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# MicroRNAs as Novel Biomarkers in IBD: Characterization and Current Status

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## Abstract

The pathophysiology of the Inflammatory Bowel Disease (IBD) has been intensively investigated but is still unknown. The theory that IBD is the result of an inadequate activation of the immune system to a luminal factor occurring in genetically predisposed subjects is the most widely accepted to date. MicroRNAs (miRNAs) are a class of small non-coding RNAs which regulate gene expression at post-transcriptional level and are involved in the regulation of many biological processes, as well as in the induction of several cancers, chronic inflammatory diseases and autoimmune diseases. The currently evidence has demonstrated that miRNAs are differentially expressed in diverse circumstances of the IBD course. These molecules open a new opportunity to employ as a non-invasive biomarker for diagnosis, prognosis and follow up. Knowing the role of miRNA in IBD will improve our knowledge of the pathogenesis. In addition, the development of miRNA-based therapeutics technologies supposes a qualitative advance in the management of IBD.

**Keywords:** Novel biomarkers; miRNA; IBD

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a gastrointestinal chronic inflammatory disorder in which the pathophysiology has been extensively studied in the last decades, but much is still unknown. The theory that IBD and its gastrointestinal inflammation is the result of an inadequate activation of the innate immune system to a luminal factor (intestinal flora) occurring in genetically predisposed subjects is the most widely accepted to date [1-6]. In the literature, several genetic factors have been described to influence the development and severity of IBD and are responsible for disease susceptibility. Nevertheless, no locus has been detected of constant form in all the studies, suggesting the existence of a genetic heterogeneity. In addition, a variety of alternative mechanisms of gene regulation have been studied with special focus on epigenetic mechanisms. Considering the robust evidence it has been shown that epigenetic modifications, such as microRNAs (miRNA) are associated with IBD pathogenesis.

MiRNAs are a class of small non-coding RNAs which regulate gene expression at post-transcriptional level. MiRNAs bind to complementary sequences in the 3' untranslated region (UTR) of specific target mRNAs and can prevent protein synthesis. MiRNA-mediated gene regulation is implicated in many biological processes such as the cell cycle, differentiation, proliferation, apoptosis and immune functions [7]. It has been already shown that changes in miRNA expression can also regulate inflammatory response in human and are involved in the induction of several cancers and chronic inflammatory disease [8,9].

MiRNAs have been found in tissues, serum, plasma and other body fluids (i.e. urine, tear, ascetic and amniotic fluid), in a stable form that is protected from endogenous RNase activity due to their incorporation into the RNA-induced silencing complex (RISC) which is either free in blood or in exosomes [10]. For this reason, miRNA is resistant to harsh conditions and it is now being used as a biomarker for different pathologies (i.e. cancer, autoimmune disease, inflammation).

Although the majority of studies are focused on the potential role of miRNAs in the development of cancer, in the last years the number of publications regarding the biogenesis and functions of miRNAs in IBD is increasing exponentially [11]. There are emerging data from IBD patients studying miRNAs as novel biomarkers in diagnosis, predicting disease course and response to therapy. MiRNAs expression patterns will improve an improvement in the knowing of the IBD pathogenesis. Several miRNA-based therapies are now in clinical or preclinical trials and suppose and advance in the IBD management.

## MiRNAs as Novel Biomarkers in IBD

Biomarker generally refers to a measurable indicator of some biological state or condition. The colonoscopy is the gold standard technique for the diagnosis of activity in IBD. Several limitations of this invasive technique involve dietary restriction and the preparation of the colon. Thus, there is a pressing need for new non-invasive biomarkers to improve the detection of disease activity, to predict prognosis and the treatment response. Serum biomarkers are attractive because blood samples are easy to collect, cheaper and are non-invasive and can be used to differentiate healthy vs disease and inactive vs active disease, in order to determine prognosis and to monitor response to therapy. Biomarkers are often measured and evaluated to examine normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

To date, several papers have focused investigation on the altered expression of miRNAs in IBD and their important role as regulators and possible diagnostic biomarkers in IBD [7,12-14]. The majority of studies in IBD have been conducted in tissue and cellular cultures, and there are currently few reports on the quantitative assessment of circulating miRNA in IBD patients [15-18]. These works have identified peripheral blood miRNAs expression profiles in IBD patients [15,17] and have demonstrated their potential utility as non-invasive biomarkers [16].

