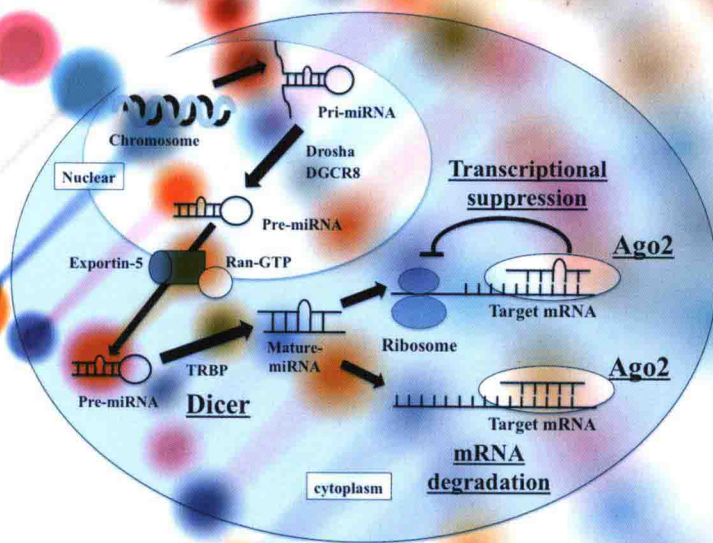


Editor SAURA C. SAHU

microRNAs in Toxicology and Medicine



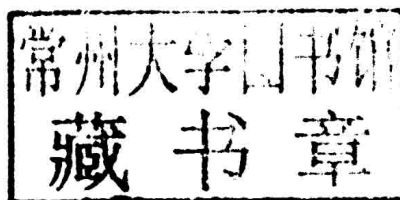
WILEY

microRNAs in Toxicology and Medicine

Editor

SAURA C. SAHU

Division of Toxicology, Center for Food Safety and Applied Nutrition,
Food and Drug Administration, USA



WILEY

This edition first published 2014
© 2014 John Wiley & Sons, Ltd.

Registered office

John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, United Kingdom

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com.

The right of the author to be identified as the author of this work has been asserted in accordance with the Copyright, Designs and Patents Act 1988.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, except as permitted by the UK Copyright, Designs and Patents Act 1988, without the prior permission of the publisher.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Designations used by companies to distinguish their products are often claimed as trademarks. All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The publisher is not associated with any product or vendor mentioned in this book.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. It is sold on the understanding that the publisher is not engaged in rendering professional services and neither the publisher nor the author shall be liable for damages arising herefrom. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

The advice and strategies contained herein may not be suitable for every situation. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of experimental reagents, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each chemical, piece of equipment, reagent, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. The fact that an organization or Website is referred to in this work as a citation and/or a potential source of further information does not mean that the author or the publisher endorses the information the organization or Website may provide or recommendations it may make. Further, readers should be aware that Internet Websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the publisher nor the author shall be liable for any damages arising herefrom.

Library of Congress Cataloging-in-Publication Data

microRNAs in Toxicology and Medicine / editor, Saura C. Sahu.
pages cm

Includes bibliographical references and index.

ISBN 978-1-118-40161-3 (cloth)

1. Small interfering RNA. 2. Small interfering RNA – Therapeutic use. 3. Genetic regulation. I. Sahu, Saura C., editor of compilation.

QP623.5.S63M536 2014

572.8'8 – dc23

2013020036

A catalogue record for this book is available from the British Library.

ISBN: 9781118401613

Set in 10/12pt Times by Laserwords Private Limited, Chennai, India

Printed and bound in Singapore by Markono Print Media Pte Ltd

1 2014

microRNAs in Toxicology and Medicine

I lovingly dedicate this book to:

*My parents, Gopinath and Ichhamoni, for their gifts of life,
love and living examples*

*My wife, Jharana, for her life-long friendship, love and support,
as well as for her patience and understanding of the long hours spent at
home on planning, writing and editing this book.*

