DNA AND CELL BIOLOGY
Volume 26, Number 4, 2007

Pp. 193–194
DOI: 10.1089/dna.2006.0567

Editorial

miRNA: Licensed to Kill the Messenger

CHANDAN K. SEN and SASHWATI ROY

ABSTRACT

Current developments have brought non-coding genes under limelight together with their better-known siblings, the coding genes or mRNA. The 2006 Nobel Prize in Physiology or Medicine was awarded to Andrew Fire and Craig Mello for their 1998 discovery that double-stranded RNA triggers suppression of gene activity in a homology-dependent manner, a process named RNA interference (RNAi). Post-transcriptional regulation of genes was generally regarded as an odd regulatory mechanism for several years until it was learnt that regulatory trans-acting antisense RNAs exist in several species. Identification of a large number of small RNA molecules called microRNAs (miRNAs) elevated the overall field of biomedical RNAi to the striking level of current recognition. miRNAs represent a class of endogenous small (~22 nucleotides) RNA molecules that can repress protein synthesis. It is estimated that there are over 600 miRNAs in mammalian cells, and that about 30% of all genes are regulated by miRNA. Current understanding of the molecular mechanism of any disease would be incomplete without factoring in the functional significance of miRNA. In the category of the futuristic RNAi drugs, miRNA-based therapies are promising. The field has progressed rapidly as it relates to cancer research (highlighted in *DNA and Cell Biology* Volume 26, Number 4), while development in most other areas (highlighted in *DNA and Cell Biology* Volume 26, Number 3) of biomedical research remains in its infancy, offering significant opportunity for researchers. Approaches to interfere with miRNA function *in vivo* offer novel therapeutic opportunities. Lessons in gene therapy have taught us that tinkering with the genetic machinery comes with its own set of risks, especially in a clinical setting. miRNA-based therapies are also subject to such risks, which need to be prudently managed. Having acknowledged the potential risk, we have to recognize that new knowledge about the functional roles of miRNA is revolutionizing cell biology and will have a major impact on biomedical research imminently.

The biology of non-coding genes arguably represents the hottest topic in biomedical research today (Mattick and Makunin, 2006). The 2006 Nobel Prize in Physiology or Medicine was shared by Professor Andrew Z. Fire at Stanford University, CA, and Professor Craig C. Mello at the University of Massachusetts Medical School in Worcester. They received the prize for their 1998 discovery that double-stranded RNA triggers suppression of gene activity in a homology-dependent manner, a process named RNA interference (RNAi) (Fire *et al.*, 1998). Inhibition of translation by small RNA molecules, approximately 100 nucleotides in length, was reported in *Escherichia coli* over 2 decades ago (Mizuno *et al.*, 1984). Regulatory trans-acting antisense RNAs are commonly known today (Gottesman, 2004a, 2004b). An important leap closely relevant to biomedical research was made in 1993 when it was reported that regulation of translation by antisense RNA also occurs in the eukaryote *Caenorhabditis elegans* (Lee *et al.*, 1993; Wightman *et al.*, 1993). Post-transcriptional regulation of genes was generally regarded as an odd regulatory mechanism for several years until it was learnt that regulatory trans-acting antisense RNAs exist in several species. Identification of a large number of small RNA molecules called microRNAs (miRNAs) elevated the overall field of biomedical RNAi to a striking level of recognition (Lagos-Quintana *et al.*, 2001; Lau *et al.*, 2001; Lee and Ambros, 2001).

miRNAs represent a class of endogenous RNA molecules, of the same size in worms, flies, mice, and humans. miRNAs can repress protein synthesis and regulate the development of

Laboratory of Molecular Medicine, Department of Surgery, Davis Heart and Lung Research Institute, The Ohio State University Medical Center, Columbus, Ohio.

