Cell Cycle 13:1, 11–12; January 1, 2014; © 2014 Landes Bioscience

miR-22 in tumorigenesis

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microRNAs (miRNAs), a newly characterized class of regulatory genes, have revolutionized classical biomolecular principles. These small non-coding RNAs, which are around 22 nucleotides long, negatively regulate gene expression through translational repression or targeting mRNAs for degradation. miRNAs function in multiple cellular processes, including proliferation, differentiation, and apoptosis, and their deregulation is a hallmark of human diseases including cancer.[1]

Cancers that are resistant to conventional therapies often advance to metastasis, which further complicates successful treatment. In this process, genetic and epigenetic instability, as well as a capacity for self-renewal, allow malignant cancer cells to escape from the primary tumor and colonize secondary sites. The discovery of the contribution of epigenetic alterations in tumorigenesis has been of enormous importance to our understanding of cancer pathogenesis; hence, it is tempting to speculate that epigenetic mechanisms may also regulate miRNA-encoding genes involved in triggering the metastatic process. What is still not known, however, is whether and how miRNAs can directly modulate the epigenetic cancer landscape.

Indeed, we recently found that miR-22 acts as a very potent proto-oncogenic miRNA precisely because of its ability to epigenetically derange the biology of the cell. Intriguingly, we have shown that miR-22 antagonizes another critical miRNA, the anti-metastatic *mir-200* gene, through direct targeting of the methylcytosine dioxygenase TET (ten-11 translocation) family members and, hence, chromatin remodeling toward miR-200 transcriptional silencing.[2]

Using Cre-based mammary gland-specific transgenic mouse model, we further demonstrated that miR-22 triggers epithelial–mesenchymal transition (EMT), enhances stemness, and promotes breast cancer development and metastasis.[2] Moreover, miR-22 promotes aggressive metastatic disease in *neu* (ErbB2; Her2) or *PyVT* oncogene compound mice. We show that miR-22 exerts this metastatic potential by increasing methylation of the *mir-200* promoter, thus suppressing the expression of the anti-metastatic miR-200 family.

Through extensive bioinformatic and experimental analyses, we identified the TET family as the cognate target of miR-22 that is essential to the demethylation of the *mir-200* promoter. In keeping with this notion, high expression of miR-22 has been found to correlate with poor clinical outcomes and silencing of the TET-miR-200 axis in human breast cancer patients.[2]

In a back-to-back study, we have identified miR-22 as a key regulator of the self-renewal machinery of the hematopoietic system.[3] miR-22 was found to reduce the global level of 5-hydroxymethylcytosine (5-hmC) in the genome of mouse hematopoietic stem cells (HSCs), which triggered an increase in HSC self-renewal capability accompanied by defective differentiation and the development of a human myelodysplastic syndrome (MDS)-like disease, followed by the development of hematological malignancies at full penetrance.[3] Again we identified TET2 as a critical target of miR-22 in this context, as an ectopic expression of TET2 suppressed the phenotypes caused by miR-22 overexpression. Interestingly, miR-22 appears to be overexpressed in human MDS and leukemia, and its aberrant expression correlates with poor survival of patients and TET2 down regulation.

Several previous in vitro studies have suggested a tumor suppressive role for miR-22, but corroboration of its oncogenic potential has also been found in human prostate cancer and mouse models of cardiac hypertrophy through the targeting of the PTEN (phosphatase tensin and homolog) tumor suppressor.[4,5] It is worth noting, however, that the function of miR-22 as an epigenetic modifier in breast cancer metastasis appears to be independent of its ability to target PTEN.[2] However, it is possible that the ability of miR-22 to simultaneously repress PTEN and TET2 may confer on it a unique ability to overcome *PTEN* loss-driven HSC exhaustion while favoring MDS development and leukemogenesis.[3]

One of the most exciting findings arising from our work is that the TET-mediated chromatin remodeling activity of miR-22 uncovers a chromatin remodeling antagonism between miRNAs. As numerous miRNAs appear to be altered in cancer, it will be interesting to determine whether the miR-22-TET network contributes to genome-wide epigenetic regulation of miRNAs in cancer and stem cell biology. On the other hand, it will also be interesting to assess how miR-22 modulates TET-mediated DNA demethylation vs. miR-200-Bmi1 (B lymphoma Mo-MLV insertion region 1 homolog) polycomb protein-mediated chromatin remodeling.

More fundamental questions arising from these studies would be related to the causes of aberrant expression of miR-22 in the pathogenesis of cancer metastasis and blood disease. Therefore, the

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Submitted: 09/03/2013; Accepted: 09/25/2013
http://dx.doi.org/10.4161/cc.27027
Comment on: Song SJ, et al. Cell 2013; 154:311-24; PMID:23830207; http://dx.doi.org/10.1016/j.cell.2013.06.026

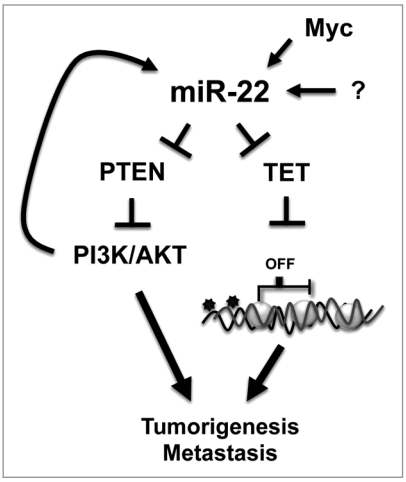

Figure 1. miR-22 directly targets PTEN and TET to promote tumorigenesis and metastasis. While miR-22 impacts cancer development through targeting of the PTEN tumor suppressor, miR-22 triggers EMT and metastasis and stem cell self-renewal via TET-mediated chromatin remodeling. miR-22 is activated by the PI3K/AKT pathway with a positive feedback loop. miR-22 is also one of the miRNAs that is regulated by the proto-oncogenic transcription factor, Myc.

identification of the oncogenic or tumor-suppressive upstream regulators of miR-22 is of critical importance. Interestingly, previous studies have demonstrated that the PI3K/AKT pathway activates *mir-22* gene transcription; miR-22 is also activated by the transcription factor Myc and, in turn, inhibits the Myc transcriptional repressor MXD4[6,7] (**Fig. 1**).

Ultimately, as the technology to inhibit miRNAs for therapy is rapidly evolving,[8] these findings could lead to treatment options for a range of diseases in the years to come. Indeed, our findings that inhibiting miR-22 by the miR-22 decoy leads to a reduction of metastatic phenotypes in the breast, while LNA (locked nucleic acid)-modified miR-22 decoy results in a signification reduction in leukemic cell proliferation; together these findings support LNA-based targeting of miR-22 as a potential treatment modality for human tumorigenesis and metastasis.

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