*My children, Megha, Sudhir and Subir,
for their love and care*

*Saura C. Sahu
Laurel, Maryland, USA*

List of Contributors

- Aamir Ahmad** Department of Pathology, Karmanos Cancer Institute, Wayne State University School of Medicine, USA
- Malin Åkerblom** Department of Experimental Medical Science, Wallenberg Neuroscience Center *and* Lund Stem Cell Center, Lund University, Sweden
- Nahid Akhtar** Department of Anatomy and Neurobiology, Northeast Ohio Medical University (NEOMED), USA
- Azfar S. Ali** Department of Pathology, Karmanos Cancer Institute, Wayne State University School of Medicine, USA
- Shadan Ali** Department of Oncology, Karmanos Cancer Institute, Wayne State University School of Medicine, USA
- Sumit Arora** Department of Oncologic Sciences, Mitchell Cancer Institute, University of South Alabama, USA
- Kathryn A. Bailey** Department of Environmental Sciences and Engineering, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, USA
- Arun Bhardwaj** Department of Oncologic Sciences, Mitchell Cancer Institute, University of South Alabama, USA
- Barbara Burwinkel** Molecular Epidemiology C080, German Cancer Research Center, Germany *and* Molecular Biology of Breast Cancer, University Women's Clinic, Germany
- Si Chen** Division of Biochemical Toxicology, National Center for Toxicological Research/US Food and Drug Administration, USA
- Tao Chen** Division of Genetic and Molecular Toxicology, National Center for Toxicological Research, Food and Drug Administration, USA
- Sang-Woon Choi** Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, USA *and* Friedman School of Nutrition Science and Policy, Tufts University, USA
- Pierre Cordelier** INSERM U1037, Cancer Research Center of Toulouse, France *and* Université Paul Sabatier Toulouse III, France
- Katarina Cuk** Molecular Epidemiology C080, German Cancer Research Center, Germany *and* Molecular Biology of Breast Cancer, University Women's Clinic, Germany
- Yang Dai** Department of Bioengineering, University of Illinois at Chicago, USA
- Christopher J. Davis** WWAMI Medical Education Program and Program in Neuroscience, Sleep and Performance Research Center, Washington State University, USA
- Joel Fontanarosa** Department of Bioengineering, University of Illinois at Chicago, USA
- Jennifer L. Freeman** School of Health Sciences, Purdue University, USA
- Simonetta Friso** University of Verona School of Medicine, Italy
- Rebecca C. Fry** Department of Environmental Sciences and Engineering, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, USA
- Luc Gailhouse** Division of Molecular and Cellular Medicine, National Cancer Center Research Institute, Japan

- Marion Gayral** INSERM U1037, Cancer Research Center of Toulouse, France and Université Paul Sabatier Toulouse III, France
- Samir N. Ghadiali** The Ohio State University, Dorothy M. Davis Heart and Lung Research Institute, USA
- Lei Guo** Division of Biochemical Toxicology, National Center for Toxicological Research/US Food and Drug Administration, USA
- Keitaro Hagiwara** Division of Molecular and Cellular Medicine, National Cancer Center Research Institute, Japan and Department of Biological Sciences, Tokyo Institute of Technology, Japan
- Tariq M. Haqqi** Department of Anatomy and Neurobiology, Northeast Ohio Medical University (NEOMED), USA
- Valerie W. Hu** Department of Biochemistry and Molecular Medicine, The George Washington University School of Medicine and Health Sciences, USA
- Yan Huang** The Ohio State University, Dorothy M. Davis Heart and Lung Research Institute, USA
- Brock Humphries** Department of Physiology, Michigan State University, USA
- Johan Jakobsson** Department of Experimental Medical Science, Wallenberg Neuroscience Center and Lund Stem Cell Center, Lund University, Sweden
- Matthias Jung** Clinic for Psychiatry, Psychotherapy, and Psychosomatic medicine, Martin Luther University, Germany
- Daniel B. Kay** Department of Psychiatry and Human Behavior University of Mississippi Medical Center, School of Medicine, USA
- Nobuyoshi Kosaka** Division of Molecular and Cellular Medicine, National Cancer Center Research Institute, Japan
- Zhenhua Liu** School of Public Health and Health Sciences, University of Massachusetts, USA *and* Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, USA
- Yang Luan** School of Public Health, Shanghai Jiao Tong University, China
- Dharanija Madhavan** Molecular Epidemiology C080, German Cancer Research Center, Germany and Molecular Biology of Breast Cancer, University Women's Clinic, Germany
- Josephine Malmevik** Department of Experimental Medical Science, Wallenberg Neuroscience Center and Lund Stem Cell Center, Lund University, Sweden
- William B. Mattes** PharmPoint Consulting, USA
- Fanxue Meng** Division of Genetic and Molecular Toxicology, National Center for Toxicological Research, Food and Drug Administration, USA
- S. Patrick Nana-Sinkam** The Ohio State University, Dorothy M. Davis Heart and Lung Research Institute, USA
- Takahiro Ochiya** Division of Molecular and Cellular Medicine, National Cancer Center Research Institute, Japan
- Philip A. Philip** Department of Oncology, Karmanos Cancer Institute, Wayne State University School of Medicine, USA
- Barry A. Rosenzweig** Division of Drug Safety Research, Center for Drug Evaluation and Research, US Food and Drug Administration, USA
- Rodney L. Rouse** Division of Drug Safety Research, Center for Drug Evaluation and Research, US Food and Drug Administration, USA
- Saura C. Sahu** Division of Toxicology, Center for Food Safety and Applied Nutrition, Food and Drug Administration, USA
- William F. Salminen** PAREXEL, USA
- Tewarit Sarachana** Department of Biochemistry and Molecular Medicine, The George Washington University School of Medicine and Health Sciences, USA