organisms. The small miRNAs are processed from larger hairpin-like precursors. Most miRNA genes come from regions of the genome quite distant from previously annotated genes, implying that they derive from different transcription units. The miRNAs within a genomic cluster are often related to each other, but not always. Through specific base pairing with mRNAs, these tiny (approximately 22 nucleotides) RNAs induce mRNA degradation, translational repression, or both. Because an miRNA can target numerous mRNAs, often in combination with other miRNAs, miRNAs operate highly complex regulatory networks. It is estimated that there are over 600 miRNAs in mammalian cells, and that about 30% of all genes are regulated by miRNAs (Rajewsky, 2006; Shilo *et al.*, 2007). Over 3000 identified mature miRNAs exist in species ranging from plants to humans, suggesting that they are ancient players in gene regulation (Wang *et al.*, 2007). Experimental identification of miRNAs is slow since some miRNAs are difficult to isolate by cloning due to low abundance, stability, and expression pattern. Computational identification of miRNAs from genomic sequences provides a valuable complement to cloning. Precursors of miRNA possess stem loop structure. Thus, computational methods aimed at finding miRNA searches for hairpins. Identification of sets of cognate mRNA for any given miRNA is a challenging task experimentally. Thus, there has been significant effort to develop computational algorithms to address that important need. While several such computational algorithms are useful hypothesis-generating tools, conclusive verification must be performed experimentally in the biology laboratory (Ioshikhes *et al.*, 2007). Prudent integration of mRNA and miRNA sequence and expression data with other comparative genomic data will lead to global and yet specific insights into post-transcriptional control.

Current understanding of the molecular mechanism of any disease would be incomplete without factoring in the functional significance of miRNA. Further, in the category of the futuristic ''RNAi drugs'' (Liu *et al.*, 2007) miRNA-based therapies are promising (Petit-Zeman, 2006; Slack and Weidhaas, 2006). The field has progressed rapidly as it relates to cancer research (Slack and Weidhaas, 2006; Osada and Takahashi, 2007), while development in most other areas of biomedical research remains in its infancy, offering significant opportunity for researchers. Approaches to interfere with miRNA function *in vitro* and *in vivo* based on synthetic anti-miRNA oligonucleotides offer novel therapeutic opportunities (Ford, 2006; Hammond, 2006; Rodriguez-Lebron and Paulson, 2006; Weiler *et al.*, 2006; Mattes *et al.*, 2007). Lessons in gene therapy have taught us that tinkering with the genetic machinery comes with its own set of risks especially in a clinical setting. miRNA-based therapies are also subject to concerns regarding various types of side effects that may restrict the use of this technology in human therapy. Having acknowledged the potential risk, we have to recognize that new knowledge about the functional roles of miRNAs as regulators of many cellular processes, including proliferation, differentiation, development, and neuronal function, is revolutionizing cell biology and will have a major impact on biomedical research imminently.

ACKNOWLEDGMENT

Supported by NIH GM069589, HL073087, NS42617 and GM 077185.

REFERENCES

FIRE, A., XU, S., MONTGOMERY, M.K., KOSTAS, S.A., DRIVER, S.E., and MELLO, C.C. (1998). Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. Nature **391,** 806–811.

FORD, L.P. (2006). Using synthetic miRNA mimics for diverting cell fate: a possibility of miRNA-based therapeutics? Leuk Res **30,** 511–513.

GOTTESMAN, S. (2004a). The small RNA regulators of *Escherichia coli*: roles and mechanisms. Annu Rev Microbiol **58,** 303–328.

GOTTESMAN, S. (2004b). Small RNAs shed some light. Cell **118,** 1–2.

HAMMOND, S.M. (2006). MicroRNA therapeutics: a new niche for antisense nucleic acids. Trends Mol Med **12,** 99–101.

IOSHIKHES, I., ROY, S., and SEN, C.K. (2007). Algorithms for mapping of mRNA targets for microRNA. DNA Cell Biol. **26,** 265–272.

