*[45] used a miRNA microarray containing 553 known human miRNA genes, but currently more than 1900 human miRNA sequences are known[13], and new ones are identified on an almost daily basis. Consequently, this area of research is in its infancy, and future studies in the field of IBD need to focus on miRNA sequencing and using

Table 2 Overview of dysregulated circulating miRNAs reported to date in sera of inflammatory bowel disease patients

miRNAs	Sample type	Population (*n*)	Approach	Reference
miRs-149*, miRplus-F1065, **199a-5p, 362-3p, 340*, 532-3p**, and **miRplus-E1271**	Peripheral blood	Active CD (*n* = 14) *vs* healthy controls (*n* = 13)	Microarray and qRT-PCR	Wu *et al*[57]
miR-149* and miR-**340***	Peripheral blood	Inactive CD (*n* = 5) *vs* healthy controls (*n* = 13)	Microarray and qRT-PCR	Wu *et al*[57]
miRs-505*, **28-5p, 151-5p, 103-2*, 199a-5p, 340*, 362-3p, 532-3p**, and **miRplus-E1271**	Peripheral blood	Active UC (*n* = 13) *vs* healthy controls (*n* = 13)	Microarray and qRT-PCR	Wu *et al*[57]
miRs-505*, **28-5p, 103-2*, 149*, 151-5p, 340*, 532-3p**, and **miRplus-E1153**	Peripheral blood	Active UC (*n* = 10) *vs* active CD (*n* = 14)	Microarray and qRT-PCR	Wu *et al*[57]
miRs-**195, 16, 93, 140, 30e, 20a, 106a, 192, 21, 484**, and **let-7b**	Serum	Active CD (*n* = 46) *vs* healthy controls (*n* = 32)	LDA qRT-PCR	Zahm *et al*[58]
miRs-**16, 23a, 29a, 106a, 107, 126, 191, 199a-5p, 200c, 362-3p**, and **532-3p**	Peripheral blood	Active CD (*n* = 128) *vs* healthy controls (*n* = 162)	qRT-PCR	Paraskevi *et al*[59]
miRs-**16, 21, 28-5p, 151-5p, 155**, and **199a-5p**	Peripheral blood	Active UC (*n* = 88) *vs* healthy controls (*n* = 162)	qRT-PCR	Paraskevi *et al*[59]
miRs-**188-5p, 422a, 378, 500, 501-5p, 769-5p**, and **874**	Peripheral blood	UC (*n* = 20) *vs* healthy controls (*n* = 20)	qRT-PCR	Duttagupta *et al*[60]

Downregulated miRNAs (miRs) as well as upregulated (bold characters) are shown. CD: Crohn's disease; LDA: Low-density array; UC: Ulcerative colitis; qRT-PCR: Quantitative real-time polymerase chain reaction.

larger cohorts to address two important challenges: (1) identification of all of the miRNAs that are consistently dysregulated in IBD; and (2) to identify all of the targets of the miRNAs involved in IBD. If these challenges are met, the subsequent possibilities regarding diagnostics and therapeutics seem endless.

The potential clinical use of miRNAs is best illustrated by the most investigated and well-described miRNA, miR-21, also classified as an "oncomiR"[61,62]. The almost omnipresent overexpression of miR-21 in human cancers[62-64], including colorectal cancer, provides new options for cancer therapy[65]. Interestingly, as listed in Tables 1 and 2, miR-21 is the only miRNA commonly found to be upregulated in inflamed tissue or sera of IBD patients[45,49-51,58]. Thus, miR-21 is a potential biomarker for active IBD. It may also be of significant importance for the pathogenesis of IBD, as expression of miR-21 is mediated by nuclear factor-κB[66] - a key transcription factor involved in the pathogenesis of various human diseases, including IBD[67,68]. Unfortunately, the importance of these miRNA pathways in disease pathogenesis is unknown. Thus, functional studies are needed to address the role of miRNAs in IBD and particularly their role in cell signaling.