- Fazlul H. Sarkar** Department of Pathology, Karmanos Cancer Institute, Wayne State University School of Medicine, USA *and* Department of Oncology, Karmanos Cancer Institute, Wayne State University School of Medicine, USA
- Insa S. Schroeder** Department of Biophysics, GSI Helmholtz Centre for Heavy Ion Research, Germany
- Maria S. Sepúlveda** Department of Forestry and Natural Resources, Purdue University, USA
- Leming Shi** School of Pharmacy, Fudan University, China
- Qiang Shi** Division of Systems Biology, National Center for Toxicological Research, Food and Drug Administration, USA
- Ajay P. Singh** Department of Oncologic Sciences, Mitchell Cancer Institute, University of South Alabama, USA *and* Department of Biochemistry and Molecular Biology, College of Medicine, University of South Alabama, USA
- Seema Singh** Department of Oncologic Sciences, Mitchell Cancer Institute, University of South Alabama, USA
- Geir Skogerbo** National Laboratory of Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, China
- Stephanie A. Tammen** Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, USA *and* Friedman School of Nutrition Science and Policy, Tufts University, USA
- Karol L. Thompson** Division of Drug Safety Research, Center for Drug Evaluation and Research, US Food and Drug Administration, USA
- Jérôme Torrisani** INSERM U1037, Cancer Research Center of Toulouse, France *and* Université Paul Sabatier Toulouse III, France
- Andrey Turchinovich** Molecular Epidemiology C080, German Cancer Research Center, Germany *and* Molecular Biology of Breast Cancer, University Women's Clinic, Germany
- Zhishan Wang** Department of Physiology, Michigan State University, USA
- Gregory J. Weber** School of Health Sciences, Purdue University, USA
- Zuquan Weng** Division of Systems Biology, National Center for Toxicological Research, Food and Drug Administration, USA
- Yaguang Xi** Mitchell Cancer Institute, University of South Alabama, USA
- Jiekun Xuan** Division of Biochemical Toxicology, National Center for Toxicological Research/US Food and Drug Administration, USA
- Dongsheng Yan** School of Ophthalmology and Optometry, Wenzhou Medical College, China
- Jian Yan** Division of Genetic and Molecular Toxicology, National Center for Toxicological Research, Food and Drug Administration, USA
- Chengfeng Yang** Department of Physiology, Michigan State University, USA *and* Center for Integrative Toxicology, Michigan State University, USA
- Xi Yang** Division of Systems Biology, National Center for Toxicological Research, Food and Drug Administration, USA
- Bin Yi** Mitchell Cancer Institute, University of South Alabama, USA

Preface

During the past decade it has become increasingly obvious that microRNAs regulate gene expressions and control many developmental and cellular processes in the eukaryotic organisms. Recent studies strongly suggest that they are likely to play important roles in a wide range of human diseases including cancer. As a result they have become an important component of the molecular mechanisms of the disease processes. Also, published reports strongly suggest that they are expected to play important roles in cellular response to xenobiotic stress affecting expression of microRNA as a mechanism of adaptation and, therefore, they have attracted great interest in toxicology. Thus microRNAs play an important role in toxicogenomics.

