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MicroRNAs as therapeutic targets in colitis and colitis-associated cancer: Tiny players with a Giant Impact

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Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), represents a constellation of autoimmune disorders that affect the entire gastrointestinal tract[1]. The incidence and prevalence of IBD is continuously increasing in different parts of the world, with an estimated ~1.5 million people affected by these two diseases in the United States alone[2]. Patients with IBD present with an increased risk for developing colorectal cancer (CRC)[3], with the relative risks for developing this malignancy about 5.6 and 30 times in patients with CD[4] and UC[5] respectively, in comparison to the general population. Risk factors for colitis-associated cancer (CAC) include disease duration of >8 years, and presence of pancolitis, colonic dysplasia, and primary sclerosing cholangitis affecting liver[1]. While moderate to severe UC can be treated with antibody-based treatments with some success, limited options exist for treating patients with mild to moderate UC that don't respond to mesalamine, underscoring the need for development of safer and robust treatment options designed for abating chronic inflammation and continuous disease activity in the colon.

With regards to its pathogenesis, the prevailing consensus is that epithelial-barrier dysfunction, host immune system, dietary and environmental factors – all play an essential role in UC and CAC. From a mechanistic standpoint, in spite of extensive research in the last two decades, specific molecular events underpinning CAC pathogenesis largely remain obscure. Due to the lack of a strong genetic basis in the pathogenesis of UC, research in the past few years has significantly focused on exploring the contribution of epigenetic mechanisms, which include alterations in DNA methylation, histone modifications and the expression patterns of non-coding RNAs. More specifically, the last decade of 'noncoding RNA revolution', has witnessed discovery of novel classes of RNAs that play critical roles in a variety of diseases, including cancer. The smallest of these non-coding RNA species, with a size of ~22 nucleotides, and known as microRNAs (miRNAs), have been at the forefront of this genomic revolution. The field of miRNA research has expanded exponentially, and according to the last release of miRNA database (www.mirbase.org), more than 2,500 mature miRNAs have been identified in humans[6], with new miRNAs continuously being

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discovered in different tissue types. MiRNAs act as powerful molecular rheostats, and are able to exert negative post-transcriptional regulation of hundreds of protein coding genes, in a tissue- and disease-specific manner.

In this issue of the Journal, Polytarchou and colleagues, provide seminal evidence for one such miRNA, miR-214, in UC and CAC[7]. Using a series of systematic and elegant experimental approaches, these authors not only illustrated the functional role of miR-214 in colitis, but also unveiled a convincing body of data supporting its potential therapeutic application in this disease[7]. Since development of UC is characterized by the activation of various inflammatory pathways, these researchers utilized a high-throughput functional screen in IL6-treated normal colonic cells and identified miR-214 to be a single, most efficient suppressor of NFκB phosphorylation. To evaluate the clinical relevance of these in-vitro findings, expression analysis revealed significantly higher levels of miR-214 in UC colonic tissues vis-à-vis control subjects and CD patients. Furthermore, miR-214 expression was significantly higher in UC patients with active disease compared to those who were in remission - highlighting the biological role this miRNA plays in the development of colitis and CAC. These authors took a huge step forward with their research when they explored the potential feasibility of therapeutic targeting of miR-214, and very exquisitely demonstrated that a miR-214 chemical inhibitor reduced the severity of dextran sodium sulfate (DSS)-induced colitis in mice and the number and size of tumors in an azoxymethane (AOM)-DSS animal model. The study concluded that IL6 upregulates STAT3-mediated transcription of miR-214 in colonic tissues, which reduces levels of its downstream target genes PDLIM2 and PTEN, increases phosphorylation of AKT, and activates NFκB. The activity of this circuit significantly correlated with the disease activity observed in patients with UC, suggesting the role it plays in disease progression to CAC.

In the context of IBD, this study by Polytarchou et al. is fascinating, considering that the first report on dysregulated expression of miRNAs in patients with UC and CD was published seven years ago[8]. It is remarkable to appreciate that this field has progressed and matured so rapidly. As is the case with many other malignancies; instead of simply exploring their potential as diagnostic and prognostic biomarkers, we can now contemplate the use of miRNA inhibitors for therapeutic targeting in patients with ulcerative colitis and possibly other inflammatory diseases. While a previous study had also identified miR-214 over-expression in UC patients[9], what made this study exciting was the rationale and approach utilized for the discovery of unique miRNAs that mediated IL6-induced suppression of NFκB activity. The strategy used by the authors allowed them to subsequently validate their in-vitro findings using clinical specimens. As such, miR-214 expression was found to be significantly upregulated in UC tissues, but not in patients with CD or irritable bowel syndrome.

