BOOK REVIEW

# Regulation of Gene Expression by Small RNAs

Editors: Rajesh K. Gaur and John J. Rossi
CRC Press (2009)
431 pp., $149.95 hardcover.

From the standpoint of discovery, the field of small RNAs (sRNAs) is perhaps still in its infancy. However, because of the fascinating concept that they represent, posttranscriptional regulation of gene expression, these tiny sequences and their complex world have already attracted an enormous amount of well-deserved attention in the research community. They have an even shorter history in human genetics, but sRNAs have become a topic of intense interest in understanding the underlying mechanism of human diseases.

The growing list of discoveries in the field of sRNAs is the best indication of why it is indispensable for those involved in the field of genetics (teachers, students, and researchers) to gain knowledge about this critical regulatory concept. *Regulation of Gene Expression by Small RNAs*, a book edited by R.K. Gaur and J.J. Rossi, is a review-style chapter book composed of 21 chapters written by 43 authors, including the two coeditors. This book is dedicated to illustrating our current understanding about the challenges and discoveries related to these noncoding RNAs (ncRNAs). It provides informative discussions about topics pertaining to the roles of sRNAs in the regulation of gene expression, including utilized methodologies and examples of identified mechanisms and pathways in different organisms. This book clearly portrays the rapid and impressive progress made in the last few years in characterizing sRNAs. It uncovers their roles in a wide range of biological processes, from *C. elegans* and plants to human diseases, and includes how they have broadened our understanding of disease mechanisms and the exploration of therapeutic tools for the most challenging and complex dilemmas such as cancer and AIDS.

In the first chapter, in silico and in vivo miRNA prediction tools, including computational and experimental methods, are discussed. The benefits and disadvantages of these two approaches are also compared, demonstrating their complementary features and thus rightfully the need for making progress in both fields, because neither is without pitfalls. Chapter 2 describes computational methods and algorithms to predict miRNA genes. A list of bioinformatics resources and databases facilitating the study of miRNA ontology and function is provided in chapter 3. Translation regulation and mRNA stability mediated by sRNAs in *E. coli*, one of the primary sRNAs discovered, under specific physiological conditions are explained in the next chapter.

Like other gene regulatory processes, miRNAs do not function in an isolated fashion but are incorporated into a protein complex known as miRNP. Sequence pairing between miRNA and the target mRNA is only one of the necessary components for miRNP. The fact that each miRNA may potentially regulate hundreds of distinct target mRNAs further demonstrates the complexity of this system and the need for a cascade format process and its fine regulation to maintain the required delegated on/off switch. Multiple mechanisms of miRNA-mediated regulation in animal cells, including their effects on translation and mRNA stability, are discussed in chapter 5.

The first-discovered and best-characterized miRNAs, *lin-4* and *let-7*, control developmental timing events in *C. elegans*. Neural development spatial patterning is being regulated by two other *C. elegans* miRNAs, *lsy-6* and *mir-273*. The current understanding of these well-studied miRNAs, a great model system to gain more insight into miRNA functions even in higher-order organisms, is discussed in chapter 6. In the subsequent chapter, isolation of *C. elegans* sRNAs and their features are described. In addition to miRNAs, there are other classes of *C. elegans* sRNAs, including endo- and exo-siRNAs, small nucleolar RNAs (snoRNAs) (C/D box and H/ACA), and spliced leader RNAs (SL RNAs), which are also briefly explained in chapter 7. The roles of sRNAs in flies, zebrafish, and plants are included in chapters 8–11. An overview of some of the technologies available to assess miRNA expression, such as RNA blot, real-time PCR, and microarray-based profiling methods, are provided in the next two chapters.

In chapter 14, the reader learns about the functional interaction and crosstalk between miRNA and alternative splicing, another layer of gene regulation. Each of these gene regulatory networks (miRNA and alternative splicing) results in increased genomic complexity and diversity. This newly discovered functional role for sRNAs involving alternative splicing demonstrates how far such tiny sequences, previously mislabeled as junk DNA, can go in regulating gene expression and maintaining required complexity in higher organisms. Biogenesis of intronic miRNAs (which reside in the introns of gene transcripts) requires RNA splicing and mRNA processing of the host gene. The biogenesis and features of this class of miRNAs are discussed in chapter 15. The expression of intronic miRNAs may be regulated by the host gene promoter, making the intronic miRNA valuable in experimental design to study disease mechanisms. Gaining an understanding of the role of this class of miRNAs has opened up another

*Correspondence: ztalebi@cmh.edu
DOI 10.1016/j.ajhg.2010.01.039. 

exciting chapter to further appreciate the multifaceted and interconnected nature of gene regulatory networks, a notion that may be a reflection for the underlying convolution seen in complex genetic disorders.