CONCLUSION

Currently, several clinical trials are testing the therapeutic efficacy of miRNA-based therapies; one such miRNA-target drug is "miravirsen"[69], a specific inhibitor of miR-122 that is currently in phase II clinical trials for Hepatitis C infections[70]. Within the next several years, further studies will undoubtedly provide a basis for more successful clinical trials and provide more insights in to the efficacy of miRNA-based therapeutics, including IBD.

REFERENCES

1 **Molodecky NA,** Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012; **142:** 46-54
2 **Nielsen OH**, Vainer B, Rask-Madsen J. Non-IBD and non-infectious colitis. *Nat Clin Pract Gastroenterol Hepatol* 2008; **5**: 28-39
3 **Abraham C**, Cho JH. Inflammatory bowel disease. *N Engl J Med* 2009; **361**: 2066-2078
4 **Baumgart DC**, Carding SR. Inflammatory bowel disease: cause and immunobiology. *Lancet* 2007; **369**: 1627-1640
5 **Danese S**, Fiocchi C. Ulcerative colitis. *N Engl J Med* 2011; **365**: 1713-1725
6 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395
7 **Glocker E**, Grimbacher B. Inflammatory bowel disease: is it a primary immunodeficiency? *Cell Mol Life Sci* 2012; **69**: 41-48
8 **Nielsen OH**, Rask-Madsen J. Mediators of inflammation in chronic inflammatory bowel disease. *Scand J Gastroenterol Suppl* 1996; **216**: 149-159
9 **Maloy KJ**, Powrie F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. *Nature* 2011; **474**: 298-306
10 **Tsianos EV**, Katsanos KH, Tsianos VE. Role of genetics in the diagnosis and prognosis of Crohn's disease. *World J Gastroenterol* 2012; **18**: 105-118
11 **Lee RC**, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* 1993; **75**: 843-854
12 **Wightman B**, Ha I, Ruvkun G. Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans. *Cell* 1993; **75**: 855-862
13 **Griffiths-Jones S**, Grocock RJ, van Dongen S, Bateman A, Enright AJ. miRBase: microRNA sequences, targets and gene nomenclature. *Nucleic Acids Res* 2006; **34**: D140-D144
14 **Alvarez-Garcia I**, Miska EA. MicroRNA functions in animal development and human disease. *Development* 2005; **132**: 4653-4662
15 **Ventura A**, Jacks T. MicroRNAs and cancer: short RNAs go