The importance of this field of research is evidenced by the increasing number of contributions published each year. It becomes increasingly clear that developments in this field are moving so rapidly that new means are needed to report the status of current ongoing research activities. The contributions presented in this monograph represent a collaborative effort by international experts working in this emerging field of science.

The main purpose of this book is to assemble up-to-date, state-of-the-art information on microRNAs presented by internationally recognized experts in a single edition. Therefore, I sincerely hope that this book will provide an authoritative source of current information on microRNA research and prove useful to the scientists interested in this scientific discipline throughout the world. It is my sincere hope that the information presented in this book will serve as a stimulus to all the investigators interested in this area of research. Also it should be of interest to a variety of other scientific disciplines including toxicology, medicine, and pharmacology, as well as food, drug, and other regulatory sciences.

Saura C. Sahu
Laurel, Maryland, USA

Acknowledgments

Editing this book has been a challenging journey. I express my sincere gratitude to all the individuals who have helped me, directly or indirectly, on this journey.

I am indebted to the internationally recognized experts, who shared my enthusiasm for this field of science and contributed generously to this book. They were selected from academia, industry, and government for their expertise in their own areas of research. Their work speaks for itself and I am grateful to them for their strong commitment, cooperation and excellent contributions in their own areas of expertise.

I thank the staff of the publisher, John Wiley & Sons, Ltd, especially Rebecca Ralf and Sarah Tilley for their excellent help, cooperation, support, and editorial assistance in the timely publication of this book.

Saura C. Sahu
Laurel, Maryland, USA

Contents

<i>List of Contributors</i>	<i>xvii</i>
<i>Preface</i>	<i>xxi</i>
<i>Acknowledgments</i>	<i>xxiii</i>
PART I microRNAs AND TOXICOLOGY	1
1 Introduction	3
<i>Saura C. Sahu</i>	
References	4
2 Environmental Toxicants and Perturbation of miRNA Signaling	5
<i>Kathryn A. Bailey and Rebecca C. Fry</i>	
2.1 Introduction	5
2.2 miRNAs: Description and Biological Significance	8
2.2.1 miRNA Biosynthesis and Processing	8
2.2.2 Interaction of miRNAs with mRNA Targets	9
2.3 Environmental Toxicant-Associated miRNA Perturbations	10
2.3.1 Toxicant Class 1: Carcinogenic Metals (Arsenic and Cadmium)	10
2.3.2 Toxicant Class 2: Air Toxicants (Formaldehyde, Diesel Exhaust Particles, Cigarette Smoke)	13
2.3.3 Toxicant Class 3: Polycyclic Aromatic Hydrocarbon (B(a)P)	17
2.3.4 Toxicant Class 4: Endocrine Disruptors (BPA, DDT, Fludioxonil, Fenhexamid, and Nonylphenol)	19
2.4 Conclusions and Future Directions	22
Acknowledgments	22
References	22
3 microRNAs in Drug-Induced Liver Toxicity	33
<i>Si Chen, Jiekun Xuan and Lei Guo</i>	
3.1 Introduction	33
3.2 miRNA Tissue Distribution and Abundance	34
3.2.1 miRNA in Solid Tissues	34
3.2.2 microRNA in Body Fluids	35
3.3 miRNA and Drug-Induced Liver Toxicity	35
3.3.1 Acetaminophen	36

