Short Communication   **open access**

Are Micrornas the Answer to Colorectal Cancer's Big Questions?

Anne E Sarver[1] and **Subbaya Subramanian**[1,2]*

[1]Department of Surgery, University of Minnesota, USA

[2]Masonic Cancer Center, University of Minnesota, USA

*Corresponding author: Subramanian S, 11-212 Moos Tower, 420 Delaware St, S.E Minneapolis, MN-55455, USA, Fax: 6126248909; Tel: 6126264330; E-mail: subree@umn.edu

Introduction

The question, "What determines whether a polyp will become cancerous?" was recently declared one of the five central puzzles critical to advancing colon cancer treatment [1]. The benign to cancerous transition is a critical intervention stage as tumors diagnosed in subsequent non-localized and malignant stages are exponentially more difficult to treat successfully. The decreasing mortality rate is largely credited to increased screening with sigmoidoscopy, colonoscopy, and fecal occult blood tests that result in early detection of precancerous polyps or early stage colon cancer. Despite the increased preventive screening, colorectal cancer remains a deadly disease, with an estimated 136,830 new cases and 50,310 deaths in the United States in 2014 [2]. There is both a critical need and opportunity for novel treatment strategies that either halt or prevent the transformation from polyp to cancer.

MicroRNA (miRNA) dysregulation is an established feature of colon cancer progression but it has not been clear whether this dysregulation is driving transformation and progression, or whether other driving events (such as p53 mutations) are incidentally causing changes in miRNA expression [3,4]. The preponderance of results published over the last couple of years clearly seems to indicate that miRNAs are active participants in cancer formation and progression. Jones et al. [5] established that miR-215 is the link between the CDX1 transcription factor and its repression of polycomb complex protein BMI, which results in increased colorectal cancer stem cell differentiation, a key step towards tumor formation. Valeri et al. [6] demonstrated that miR-135b promotes colorectal cancer progression, functioning as a downstream effector of the PTEN/PI3K oncogenic pathway. There is additional evidence that miR-135b also acts as a downstream effector of the EGFR/STAT3 pathway, making this common signaling mediator an attractive anti-cancer therapeutic target [7]. Another recent article, published by Li et al. [8] identified two additional key miRNAs, miR-182 and miR-503, which mediate malignant transformation by cooperatively targeting a key colon cancer driver gene, *FBXW7*. *FBXW7* is a key component of the ubiquitin-protease system targeting multiple transcription factors that in turn control multiple oncogenic networks [9].

Instead of the common investigative pattern of looking at potential regulators of known oncogenic networks, Li et al. used empirical expression profiles from a cohort of over 200 colon cancer patients with 12 year survival outcome data to identify miRNAs (miR-182/-503) significantly correlated with decreased patient survival. Subsequently they discovered a step-wise progression pattern where miR-182 levels increase during the transition from normal colon tissue into benign polyp, followed by an increase in miR-503 expression during the transformation from polyp to cancer. These two

miRNAs synergistically down-regulate *FBXW7* expression, which can be rescued by antimiRs targeting miR-182 and miR-503. Blocking miR-182 and miR-503 in colon cancer cell lines both increased apoptosis and decreased invasion and migration, an effect that was absent in *FBXW7* knock-out cells. These results provide a potential molecular mechanism linking increased miRNA expression with tumor progression and provide support for a model whereby miRNAs regulate a critical master tumor suppressor in a synergistic and multi-hit progression that sets the stage for malignant transformation and provides an attractive therapeutic target.

miRNAs represent a largely untapped pool of potential therapeutic targets. To date, only a few miRNA-based therapies have begun clinical trials and most utilize a mimic strategy that aims to rescue deficient miRNA expression in cancer cells. However, a key limitation of utilizing some miRNA mimics is that they require intact miRNA-processing machinery to be present in the cancer cell. Another concern is that overexpression of miRNAs beyond endogenous levels may result in other off-target effects since some miRNAs target hundreds of genes. A more successful approach may be to target overexpressed miRNAs, particularly those that have a very low baseline expression in the corresponding normal tissue. AntimiRs are antisense oligomers that are designed to be complementary to the target miRNA, forming a tight secondary structure upon binding and inhibiting miRNA activity. Until recently the main limitation to antimiR-based therapy was an effective delivery strategy but advances such as those recently published by Cheng et al. [10] are transforming these molecules into viable anti-cancer therapies.