a long way. *Cell* 2009; **136**: 586-591
16 **Cullen BR**. Viral and cellular messenger RNA targets of viral microRNAs. *Nature* 2009; **457**: 421-425
17 **Hagen JW**, Lai EC. microRNA control of cell-cell signaling during development and disease. *Cell Cycle* 2008; **7**: 2327-2332
18 **Kloosterman WP**, Plasterk RH. The diverse functions of microRNAs in animal development and disease. *Dev Cell* 2006; **11**: 441-450
19 **Miñones-Moyano E**, Porta S, Escaramís G, Rabionet R, Iraola S, Kagerbauer B, Espinosa-Parrilla Y, Ferrer I, Estivill X, Martí E. MicroRNA profiling of Parkinson's disease brains identifies early downregulation of miR-34b/c which modulate mitochondrial function. *Hum Mol Genet* 2011; **20**: 3067-3078
20 **Wang WX**, Rajeev BW, Stromberg AJ, Ren N, Tang G, Huang Q, Rigoutsos I, Nelson PT. The expression of microRNA miR-107 decreases early in Alzheimer's disease and may accelerate disease progression through regulation of beta-site amyloid precursor protein-cleaving enzyme 1. *J Neurosci* 2008; **28**: 1213-1223
21 **Lynn FC**, Skewes-Cox P, Kosaka Y, McManus MT, Harfe BD, German MS. MicroRNA expression is required for pancreatic islet cell genesis in the mouse. *Diabetes* 2007; **56**: 2938-2945
22 **Kerr TA**, Korenblat KM, Davidson NO. MicroRNAs and liver disease. *Transl Res* 2011; **157**: 241-252
23 **Thum T**, Galuppo P, Wolf C, Fiedler J, Kneitz S, van Laake LW, Doevendans PA, Mummery CL, Borlak J, Haverich A, Gross C, Engelhardt S, Ertl G, Bauersachs J. MicroRNAs in the human heart: a clue to fetal gene reprogramming in heart failure. *Circulation* 2007; **116**: 258-267
24 **Lorenzen JM**, Haller H, Thum T. MicroRNAs as mediators and therapeutic targets in chronic kidney disease. *Nat Rev Nephrol* 2011; **7**: 286-294
25 **Salta E**, De Strooper B. Non-coding RNAs with essential roles in neurodegenerative disorders. *Lancet Neurol* 2012; **11**: 189-200
26 **Esteller M**. Non-coding RNAs in human disease. *Nat Rev Genet* 2011; **12**: 861-874
27 **Calin GA**, Croce CM. MicroRNA signatures in human cancers. *Nat Rev Cancer* 2006; **6**: 857-866
28 **Lu J**, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, Downing JR, Jacks T, Horvitz HR, Golub TR. MicroRNA expression profiles classify human cancers. *Nature* 2005; **435**: 834-838
29 **O'Connell RM**, Rao DS, Baltimore D. microRNA regulation of inflammatory responses. *Annu Rev Immunol* 2012; **30**: 295-312
30 **McKenna LB**, Schug J, Vourekas A, McKenna JB, Bramswig NC, Friedman JR, Kaestner KH. MicroRNAs control intestinal epithelial differentiation, architecture, and barrier function. *Gastroenterology* 2010; **139**: 1654-1664
31 **Guo H**, Ingolia NT, Weissman JS, Bartel DP. Mammalian microRNAs predominantly act to decrease target mRNA levels. *Nature* 2010; **466**: 835-840
32 **Baek D**, Villén J, Shin C, Camargo FD, Gygi SP, Bartel DP. The impact of microRNAs on protein output. *Nature* 2008; **455**: 64-71
33 **Miska EA**. How microRNAs control cell division, differentiation and death. *Curr Opin Genet Dev* 2005; **15**: 563-568
34 **Schickel R**, Boyerinas B, Park SM, Peter ME. MicroRNAs: key players in the immune system, differentiation, tumorigenesis and cell death. *Oncogene* 2008; **27**: 5959-5974
35 **Lee Y**, Kim M, Han J, Yeom KH, Lee S, Baek SH, Kim VN. MicroRNA genes are transcribed by RNA polymerase II. *EMBO J* 2004; **23**: 4051-4060
36 **Borchert GM**, Lanier W, Davidson BL. RNA polymerase III transcribes human microRNAs. *Nat Struct Mol Biol* 2006; **13**: 1097-1101
37 **Denli AM**, Tops BB, Plasterk RH, Ketting RF, Hannon GJ. Processing of primary microRNAs by the Microprocessor complex. *Nature* 2004; **432**: 231-235