The rest of the book is devoted to the application of the concepts and principles behind these small ncRNAs in scientific discoveries, including gene silencing and generating animal models to study gene function or to understand the mechanism of diseases. As clearly shown in this book, although there remain more puzzles to be solved concerning the mechanism of action regulated by the sRNAs, the current knowledge has already provided new avenues in designing alternative methods and potential tools, from constructing gene knockout and animal models to understanding etiology of cancers or drug therapy for AIDS.

In brief, the chapters in this book are written at two levels with regard to the covered detail and their specificity. In some chapters, the authors provide an extensive level of detail, making the text more attractive for readers familiar with and, particularly, interested in the discussed topic. Such chapters clearly demonstrate the complexity of gene regulation by these small ncRNAs. However, other chapters discuss topics in a more general format that would be beneficial to a wider range of audiences. This book provides a valuable overview of historical perspectives and our current understanding of target recognition, principles, and components of the machinery system regulated by sRNAs, particularly miRNAs. It also discusses the major challenges and mysteries yet to be solved pertaining to this complex gene regulation process.

The expanding field of ncRNAs has already grown enough that perhaps it is impossible to cover all of the known aspects in one book. miRNAs are one of the most studied types of sRNAs, and the majority of the text in *Regulation of Gene Expression by Small RNAs* is dedicated to this class of ncRNAs. But it should be noted that there are other forms of ncRNAs, such as snoRNAs and piwi-interacting RNAs (piRNAs), as briefly described in chapter 7. The story about *HBII-52* [MIM 609837], a brain-specific snoRNA located at human chromosome 15q11, is an example for the growing excitement about the critical role that this class of ncRNAs may play in the etiology of human disease. The antisense element of *HBII-52* exhibits an 18 nt complementarity to the *5-HT2C* [MIM 312861] mRNA, whereby it is subject to posttranscriptional RNA editing and an alternatively spliced exon Vb.[1] Subjects with Prader-Willi syndrome (PWS [MIM 176270]), a neurodevelopmental disorder involving a chromosome 15q11 abnormality, have different *5-HT2C* mRNA processing than healthy individuals, which may contribute to their clinical symptoms.[2]

piRNAs are a newly discovered class of sRNAs that are expressed abundantly in the spermatogenic cells.[3] The majorities of piRNAs exist as clusters and occur on one or both strands, designated as monodirectional or bidirectional clusters, respectively. The biological function of piRNAs is not fully known, but their expression pattern indicates that they play roles in spermatogenesis and germline development.[3] In a book aiming to cover the role of sRNAs, I expected to find more discussion covering these other forms of sRNAs.

The biogenesis, complex processing, and function of sRNAs are very well described in this book. Perhaps another topic that demonstrates the complexity of this gene regulatory system is the fact that miRNAs are also subject to RNA editing, a process that, if occurring in the binding site, could change the target sites in the 3′UTR regions.[4–6] Edited *miR-376* was shown to silence a different set of genes compared to the unedited form.[6] This finding indicates the critical role of RNA editing of miRNAs in the regulation of gene expression. Multiple classes of ncRNAs are highly represented in the nervous system,[7,8] emphasizing the likelihood that nervous system development and function is heavily dependent on RNA regulatory networks, and alterations of these networks may result in neurological diseases.[9,10] Although ncRNAs are a relatively new concept in human genetics, an exciting array of evidence has already emerged, showing their vital role in genetic disorders. Dysregulation of miRNAs has been reported in association with Alzheimer disease,[11] X-linked mental retardation,[12] Parkinson disease,[12] and Tourette syndrome.[13] Including an overview of these topics would have been beneficial for the reader of this book.

With regard to the formatting and typography of this book, the chapters are written as a completely independent text, and thus they do not need to be read in a consecutive order. Such flexibility could be a plus. However, it also introduces a great deal of redundancy in discussing basic topics. For example, the definition of miRNA and its biogenesis or historical perspectives, such as the discovery of *C. elegans* miRNAs, are discussed in several chapters. Perhaps inclusion of an introductory chapter covering these fundamental principles would have reduced some unnecessary redundancy throughout the book. There are a number of inconsistencies in the bibliography of references among different chapters. Such editorial inconsistencies are not expected for a collection of such high caliber and can be at times confusing to the readers. Employing a uniform bibliography format for the chapters of this book would have enhanced its consistency and made reading this book smoother.

