Cell Cycle 12:24, 3703–3704; December 15, 2013; © 2013 Landes Bioscience

"Sister" miRNAs in cancers

Reema Wahdan-Alaswad and Bolin Liu*

Department of Pathology; School of Medicine; University of Colorado Anschutz Medical Campus; Aurora, CO USA

microRNAs (miRNAs) are short non-coding RNAs of ~22 nucleotides that negatively regulate gene expression at the post-transcriptional level. In general, miRNAs bind to the 3′ untranslated region (UTR) of its target mRNA via sequence-guided specific recognition to trigger mRNA degradation or translational repression. The biogenesis of a miRNA enables transcribed primary miRNA (pri-miRNA) to be processed by RNase II (Drosha) into precursor miRNA (pre-miRNA), which is, in turn, exported to the cytosol and further processed by Dicer to generate a mature miRNA. Over one-third of human genes are thought to be regulated by miRNAs. In human cancers, miRNAs play highly diverse roles via their influences on a wide of variety of biological process, including cell proliferation, differentiation, signal transduction, and apoptosis.[1] Tissue-specific signatures and temporal restrictions may alter the expression levels of miRNAs, thus they can act as either tumor suppressors or oncogenes in a context-dependent manner.[2,3]

Recent studies highlight the role of epigenetic modulations, such as DNA methylation and chromatin remodeling, in impacting the expression and biological functions of tumor-initiating and -suppressive genes, also contributing to (1) dysregulation of gene expression in human cancers by altering the production of pri-miRNAs and (2) impairment of miRNA processing and maturation. For example, aberrant promoter methylation of miRNAs has been frequently observed in various human tumors that lead to reduced expression of pri-miRNAs.[4] Xhemalce et al.[5] recently identified BCDIN3D, a RNA methyltransferase that can methylate pre-miRNAs to evade efficient association with Dicer and thereby impair miRNA processing and decrease the overall production of mature miRNAs. Nonetheless, the precise molecular mechanism of epigenetic regulation of miRNA expression remains largely unknown.

In the March 22, 2013 issue of *Cell Death and Disease*, Dr Bolin Liu and his colleagues[6] tested whether modulation of chromatin remodeling alters expression of erbB2/erbB3 receptors, members of the type I receptor tyrosine kinase (RTK) family critical for breast cancer initiation and progression. For the first time, this study revealed that a selective class I histone deacetylase (HDAC) inhibitor (HDACi) entinostat (also known as MS-275 or SNDX-275) downregulated erbB2/erbB3 in erbB2-overexpressing breast cancer cells through a transcription-independent manner via upregulation of specific miRNAs (miR-125a, miR-125b, and miR-205) that have been reported to target *erbB2*/*erbB3* mRNAs. These "sister" miRNAs (so called because they share common targets) act in concert with one another to reduce erbB2/erbB3 protein, but not mRNA, levels and thereby inhibit their downstream signaling in breast cancer cells. Furthermore, direct inhibition of two or more miRNAs, but not one, significantly attenuated entinostat-induced downregulation of erbB2/erbB3 and apoptosis in breast cancer cells.[6] This study provides novel insights regarding the complexity of miRNA-mediated translational suppression of an oncogene targeted by multiple miRNAs, which could be exploited for therapeutic effect in human cancers.

Development of effective molecularly targeted therapy for human cancers is challenging due to unpredictable responses and/or potential resistance to the therapy. A new generation of cancer drugs may involve the use of miRNA mimics or antagonists that aim to down- or upregulate their gene targets. The data generated from Liu's laboratory support the utilization of more than one miRNA in order to efficiently downregulate the oncogenes that play a pivotal role in the development of human cancers. Previously, skepticism regarding miRNA as a therapeutic modality might be attributed to their off-target effects and/or unwanted toxicities associated with upregulation of the miRNAs by 100- and 1000-fold. In an attempt to improve our understanding of miRNA regulation of gene expression, researchers have postulated using multiple miRNAs that bind to the 3′UTR of one target (multiple-to-one[7]) as opposed to multiple miRNAs that target multiple genes (multiple-to-multiple[8]). When examining multiple-to-one scenario, Wu et al.[7] analyzed combinations of miRNAs (miR-181c/miR-340, miR-224/miR-452) that were able to target *KRAS*/*MECP2* and *KRAS*/*DPYSL2*, respectively. Unlike these studies, Wang et al.[6] provide supportive data indicating that combinations of "sister" miRNAs (miR-125a/miR-125b/miR-205) may exhibit synergistic/additive inhibitory effects on a target gene more so than any single miRNA. Restoration of such "sister" miRNAs at lower regulatory levels may serve as a novel strategy to combat tumorigenesis via more effective and efficient downregulation of critical oncogenes (**Fig. 1**). These studies highlight the significance of multiple miRNAs working in sync on target regulation; however, issues regarding spatial and temporal constrains associated with miRNAs docking to their seed sequences are still poorly understood. It is not clear whether and how a miRNA's binding location and timing may alter its effectiveness on regulation