The first study where miRNAs were directly examined in the mucosa of UC patients was performed by Wu et al. [19] in 2008. They reported differential expression of miRNA in the mucosa of patients with active UC tissues compared with inactive UC patients and healthy tissues. Following publication of this study, other works have emerged aiming to identify all of the miRNAs de-regulated in IBD. It has been identified different expression

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patterns capable to distinguish between UC and CD [20,21], and between inflamed and non-inflamed mucosa in IBD patients [22,23]. Specific miRNAs expression patterns associated with the diverse IBD subtypes [24], and with their different stages (active or inactive disease) [7,15,18] have been described. The identification of the different expression patterns of miRNAs involved in IBD suggests that these molecules are involved in the different pathogenic mechanisms of IBD.

Intestinal fibrosis is a major complication in CD, which may require surgery. Some publications have demonstrated the existence of miRNAs that would be associated fibrotic process including the family of miR-200 [25]. In vitro experiments have shown that specific miR-200b, can improve fibrosis by transforming growth factor beta 1 induced (TGF-β1) and miR-200b is increased in serum of CD patients with intestinal fibrosis [25].

Another important consideration is the identification of possible biomarkers predictive of the therapeutic effect. In this sense, it has identified two miRNAs as possible therapeutic biomarkers in patients with CD. MiRNA levels of let-7d and let-7e were significantly increased in the group of patients who had a good response to anti-TNF drug (infliximab) [26].

Aberrant miRNA expression has been linked to carcinogenesis by affecting the expression of oncogenes or tumor suppressors. MiRNAs that are over-expressed can cause down-regulating of tumor-suppressor genes and/or genes that control cell differentiation or apoptosis, in a similar manner to oncogenes. In addition, miRNAs that are down-regulated can act as tumor-suppressor genes by negatively regulating oncogenes and/or genes that control cell differentiation or apoptosis [27]. The chronic inflammation produced in IBD is associated with increased risk of developing colon adenocarcinoma. In this sense several miRNAs have been related with the risk of malignancy in IBD patients. MiR-143 and miR-145 could contribute to malignant transformation of colonic epithelium in longstanding UC [27] and increased levels of miR-31 have been related with the progression dysplasia-cancer in IBD by factor inhibiting hypoxia inducible factor 1 (FIH-1) mediated [28].

## Role of miRNAs in the IBD Pathogenesis

MiRNA-mediated gene regulation is implicated in normal cellular processes such as the cell cycle, differentiation, proliferation, apoptosis and immune functions. It has been already shown that changes in miRNA expression can also regulate inflammatory responses in human. Several studies explain that miRNA over-expression and/or inhibition can regulate the release of several pro-inflammatory chemokines. Specific miRNAs such as miR-132, miR-146 and miR-155 can be regulated by inflammatory mediators (NF-κβ, TNF-α, IFN-β), microbial components (lipopolysaccharides and flagelin) and a variety of Toll-like receptors ligands (TLR), led to physiological granulocyte/monocyte diffusion and growth during inflammation [29,30]. MiR-9 was also induced by TLR2 and TLR7/8 agonists and by the pro-inflammatory cytokines TNF- α and IL-1β, but not by IFNγ [31]. Many additional miRNAs can regulate the inflammatory response such as miR-21, miR-147, miR-513, let-7 and miR98. All these findings reveal a role for miRNAs as important regulators of inflammation.

In the other hand, a recent review has elucidated the role of miRNAs in the development and regulation of the innate and adaptive immune system [32]. In addition, the authors show functional studies based on the cellular process of autophagy and on the Th17 pathway regulation in IBD [32].

## Future Perspectives

Knowing the typical miRNA pattern of IBD will improve our knowledge of the pathogenesis of the disease and will lead to future well-focused projects to study the regulatory function of such miRNA. Furthermore, it is possible that some miRNA are specific of IBD and could serve as biomarkers with clinical application for diagnosis or to asses' disease activity. Blood samples are easier to obtain and generally better accepted by patients than endoscopic explorations which are more invasive.