LAGOS-QUINTANA, M., RAUHUT, R., LENDECKEL, W., and TUSCHL, T. (2001). Identification of novel genes coding for small expressed RNAs. Science **294,** 853–858.

LAU, N.C., LIM, L.P., WEINSTEIN, E.G., and BARTEL, D.P. (2001). An abundant class of tiny RNAs with probable regulatory roles in *Caenorhabditis elegans*. Science **294,** 858–862.

LEE, R.C., and AMBROS, V. (2001). An extensive class of small RNAs in *Caenorhabditis elegans*. Science **294,** 862–864.

LEE, R.C., FEINBAUM, R.L., and AMBROS, V. (1993). The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell **75,** 843–854.

LIU, G., WONG-STAAL, F., and LI, Q.X. (2007). Development of new RNAi therapeutics. Histol Histopathol **22,** 211–217.

MATTES, J., YANG, M., and FOSTER, P.S. (2007). Regulation of microRNA by antagomirs: a new class of pharmacological antagonists for the specific regulation of gene function? Am J Respir Cell Mol Biol **36,** 8–12.

MATTICK, J.S., and MAKUNIN, I.V. (2006). Non-coding RNA. Hum Mol Genet **15 Spec No 1,** R17–R29.

MIZUNO, T., CHOU, M.Y., and INOUYE, M. (1984). A unique mechanism regulating gene expression: translational inhibition by a complementary RNA transcript (micRNA). Proc Natl Acad Sci USA **81,** 1966–1970.

OSADA, H., and TAKAHASHI, T. (2007). MicroRNAs in biological processes and carcinogenesis. Carcinogenesis **28,** 2–12.

PETIT-ZEMAN, S. (2006). MicroRNAs hit the big time. Nat Rev Drug Discov **5,** 5.

RAJEWSKY, N. (2006). MicroRNA target predictions in animals. Nat Genet **38 Suppl.,** S8–S13.

RODRIGUEZ-LEBRON, E., and PAULSON, H.L. (2006). Allele-specific RNA interference for neurological disease. Gene Ther **13,** 576–581.

SHILO, S., ROY, S., KHANNA, S., and SEN, C.K. (2007). MicroRNA in cutaneous wound healing: a new paradigm. DNA Cell Biol. **26,** 227–237.

SLACK, F.J., and WEIDHAAS, J.B. (2006). MicroRNAs as a potential magic bullet in cancer. Future Oncol **2,** 73–82.

WANG, Y., STRICKER, H.M., GOU, D., and LIU, L. (2007). MicroRNA: past and present. Front Biosci **12,** 2316–2329.

WEILER, J., HUNZIKER, J., and HALL, J. (2006). Anti-miRNA oligonucleotides (AMOs): ammunition to target miRNAs implicated in human disease? Gene Ther **13,** 496–502.

WIGHTMAN, B., HA, I., and RUVKUN, G. (1993). Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in *C. elegans*. Cell **75,** 855–862.

Address reprint requests to:
Chandan K. Sen
512 Heart and Lung Research Institute
473 W. 12th Avenue
Columbus, OH 43210

E-mail: chandan.sen@osumc.edu

Received for publication December 26, 2006; accepted January 2, 2007.

This article has been cited by:

