Editorial

Stem Cell INVESTIGATION

A role for miR-34 in colon cancer stem cell homeostasis

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In recent years, cancer stem cells have taken center stage in studies involving cancer origins and metastasis (1). Unlike somatic cells, which often follow symmetric cell division yielding two identical daughter cells, stem cells often undergo asymmetric division leading to non-identical cell types such as progenitor cells of various tissue origins during embryogenesis (2). This unique asymmetric division feature helps stem cells maintain homeostasis, with a constant number of daughter stem cells and differentiated cells. Even though stem cells undergo asymmetric division in most cases, they do undergo symmetric division in some tissue contexts such as $Lgr5^+$ crypt base columnar cells in intestine to stabilize the number of cells (3). Cancer stem cells, which are also known as tumor initiating cells, behave in a similar manner to stem cells and undergo asymmetric division in response to loss of tumor suppressors. Now a recent paper reveals an intriguing connection between colon cancer stem cells and a non-coding RNA called miR-34 (4).

MicroRNAs (miRNAs) belong to the family of noncoding RNAs and are approximately 20 nucleotides in length. Binding of these small RNA molecules to target mRNA results in translation inhibition or mRNA degradation. Since the discovery of first miRNAs *lin-4* and *let-7* and their role in embryonic stem cell development, the field of miRNA has expanded to include several hundred miRNAs involved in various cellular homeostasis steps (5-9). Due to their involvement in myriad number of cell functions by targeting crucial mRNA-protein signaling factors, they are often implicated in disease processes, including cancer. In cancer, miRNAs can target crucial tumor suppressor pathways resulting in the loss of tumor suppressor genes, or in the loss of important check point miRNAs targeting oncogenes, which can result in aberrant expression of corresponding oncogenes. One of the important tumor suppressor miRNA often lost in cancers is miR-34, a direct transcriptional target of p53 (10-15). Loss of miR-34 in cancers results in increased expression of several cell proliferation, anti-apoptosis, metastasis-associated genes such as *BCL2*, *CD44*, *Notch1* (13).

In recent years, a role for miR-34 has been explored in the field of cancer stem cells. The first study elucidating role of miR-34 in regulation of cancer stem cells reported direct targeting of CD44 by miR-34 (12). Using *in vitro* and *in vivo* mouse model studies, the authors demonstrated that rescue of expression of miR-34 in cancer cells lead to decreased tumorigenic properties of cancer cells. Decreased invasion and migration as a result of decreased CD44 expression was observed. Furthermore, systemic delivery of therapeutic miR-34 mimics resulted in tumor regression and extended survival of mice with prostate cancer. In breast cancer, treatment of cells with miR-34 resulted in decreased stemness factor $ALDH1^+$ in cells. Interestingly, miR-34 treatment enhanced sensitivity of breast cancer cells to paclitaxel, a microtubule destabilizing chemotherapeutic agent. Notch1 is miR-34 target, shown to play role in this increased chemosensitivity (16).

Early this year, in colon cancer stem cells, it was shown that miR-34 targets *NUMB*, coding for a protein involved in asymmetrical cell division during development and *Notch1*, coding for a protein involved in cell proliferation signaling (4). The authors demonstrated a feed forward loop signaling involving miR-34, NUMB and Notch1, leading to increased cancer stem cell asymmetric division. This feed forward loop, is termed as incoherent feedback loop since miR-34 targets NUMB and Notch1, while Notch1 is inhibited by NUMB protein in a converging

pathway. It is intriguing question—if miR-34 targets both Notch1 and Numb, while resulting in a release of Notch1 suppression by Numb, does this loop lead to general accumulation of Notch1, or an imbalance leading to promotion of differentiation? To address this question, the authors performed computational analysis using modeling and *in vitro* data on doxycycline-induced expression of miR-34 and measurement of Notch1, NUMB levels. Data shows that this loop acts as bimodal switch in determining cell fate. While NUMB is intact in the cells, miR-34 expression lead to a constant increase in Notch1 expression in bimodal fashion, however, upon NUMB knockdown and doxycycline mediated miR-34 expression, Notch1 level showed significantly poor bimodality. To understand the significance of these perturbations, the authors tested the expression of stem cell marker ALDH1 and differentiation marker CK20 in cells with varying levels of Notch1. Cells with intermediate levels of Notch1 showed plastic behavior suggesting the role of this bimodal switch in stem cell maintenance. Further evidence for this hypothesis came from experiments involving LGR5 (an adult stem cell marker) knockout mice. During simulated inflammation by TNF-alpha, loss of miR-34 resulted in stem cells shifting to symmetric division leading to an increase in intestinal stem cells. Since during cancer development, inflammation is one of the hallmarks, we can hypothesize that the loss of miR-34 in this setting leads to increased colon cancer stem cells/progenitor cells leading to aggressive cancer development. However, direct data from cultured colon cancer stem cells with miR-34 modulation is still pending.

The link between miR-34, inflammation, and cancer is of particular importance considering that recent evidence has suggested a significant role of the loss of miR-34 in cancer. With current evidence showing a large set of oncogenic mRNAs being targeted by miR-34, therapeutics involving replenishment of miR-34 has evolved into clinical trials following early discoveries of its role as tumor suppressor. This new and innovative therapeutic shows a promising future path towards becoming one of the effective therapies against cancer.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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