Currently, there are several miRNAs-based therapies are now in clinical and pre-clinical trials. Two methods are employed to control miRNA activity. The first is by restoring the function of a miRNA using synthetic double-stranded miRNAs or viral vector based overexpression. And the second is by inhibition of the function of a miRNA using chemically modified antimiR oligonucleotides [33].

The pharmacological modulation of miRNA activity has demonstrated benefit for the treatment of cancer, cardiovascular disease and hepatitis C virus infection. MiR-34 is down-regulated in cancer cells and can stimulate p-53 activity by SIRT1. Systemic or intra-tumor miR-34 has showed a benefit in unresectable primary liver cancer. Targeting of miR-33 by SREBF1 and SREBF2 has demonstrated to be a good treatment for atherosclerosis. And the inhibition of miR-208 and miR-122 has been used for the treatment of the heart failure and diabetes and hepatitis C virus infection respectively [33].

## Conclusion

The entire above highlight that miRNA could be implicated in the pathogenesis of IBD. Differentially expressed MiRNA in diverse circumstances opens new opportunities to employ miRNA as an excellent biomarker for activity, diagnosis, severity, therapeutic response and even degeneration associated to IBD. Researchers worldwide are interested in miRNAs as potential therapeutic targets and potential non-invasive test for CD patients. The *in vivo* application of miRNAs-based therapeutic technologies offers a new opportunity of the future translational potential of miRNA-based research in chronic inflammatory diseases.

### References

1. D K (2002) Inflammatory bowel disease. N Engl J Med 347: 417-29.
2. Logan I, Bowlus CL (2010) The geoepidemiology of autoimmune intestinal diseases. Autoimmun Rev. 9: A372-8.
3. Pisetsky DS (2008) The role of innate immunity in the induction of autoimmunity. Autoimmun Rev 8: 69-72.
4. Poletaev AB, Stepanyuk VL, Gershwin ME (2008) Integrating immunity: the immunculus and self-reactivity. J Autoimmun 30: 68-73.
5. Waldner H (2009) The role of innate immune responses in autoimmune disease development. Autoimmun Rev 8: 400-404.
6. Cuadrado E (2009) Granulocyte/monocyte apheresis as immunotherapic tool: cellular adsorption and immune modulation. Autoimmun Rev 8: 292-296.
7. Iborra M, Bernuzzi F, Invernizzi P, Danese S (2012) MicroRNAs in autoimmunity and inflammatory bowel disease: crucial regulators in immune response. Autoimmun Rev 11: 305-14.
8. Ruan K, Fang X, Ouyang G (2009) MicroRNAs: novel regulators in the hallmarks of human cancer. Cancer Lett, 2009. 285: 116-26.
9. Miska EA (2005) How microRNAs control cell division, differentiation and death. Curr Opin Genet Dev 15: 563-8.
10. Lodes MJ, Caraballo M, Suciu D, Munro S, Kumar A, et al. (2009) Detection of cancer with serum miRNAs on an oligonucleotide microarray. PLoS One 4: e6229.
11. Kozomara A, Griffiths-Jones S (2014) miRBase: annotating high confidence microRNAs using deep sequencing data. Nucleic Acids Res 42: D68-73.

12. Archanioti P, Gazouli M, Theodoropoulos G, Vaiopoulou A, Nikiteas N (2011) Micro-RNAs as regulators and possible diagnostic bio-markers in inflammatory bowel disease. J Crohns Colitis 5: 520-4.

13. Pekow JR, Kwon JH (2012) MicroRNAs in inflammatory bowel disease. Inflamm Bowel Dis 18: 187-93.

14. Coskunm M , Bjerrum JT, Seidelin JB, Nielsen OH (2012) MicroRNAs in inflammatory bowel disease - pathogenesis, diagnostics and therapeutics. World J Gastroenterol, 2012. 18: 4629-34.

15. F, Guo NJ, Tian H, Marohn M, Gearhart S, et al. (2011) Peripheral blood microRNAs distinguish active ulcerative colitis and Crohn's disease. Inflamm Bowel Dis 17: 241-50.