Saving energy and managing genome complexity is the mission of these tiny nonprotein coding members. The ongoing efforts made toward their discovery and comprehension, including those by valued scientists who contributed to the content of this book, have already made an indispensable impact in promoting the field and uncovering mysteries in genetic disorders. Learning about sRNAs has created new concepts and revolutionized our perspectives about gene regulation. Without a doubt, we should be ready for more surprises as new discoveries are made in the field of sRNAs. For readers unfamiliar with sRNAs, this book provides a comprehensive understanding of this

gene regulatory system from a historical perspective to practical applications while discussing the answered and unanswered questions. For those already familiar with this topic, the range and variation of topics covered in this book provide a useful information base to further appreciate the complexity of the sRNA world. This book is a valuable resource for anyone interested in learning about the role of sRNAs and gene regulation, including graduate students and researchers interested in having an in-depth understanding of this topic. I would also recommend it to those of us who teach this topic.

## Web Resources

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man: http://www.ncbi.nlm.nih.gov/Omim/

## References


1. Cavaillé, J., Buiting, K., Kiefmann, M., Lalande, M., Brannan, C.I., Horsthemke, B., Bachellerie, J.P., Brosius, J., and Hüttenhofer, A. (2000). Identification of brain-specific and imprinted small nucleolar RNA genes exhibiting an unusual genomic organization. Proc. Natl. Acad. Sci. USA *97*, 14311–14316.
2. Kishore, S., and Stamm, S. (2006). The snoRNA HBII-52 regulates alternative splicing of the serotonin receptor 2C. Science *311*, 230–232.
3. Kim, V.N. (2006). Small RNAs just got bigger: Piwi-interacting RNAs (piRNAs) in mammalian testes. Genes Dev. *20*, 1993–1997.
4. Borchert, G.M., Gilmore, B.L., Spengler, R.M., Xing, Y., Lanier, W., Bhattacharya, D., and Davidson, B.L. (2009). Adenosine deamination in human transcripts generates novel microRNA binding sites. Hum. Mol. Genet. *18*, 4801–4807.
5. Blow, M.J., Grocock, R.J., van Dongen, S., Enright, A.J., Dicks, E., Futreal, P.A., Wooster, R., and Stratton, M.R. (2006). RNA editing of human microRNAs. Genome Biol. *7*, R27.
6. Kawahara, Y., Zinshteyn, B., Sethupathy, P., Iizasa, H., Hatzigeorgiou, A.G., and Nishikura, K. (2007). Redirection of silencing targets by adenosine-to-inosine editing of miRNAs. Science *315*, 1137–1140.
7. Rogelj, B., and Giese, K.P. (2004). Expression and function of brain specific small RNAs. Rev. Neurosci. *15*, 185–198.
8. Cao, X., Yeo, G., Muotri, A.R., Kuwabara, T., and Gage, F.H. (2006). Noncoding RNAs in the mammalian central nervous system. Annu. Rev. Neurosci. *29*, 77–103.
9. Mehler, M.F., and Mattick, J.S. (2006). Non-coding RNAs in the nervous system. J. Physiol. *575*, 333–341.
10. Maes, O.C., Chertkow, H.M., Wang, E., and Schipper, H.M. (2009). MicroRNA: Implications for Alzheimer disease and other human CNS disorders. Curr. Genomics *10*, 154–168.
11. Krichevsky, A.M., King, K.S., Donahue, C.P., Khrapko, K., and Kosik, K.S. (2003). A microRNA array reveals extensive regulation of microRNAs during brain development. RNA *9*, 1274–1281.
12. Dostie, J., Mourelatos, Z., Yang, M., Sharma, A., and Dreyfuss, G. (2003). Numerous microRNPs in neuronal cells containing novel microRNAs. RNA *9*, 180–186.
13. Abelson, J.F., Kwan, K.Y., O'Roak, B.J., Baek, D.Y., Stillman, A.A., Morgan, T.M., Mathews, C.A., Pauls, D.L., Rasin, M.R., Gunel, M., et al. (2005). Sequence variants in SLITRK1 are associated with Tourette's syndrome. Science *310*, 317–320.



Zohreh Talebizadeh[1,*]

[1]Faculty of Pediatrics, Children's Mercy Hospital and University of Missouri Kansas City School of Medicine, Kansas City, MO 64108, USA