38 **Lund E**, Güttinger S, Calado A, Dahlberg JE, Kutay U. Nuclear export of microRNA precursors. *Science* 2004; **303**: 95-98
39 **Okada C**, Yamashita E, Lee SJ, Shibata S, Katahira J, Nakagawa A, Yoneda Y, Tsukihara T. A high-resolution structure of the pre-microRNA nuclear export machinery. *Science* 2009; **326**: 1275-1279
40 **Lee Y**, Ahn C, Han J, Choi H, Kim J, Yim J, Lee J, Provost P, Rådmark O, Kim S, Kim VN. The nuclear RNase III Drosha initiates microRNA processing. *Nature* 2003; **425**: 415-419
41 **Gregory RI**, Chendrimada TP, Cooch N, Shiekhattar R. Human RISC couples microRNA biogenesis and posttranscriptional gene silencing. *Cell* 2005; **123**: 631-640
42 **Selbach M**, Schwanhäusser B, Thierfelder N, Fang Z, Khanin R, Rajewsky N. Widespread changes in protein synthesis induced by microRNAs. *Nature* 2008; **455**: 58-63
43 **Lim LP**, Lau NC, Garrett-Engele P, Grimson A, Schelter JM, Castle J, Bartel DP, Linsley PS, Johnson JM. Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. *Nature* 2005; **433**: 769-773
44 **Bartel DP**. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004; **116**: 281-297
45 **Wu F**, Zikusoka M, Trindade A, Dassopoulos T, Harris ML, Bayless TM, Brant SR, Chakravarti S, Kwon JH. MicroRNAs are differentially expressed in ulcerative colitis and alter expression of macrophage inflammatory peptide-2 alpha. *Gastroenterology* 2008; **135**: 1624-1635
46 **Wu F**, Dassopoulos T, Cope L, Maitra A, Brant SR, Harris ML, Bayless TM, Parmigiani G, Chakravarti S. Genome-wide gene expression differences in Crohn's disease and ulcerative colitis from endoscopic pinch biopsies: insights into distinctive pathogenesis. *Inflamm Bowel Dis* 2007; **13**: 807-821
47 **Bian Z**, Li L, Cui J, Zhang H, Liu Y, Zhang CY, Zen K. Role of miR-150-targeting c-Myb in colonic epithelial disruption during dextran sulphate sodium-induced murine experimental colitis and human ulcerative colitis. *J Pathol* 2011; **225**: 544-553
48 **Xiao C**, Calado DP, Galler G, Thai TH, Patterson HC, Wang J, Rajewsky N, Bender TP, Rajewsky K. MiR-150 controls B cell differentiation by targeting the transcription factor c-Myb. *Cell* 2007; **131**: 146-159
49 **Takagi T**, Naito Y, Mizushima K, Hirata I, Yagi N, Tomatsuri N, Ando T, Oyamada Y, Isozaki Y, Hongo H, Uchiyama K, Handa O, Kokura S, Ichikawa H, Yoshikawa T. Increased expression of microRNA in the inflamed colonic mucosa of patients with active ulcerative colitis. *J Gastroenterol Hepatol* 2010; **25** Suppl 1: S129-S133
50 **Wu F**, Zhang S, Dassopoulos T, Harris ML, Bayless TM, Meltzer SJ, Brant SR, Kwon JH. Identification of microRNAs associated with ileal and colonic Crohn's disease. *Inflamm Bowel Dis* 2010; **16**: 1729-1738
51 **Fasseu M**, Tréton X, Guichard C, Pedruzzi E, Cazals-Hatem D, Richard C, Aparicio T, Daniel F, Soulé JC, Moreau R, Bouhnik Y, Laburthe M, Groyer A, Ogier-Denis E. Identification of restricted subsets of mature microRNA abnormally expressed in inactive colonic mucosa of patients with inflammatory bowel disease. *PLoS One* 2010; **5**: e13160
52 **Pekow JR**, Dougherty U, Mustafi R, Zhu H, Kocherginsky M, Rubin DT, Hanauer SB, Hart J, Chang EB, Fichera A, Joseph LJ, Bissonnette M. miR-143 and miR-145 are downregulated in ulcerative colitis: putative regulators of inflammation and protooncogenes. *Inflamm Bowel Dis* 2012; **18**: 94-100
53 **Nguyen HT**, Dalmasso G, Yan Y, Laroui H, Dahan S, Mayer L, Sitaraman SV, Merlin D. MicroRNA-7 modulates CD98 expression during intestinal epithelial cell differentiation. *J Biol Chem* 2010; **285**: 1479-1489
54 **Brest P**, Lapaquette P, Souidi M, Lebrigand K, Cesaro A, Vouret-Craviari V, Mari B, Barbry P, Mosnier JF, Hébuterne