One of the key aspects of this study was the use of functional assays to delineate the binding between miR-214 promoter and STAT3 transcription factor[7]. This conspicuous miRNA-mRNA physical interaction was an important piece of the puzzle, because this provided the much needed support favoring the hypothesis that miR-124 induced inflammatory response was amplified via a feedback loop circuit mediated by its downstream target genes, PTEN and PDLIM2. These results coupled with the observations that treatment with a miR-214

synthetic chemical inhibitor successfully inhibited miR-214 expression and suppressed inflammation in colonic explants from UC patients, as well as inhibited DSS-colitis and tumor development in an AOM-DSS animal model is intriguing. It was surmised that blockade of this feedback loop led to inhibition of NFκB activation and upregulation of PTEN and PDLIM2, in these ex-vivo and in-vivo experimental models. Although this study did not perform toxicity studies or studied the off-target effects of the chemical inhibitor, nonetheless, these data clearly highlight that miR-214 overexpression may be one of the primary mechanisms for activating and maintaining a perpetual inflammatory stress in patients with colitis and CAC. Since this inflammatory signaling pathway represents a specific, closed-circuit loop that can be effectively and efficiently targeted by a chemical miR-214 antagonist, such treatment strategies may be promising in UC and possibly other inflammatory diseases. The most logical question then becomes "*will these animal findings be corroborated in a human model*"? Time will provide the answer; nonetheless, data from this preclinical study provide an ideal springboard for evaluating the role of miR-214 inhibitors as therapeutic choices in future clinical studies in patients with UC and CAC.

In mammals, miRNA-mediated degradation of the target gene repression occurs at a translational level via imperfect base pairing to the 3-untranslated region of the target mRNA. Such translational regulation provides the cell with a more precise, immediate and energy-efficient way of controlling protein expression[10]. Considering that miRNA expression is ubiquitously dysregulated in human diseases, miRNA-therapeutics involving the use of either miRNA antagonists (for allowing gain of function) or miRNA mimics (for restoring loss of function) are currently being investigated. The first two miRNA-based clinical trials for the treatment of HCV by targeting miR-122 with a locked nucleic acid (LNA)-antimiR (miravirsen or SPC3649; Santaris Pharma, Denmark) have yielded promising results[11]. In addition, another phase-I clinical trial is underway in which miR-34a mimics are used for therapeutic targeting of cancer (MRX34, Mirna Therapeutics; clinicaltrials.gov number NCT01829971).

Although miRNAs have shown some promise as a novel class of therapeutic targets, several practical concerns must be kept in mind as this field continues to evolve. First, a single miRNA can target several mRNAs (or genes), often coding for functionally similar proteins. This may be advantageous in the sense that complete pathways may be targeted by a single therapy; however, genes in unrelated pathways may experience unwanted or even detrimental off-target effects. This might be a concern with the use of miR-214 antagomirs in UC patients, because in addition to PTEN and PDLIM2, it has dozens of other cellular targets including oncogenes, such as MEK3 and JNK1, which may inadvertently promote carcinogenesis[12]. Second, the optimal delivery method for miRNA mimics or antagomirs, modified to withstand degradation while in circulation and be specifically delivered to target tumor sites in order to achieve significant therapeutic effect can be a significantly cumbersome and challenging. Some of the innovative techniques that are currently being explored as delivery vehicles include 3′-end-cholesterol conjugation[13] and locked nucleic acid (LNA)-modification[14] of miRNA antagonists to allow cellular entry; or adeno-associated viral vectors[15], nanoparticles and exosomal delivery of miRNA mimics to a target organ[16, 17].

There is no denying that we are in midst of critical and exciting times in miRNA-based research and anticancer therapeutic development. However, much more needs to be learned about miRNA biology and function to overcome hurdles facing the use of miRNA-targeting approaches for clinical applications in patients with IBD and other human diseases. Nonetheless, data from this study when combined with the unprecedented advances in the field of miRNA research, paints a rosy picture for these tiny RNAs to have a giant impact in the personalized management of patients with colitis, colitis-associated cancer and other inflammatory diseases.