Therapeutic interventions that target the first step in an oncogenic signaling cascade provide an opportunity not only to treat cancer, but also potentially to transform it into a chronic benign disease that can be safely managed for the duration of a patient's lifetime. Halting the disease at a benign stage provides the opportunity for progression-free survival without the painful and deleterious side-effects of more aggressive conventional therapies such as radiation and chemotherapy. Non-invasive monitoring techniques would also need to be employed to ensure that the disease remains in a benign stage. miRNAs that control oncogenic and tumor suppressor networks may be both attractive therapeutic targets and sensitive biomarkers for disease presence and progression. Understanding how these miRNAs control master nodes by both cell autonomous and non-cell autonomous mechanisms will elucidate many different aspects of cancer including formation of the tumor microenvironment and progression to metastasis.

miRNAs may also hold the keys to solving the other four central puzzles critical to advancing colon cancer treatment. Colon cancer in particular is a disease of the modern world, with rates in developed countries significantly higher than those in developing areas [11]. It

has been postulated that this is due to diets dominated by processed foods that are higher in fat and sodium. High-fat diet-induced obesity increases miR-21 expression in adipose tissues where is controls the adipogenic differentiation of mesenchymal stem cells [12]. miR-21 is also one of the most consistently upregulated miRNAs across many different tumor types; its expression level correlates with cancer progression and patient prognosis [13]. It is intriguing to think that this is not mere coincidence and that it may in fact provide a direct link between the two conditions. Future studies should continue to explore the critical conserved roles that miRNAs such as miR-182 and miR-503 play in cancer development and progression. In addition, miRNAs also play a major in non-cell autonomous functions, it will be critical to evaluate the gene networks and signaling pathways that are regulated in the tumor microenvironment.

References

1. Chakradhar S (2015) Colorectal cancer: 5 big questions. Nature 521: S16.

2. Society AC (2014) Colorectal Cancer Facts & Figures 2014-2016.

3. Oberg AL, French AJ, Sarver AL, Subramanian S, Morlan BW, et al. (2011) miRNA expression in colon polyps provides evidence for a multihit model of colon cancer. PLoS One 6: e20465.

4. Starr TK, Allaei R, Silverstein KA, Staggs RA, Sarver AL, et al. (2009) A transposon-based genetic screen in mice identifies genes altered in colorectal cancer. Science 323: 1747-1750.

5. Jones MF, Hara T, Francis P, Li XL, Bilke S, et al. (2015) The CDX1-microRNA-215 axis regulates colorectal cancer stem cell differentiation. Proc Natl Acad Sci USA 112: E1550-1558.

6. Valeri N, Braconi C, Gasparini P, et al. (2014) MicroRNA-135b promotes cancer progression by acting as a downstream effector of oncogenic pathways in colon cancer. Cancer Cell 25: 469-483.

7. Valeri N, Braconi C, Pierluigi Gasparini P, Murgia C, Lampis A, et al. (2013) MicroRNA-135b and Its Circuitry Networks as Potential Therapeutic Targets in Colon Cancer. Front Oncol 3: 268.

8. Li L, Sarver AL, Khatri R, Hajeri PB, Kamenev I, et al. (2014) Sequential expression of miR-182 and miR-503 cooperatively targets FBXW7, contributing to the malignant transformation of colon adenoma to adenocarcinoma. J Pathol 234: 488-501.

9. Davis RJ, Welcker M, Clurman BE (2014) Tumor suppression by the Fbw7 ubiquitin ligase: mechanisms and opportunities. Cancer Cell 26: 455-464.

10. Cheng CJ, Bahal R, Babar IA, et al. (2015) MicroRNA silencing for cancer therapy targeted to the tumour microenvironment. Nature 518: 107-110.

11. Holmes D (2015) A disease of growth. Nature 521: S2-S3.

12. Kim YJ, Hwang SH, Cho HH, Shin KK, Bae YC, et al. (2012) MicroRNA 21 regulates the proliferation of human adipose tissue-derived mesenchymal stem cells and high-fat diet-induced obesity alters microRNA 21 expression in white adipose tissues. J Cell Physiol 227: 183-193.

13. Wang W, Li J, Zhu W, et al. (2014) MicroRNA-21 and the clinical outcomes of various carcinomas: a systematic review and meta-analysis. BMC Cancer 14: 819.