16. Zahm AM, Thayu M, Hand NJ, Horner A, Leonard MB, et al. (2011) Circulating microRNA is a biomarker of pediatric Crohn disease. J Pediatr Gastroenterol Nutr 53: 26-33.

17. Paraskevi A, Theodoropoulos G, Papaconstantinou I, Mantzaris G, Nikiteas N, et al. (2012) Circulating MicroRNA in inflammatory bowel disease. J Crohns Colitis 6: 900-4.

18. Iborra M, Bernuzzi F, Correale C, Vetrano S, Fiorino G, et al. (2013) Identification of serum and tissue micro-RNA expression profiles in different stages of inflammatory bowel disease. Clin Exp Immunol 173: 250-8.

19. Wu F, Zikusoka M, Trindade A, Dassopoulos T, Harris ML, et al. (2008) MicroRNAs are differentially expressed in ulcerative colitis and alter expression of macrophage inflammatory peptide-2 alpha. Gastroenterology 135: 1624-1635 e24.

20. Chen WX, Ren LH, Shi RH (2014) Implication of miRNAs for inflammatory bowel disease treatment: Systematic review. World J Gastrointest Pathophysiol 5: 63-70.

21. Glinsky GV (2008) Disease phenocode analysis identifies SNP-guided microRNA maps (MirMaps) associated with human "master" disease genes. Cell Cycle 7: 3680-94.

22. Fasseu M, Tréton X, Guichard C, Pedruzzi E, Cazals-Hatem D, et al. (2010) Identification of restricted subsets of mature microRNA abnormally expressed in inactive colonic mucosa of patients with inflammatory bowel disease. PLoS One 5(10).

23. Takagi T, Naito Y, Mizushima K, Hirata I, Yagi N, et al. (2010) Increased expression of microRNA in the inflamed colonic mucosa of patients with active ulcerative colitis. J Gastroenterol Hepatol 25: S129-33.

24. Wu F, Zhang S, Dassopoulos T, Harris ML, Bayless TM, et al. (2010) Identification of microRNAs associated with ileal and colonic Crohn's disease. Inflamm Bowel Dis 16: 1729-38.

25. Gazouli M, Papaconstantinou I, Stamatis K, Vaiopoulou A, Zeglinas C, et al. (2013) Association study of genetic variants in miRNAs in patients with inflammatory bowel disease: preliminary results. Dig Dis Sci 58: 2324-8.

26. Fujioka S, Nakamichi I, Esaki M, Asano K, Matsumoto T, et al. (2014) Serum microRNA levels in patients with Crohn's disease during induction therapy by infliximab. J Gastroenterol Hepatol 29: 1207-14.

27. JR, Dougherty U, Mustafi R, Zhu H, Kocherginsky M, et al. (2012) miR-143 and miR-145 are downregulated in ulcerative colitis: putative regulators of inflammation and protooncogenes. Inflamm Bowel Dis 18: 94-100.

28. Olaru AV, Selaru FM, Mori Y, Vazquez C, David S, et al. (2011) Dynamic changes in the expression of MicroRNA-31 during inflammatory bowel disease-associated neoplastic transformation. Inflamm Bowel Dis 17: 221-31.

29. KD, Boldin MP, Chang KJ, Baltimore D (2006) NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc Natl Acad Sci U S A 103: 12481-6.

30. O'Connell RM, et al. (2008) Sustained expression of microRNA-155 in hematopoietic stem cells causes a myeloproliferative disorder. J Exp Med 205: 585-94.

31. Bazzoni F, Marzia Rossatoa, Marco Fabbrib, Daniele Gaudiosib, Massimiliano Mirolob, et al. (2009) Induction and regulatory function of miR-9 in human monocytes and neutrophils exposed to proinflammatory signals. Proc Natl Acad Sci U S A 106: 5282-7.

32. Kalla R, Ventham NT, Kennedy NA, Quintana JF, Nimmo ER, et al. (2015) MicroRNAs: new players in IBD. Gut 64: 504-17

33. van Rooij E, Kauppinen S (2014) Development of microRNA therapeutics is coming of age. EMBO Mol Med 6: 851-64.