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References

1. Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. Gastroenterology. 2011; 140:1807–16. [PubMed: 21530747]
2. 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 e42. quiz e30. [PubMed: 22001864]
3. Rhodes JM, Campbell BJ. Inflammation and colorectal cancer: IBD-associated and sporadic cancer compared. Trends in molecular medicine. 2002; 8:10–6. [PubMed: 11796261]
4. Feagins LA, Souza RF, Spechler SJ. Carcinogenesis in IBD: potential targets for the prevention of colorectal cancer. Nature reviews Gastroenterology & hepatology. 2009; 6:297–305. [PubMed: 19404270]
5. Viscido A, Bagnardi V, Sturniolo GC, Annese V, Frieri G, D'Arienzo A, Papi C, Riegler G, Corrao G, Caprilli R. Survival and causes of death in Italian patients with ulcerative colitis. A GISC nationwide study. Digestive and liver disease: official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2001; 33:686–92.
6. Kozomara A, Griffiths-Jones S. miRBase: annotating high confidence microRNAs using deep sequencing data. Nucleic acids research. 2014; 42:D68–73. [PubMed: 24275495]
7. Polytarchou C, Hommes DW, Palumbo T, Hatziapostolou M, Koutsioumpa M, Koukos G, van der Meulen-de Jong AE, Oikonomopoulos A, van Deen WK, Vorvis C, Serebrennikova OB, Birli E, Choi J, Chang L, Anton PA, Tsichlis PN, Pothoulakis C, Verspaget HW, Iliopoulos D. MicroRNA214 is Associated with Progression of Ulcerative Colitis, and Inhibition Reduces Development of Colitis and Colitis-associated Cancer in Mice. Gastroenterology. 2015
8. 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 e24. [PubMed: 18835392]
9. Kanaan Z, Barnett R, Gardner S, Keskey B, Druen D, Billeter A, Cheadle WG. Differential microRNA (miRNA) expression could explain microbial tolerance in a novel chronic peritonitis model. Innate immunity. 2013; 19:203–12. [PubMed: 23060456]
10. Dony C, Kessel M, Gruss P. Post-transcriptional control of myc and p53 expression during differentiation of the embryonal carcinoma cell line F9. Nature. 1985; 317:636–9. [PubMed: 2414665]
11. Janssen HL, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Patel K, van der Meer AJ, Patick AK, Chen A, Zhou Y, Persson R, King BD, Kauppinen S, Levin AA, Hodges MR. Treatment of HCV infection by targeting microRNA. The New England journal of medicine. 2013; 368:1685–94. [PubMed: 23534542]

12. Yang Z, Chen S, Luan X, Li Y, Liu M, Li X, Liu T, Tang H. MicroRNA-214 is aberrantly expressed in cervical cancers and inhibits the growth of HeLa cells. IUBMB life. 2009; 61:1075–82. [PubMed: 19859982]
13. Krutzfeldt J, Rajewsky N, Braich R, Rajeev KG, Tuschl T, Manoharan M, Stoffel M. Silencing of microRNAs in vivo with 'antagomirs'. Nature. 2005; 438:685–9. [PubMed: 16258535]
14. Obad S, dos Santos CO, Petri A, Heidenblad M, Broom O, Ruse C, Fu C, Lindow M, Stenvang J, Straarup EM, Hansen HF, Koch T, Pappin D, Hannon GJ, Kauppinen S. Silencing of microRNA families by seed-targeting tiny LNAs. Nature genetics. 2011; 43:371–8. [PubMed: 21423181]
15. Chen C, Akerstrom V, Baus J, Lan MS, Breslin MB. Comparative analysis of the transduction efficiency of five adeno associated virus serotypes and VSV-G pseudotype lentiviral vector in lung cancer cells. Virology journal. 2013; 10:86. [PubMed: 23497017]
16. Valadi H, Ekstrom K, Bossios A, Sjostrand M, Lee JJ, Lotvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nature cell biology. 2007; 9:654–9. [PubMed: 17486113]
17. Chen Y, Zhu X, Zhang X, Liu B, Huang L. Nanoparticles modified with tumor-targeting scFv deliver siRNA and miRNA for cancer therapy. Molecular therapy: the journal of the American Society of Gene Therapy. 2010; 18:1650–6. [PubMed: 20606648]