X, Harel-Bellan A, Mograbi B, Darfeuille-Michaud A, Hofman P. A synonymous variant in IRGM alters a binding site for miR-196 and causes deregulation of IRGM-dependent xenophagy in Crohn's disease. *Nat Genet* 2011; **43**: 242-245

55 **Parkes M**, Barrett JC, Prescott NJ, Tremelling M, Anderson CA, Fisher SA, Roberts RG, Nimmo ER, Cummings FR, Soars D, Drummond H, Lees CW, Khawaja SA, Bagnall R, Burke DA, Todhunter CE, Ahmad T, Onnie CM, McArdle W, Strachan D, Bethel G, Bryan C, Lewis CM, Deloukas P, Forbes A, Sanderson J, Jewell DP, Satsangi J, Mansfield JC, Cardon L, Mathew CG. Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn's disease susceptibility. *Nat Genet* 2007; **39**: 830-832

56 **Zwiers A**, Kraal L, van de Pouw Kraan TC, Wurdinger T, Bouma G, Kraal G. Cutting edge: a variant of the IL-23R gene associated with inflammatory bowel disease induces loss of microRNA regulation and enhanced protein production. *J Immunol* 2012; **188**: 1573-1577

57 **Wu F**, Guo NJ, Tian H, Marohn M, Gearhart S, Bayless TM, Brant SR, Kwon JH. Peripheral blood microRNAs distinguish active ulcerative colitis and Crohn's disease. *Inflamm Bowel Dis* 2011; **17**: 241-250

58 **Zahm AM**, Thayu M, Hand NJ, Horner A, Leonard MB, Friedman JR. Circulating microRNA is a biomarker of pediatric Crohn disease. *J Pediatr Gastroenterol Nutr* 2011; **53**: 26-33

59 **Paraskevi A,** Theodoropoulos G, Papaconstantinou I, Mantzaris G, Nikiteas N, Gazouli M. Circulating MicroRNA in inflammatory bowel disease. *J Crohns Colitis* 2012 Feb 28; Epub ahead of print

60 **Duttagupta R**, DiRienzo S, Jiang R, Bowers J, Gollub J, Kao J, Kearney K, Rudolph D, Dawany NB, Showe MK, Stamato T, Getts RC, Jones KW. Genome-wide maps of circulating miRNA biomarkers for ulcerative colitis. *PLoS One* 2012; **7**: e31241

61 **Esquela-Kerscher A**, Slack FJ. Oncomirs - microRNAs with a role in cancer. *Nat Rev Cancer* 2006; **6**: 259-269

62 **Pan X**, Wang ZX, Wang R. MicroRNA-21: a novel therapeutic target in human cancer. *Cancer Biol Ther* 2011; **10**: 1224-1232

63 **Si ML**, Zhu S, Wu H, Lu Z, Wu F, Mo YY. miR-21-mediated tumor growth. *Oncogene* 2007; **26**: 2799-2803

64 **Iorio MV**, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S, Magri E, Pedriali M, Fabbri M, Campiglio M, Ménard S, Palazzo JP, Rosenberg A, Musiani P, Volinia S, Nenci I, Calin GA, Querzoli P, Negrini M, Croce CM. MicroRNA gene expression deregulation in human breast cancer. *Cancer Res* 2005; **65**: 7065-7070

65 **Medina PP**, Nolde M, Slack FJ. OncomiR addiction in an in vivo model of microRNA-21-induced pre-B-cell lymphoma. *Nature* 2010; **467**: 86-90

66 **Zhou R**, Hu G, Gong AY, Chen XM. Binding of NF-kappaB p65 subunit to the promoter elements is involved in LPS-induced transactivation of miRNA genes in human biliary epithelial cells. *Nucleic Acids Res* 2010; **38**: 3222-3232

67 **Pasparakis M**. Regulation of tissue homeostasis by NF-kappaB signalling: implications for inflammatory diseases. *Nat Rev Immunol* 2009; **9**: 778-788

68 **Vallabhapurapu S**, Karin M. Regulation and function of NF-kappaB transcription factors in the immune system. *Annu Rev Immunol* 2009; **27**: 693-733

69 **Janssen HL,** Reesink HW, Zeuzem S, Lawitz E, Rodriguez-Torres M, Chen A, Davis C, King B, Levin AA, Hodges MR. A randomized, double-blind, placebo (plb) controlled safety and anti-viral proof of concept study of miravirsen (MIR), an oligonucleotide targeting miR-122, in treatment naïve patients with genotype 1 (gt1) chronic HCV infection [abstract]. *Hepatology* 2011; **54:** 1430A

70 **Rosen HR**. Clinical practice. Chronic hepatitis C infection. *N Engl J Med* 2011; **364**: 2429-2438

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