1. Suman Santra, Atul Rawat, Dhamotharan Pattarayan, Sashwati Roy. Chronic infection and inflammation: Hallmarks of diabetic foot ulcers 39-47. [Crossref]
2. Jessica Gasparello, Michela Lomazzi, Chiara Papi, Elisabetta D'Aversa, Francesco Sansone, Alessandro Casnati, Gaetano Donofrio, Roberto Gambari, Alessia Finotti. 2019. Efficient Delivery of MicroRNA and AntimiRNA Molecules Using an Argininocalix[4]arene Macrocycle. *Molecular Therapy - Nucleic Acids* **18**, 748-763. [Crossref]
3. Roy Sashwati. 2016. miRNA in Macrophage Development and Function. *Antioxidants & Redox Signaling* **25**:15, 795-804. [Abstract] [Full Text] [PDF] [PDF Plus]
4. Ying Wang, Xiaoye Li, Bairui Tao. 2016. Improving classification of mature microRNA by solving class imbalance problem. *Scientific Reports* **6**:1. . [Crossref]
5. Amitava Das, Chandan K. Sen. NutrimiRomics 53-60. [Crossref]
6. Sinha Mithun, Ghatak Subhadip, Roy Sashwati, Sen Chandan K.. 2015. microRNA–200b as a Switch for Inducible Adult Angiogenesis. *Antioxidants & Redox Signaling* **22**:14, 1257-1272. [Abstract] [Full Text] [PDF] [PDF Plus]
7. Guangxian Xu, Yilin Zhang, Jun Wei, Wei Jia, Zhaohui Ge, Zhaobo Zhang, Xiaoming Liu. 2013. MicroRNA-21 promotes hepatocellular carcinoma HepG2 cell proliferation through repression of mitogen-activated protein kinase-kinase 3. *BMC Cancer* **13**:1. . [Crossref]
8. Sashwati Roy, Amitava Das, Chandan K. Sen. Disorder of Localized Inflammation in Wound Healing: A Systems Perspective 173-183. [Crossref]
9. Bin Wang. 2013. Base Composition Characteristics of Mammalian miRNAs. *Journal of Nucleic Acids* **2013**, 1-6. [Crossref]
10. Amitava Das, Sashwati Roy. Resolution of Inflammation 119-128. [Crossref]
11. YUK C. CHAN, JAIDEEP BANERJEE, SANG YONG CHOI, CHANDAN K. SEN. 2012. miR-210: The Master Hypoxamir. *Microcirculation* **19**:3, 215-223. [Crossref]
12. Jeffrey A. Loeb. 2011. Identifying targets for preventing epilepsy using systems biology. *Neuroscience Letters* **497**:3, 205-212. [Crossref]
13. Sashwati Roy, Chandan K. Sen. 2011. MiRNA in innate immune responses: novel players in wound inflammation. *Physiological Genomics* **43**:10, 557-565. [Crossref]
14. Xiaowei (Sylvia) Chen, Lesley J. Collins, Patrick J. Biggs, David Penny. 2009. High Throughput Genome-Wide Survey of Small RNAs from the Parasitic Protists Giardia intestinalis and Trichomonas vaginalis. *Genome Biology and Evolution* **1**, 165-175. [Crossref]
15. D Karan, J B Thrasher, D Lubaroff. 2008. Prostate cancer: genes, environment, immunity and the use of immunotherapy. *Prostate Cancer and Prostatic Diseases* **11**:3, 230-236. [Crossref]
16. Adil I. Daud, Vernon K. Sondak, Ashani Weeraratna. Melanoma Genomics—Techniques and Implications for Therapy 37-54. [Crossref]
17. Derek A Mann, Jelena Mann. 2008. Epigenetic regulation of hepatic stellate cell activation. *Journal of Gastroenterology and Hepatology* **23**:s1, S108-S111. [Crossref]
18. Shani Shilo, Sashwati Roy, Savita Khanna, Chandan K. Sen. 2008. Evidence for the Involvement of miRNA in Redox Regulated Angiogenic Response of Human Microvascular Endothelial Cells. *Arteriosclerosis, Thrombosis, and Vascular Biology* **28**:3, 471-477. [Crossref]
19. Ramanuj DasGupta, Foster C. Gonsalves. High-Throughput RNAi Screen in Drosophila 163-184. [Crossref]
20. Qingning Su, Shengwen Li. 2008. Small activating mRNA (samRNA): A hypothesis for a specific positive feedback regulation of gene expression. *Bioscience Hypotheses* **1**:1, 44-47. [Crossref]