*Correspondence to: Bolin Liu; Email: bolin.liu@ucdenver.edu
Submitted: 08/16/2013; Accepted: 08/18/2013
http://dx.doi.org/10.4161/cc.26875
Comment on: Wang S, et al. Cell Death Dis 2013; 4:e556; PMID:23519125; http://dx.doi.org/10.1038/cddis.2013.79

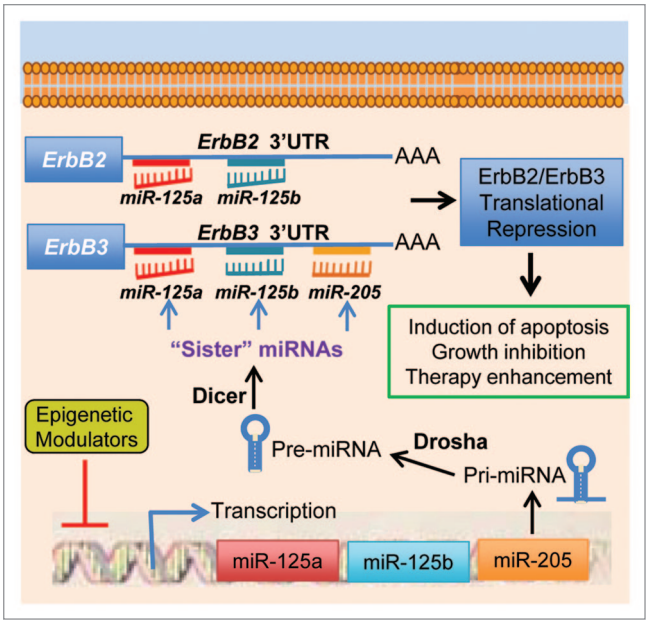

Figure 1. Schema of "sister" miRNAs working in sync to regulate erbB2/erbB3. Epigenetic modulators trigger chromatin remodeling to enhance miRNA expression. The increased "sister" miRNAs simultaneously bind to 3′UTRs of their common targets and act in concert to more effectively downregulate expression of the targets. We hypothesize that cooperative miRNA targeting of *erbB2/erbB3* represents a novel strategy for cancer therapy.

of gene expression. Moreover, whether the cooperative interaction between multiple miRNAs that bind to the 3′UTR of one target solely or predominantly modulate the gene's translational machinery remains in question. Thus, basic research is needed to further optimize the experimental approach and expand our understanding of miRNA regulation of gene expression. We believe that such studies will likely usher in an innovative platform for robust miRNA-based therapies for cancer patients.

References

1. Yates LA, et al. Cell 2013; 153:516-9; PMID:23622238; http://dx.doi.org/10.1016/j.cell.2013.04.003
2. Gebeshuber CA, et al. EMBO Rep 2009; 10:400-5; PMID:19247375; http://dx.doi.org/10.1038/embor.2009.9
3. Zhou M, et al. J Biol Chem 2010; 285:21496-507; PMID:20460378; http://dx.doi.org/10.1074/jbc.M109.083337
4. Baer C, et al. Cancer Res 2013; 73:473-7; PMID:23316035; http://dx.doi.org/10.1158/0008-5472.CAN-12-3731
5. Xhemalce B, et al. Cell 2012; 151:278-88; PMID:23063121; http://dx.doi.org/10.1016/j.cell.2012.08.041
6. Wang S, et al. Cell Death Dis 2013; 4:e556; PMID:23519125; http://dx.doi.org/10.1038/cddis.2013.79
7. Wu S, et al. Oncogene 2010; 29:2302-8; PMID:20190813; http://dx.doi.org/10.1038/onc.2010.34
8. Hashimoto Y, et al. PLoS One 2013; 8:e62589; PMID:23667495; http://dx.doi.org/10.1371/journal.pone.0062589