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

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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 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.

MicroRNAs (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 it 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.

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