3.3.2	Carbon Tetrachloride (CCl ₄)	37
3.3.3	2,3,7,8-Tetrachlorodibenzo- <i>p</i> -Dioxin (TCDD)	37
3.3.4	Benzo[<i>a</i>]pyrene	37
3.3.5	Tamoxifen	38
3.3.6	Others	38
3.4	Circulating miRNAs as Potential Biomarkers for Drug-Induced Liver Toxicity	38
3.4.1	Introduction of Circulating miRNAs	38
3.4.2	Blood miRNAs in Drug-Induced Liver Toxicity	39
3.4.3	Urine miRNAs in Drug-Induced Liver Toxicity	41
3.4.4	Technique Challenges	42
3.5	Mechanistic Studies and Perspectives	42
	Disclaimer	44
	References	44
4	Fishing for microRNAs in Toxicology	49
	<i>Jennifer L. Freeman, Gregory J. Weber and Maria S. Sepúlveda</i>	
4.1	microRNAs in Toxicology	49
4.2	Fish Models in Toxicology	49
4.2.1	Small Fish Models in Toxicology	50
4.2.2	Large Fish Models in Toxicology	51
4.3	Fish as Models for Studying miRNA Function	51
4.3.1	miRNA Studies in Zebrafish	51
4.3.2	miRNA Studies in Other Fish Models	52
4.4	Application of Fish Models in Toxicity Studies of miRNA Alterations	52
4.4.1	Zebrafish in Toxicity Studies of miRNA Alterations	52
4.4.2	Other Fish Models in Toxicity Studies of miRNA Alterations	68
4.5	Summary	68
	Acknowledgments	68
	References	68
PART II	microRNAs AND DISEASE STATES	77
5	microRNAs and Inflammation	79
	<i>Yan Huang, Samir N. Ghadiali and S. Patrick Nana-Sinkam</i>	
5.1	Introduction	79
5.2	miRNA Biogenesis and Functions	80
5.3	miRNAs in Hematopoietic Systems	80
5.4	miRNA and Inflammatory Diseases	81
5.5	Regulation of the Immune System	86
5.5.1	Acquired Immunity	86
5.5.2	Innate Immunity	86
5.6	Regulation of miRNA Expression	87
5.6.1	Regulation of miRNA by Cytokines and Bacterial Toxins	87
5.6.2	Regulation of miRNA by Mechanical Stimuli	88
5.7	Select miRNA Regulation of Inflammation	89

5.7.1	miR-146a: Negative Regulator of Immune Response	89
5.7.2	Role of miR-155 in Mediating Inflammatory Responses	91
5.7.3	miR-125a/b	92
5.7.4	miR-181a	93
5.8	Conclusion	94
	References	94
6	Regulatory Role of microRNAs in Mutagenesis	101
	<i>Fanxue Meng, Yang Luan, Jian Yan and Tao Chen</i>	
6.1	Introduction	101
6.2	miRNA Roles in Xenobiotic Metabolism	102
6.3	miRNA Roles in the Cell Cycle	105
6.4	miRNA Roles in DNA Repair	106
6.5	Apoptosis	107
6.6	miRNA Regulation and Mutation Formation	108
6.7	Conclusions	109
	Disclaimer	109
	References	110
7	microRNAs and Cancer	113
	<i>Dongsheng Yan and Geir Skogerbo</i>	
7.1	Introduction	113
7.2	miRNAs are Deregulated in Cancer	114
7.3	miRNAs Function as Oncogenes and Tumor Suppressor Genes	116
7.4	miRNAs in Cancer Metastasis	117
7.5	miRNAs in Cancer Stem Cells	119
7.6	Mutations in miRNA Loci	119
7.7	Mutations in miRNA Target Genes	120
7.8	Prospective: miRNA as Biomarkers and Therapeutics	121
	Acknowledgments	121
	References	121
8	miRNAs in Cancer Invasion and Metastasis	133
	<i>Brock Humphries and Chengfeng Yang</i>	
8.1	Introduction	133
8.2	miRNAs and Cancer Invasion and Metastasis	136
8.2.1	miRNAs Involved in Angiogenesis	136
8.2.2	miRNAs Involved in Cancer Cell Detachment, Migration, and Invasion	138
8.2.3	miRNAs Involved in Cancer Cell Intravasation	140
8.2.4	miRNAs Involved in Circulating Cancer Cell Survival	142
8.2.5	miRNAs Involved in Cancer Cell Extravasation	143
8.2.6	miRNAs Involved in Metastatic Colonization	144
8.3	miRNAs as Useful Cancer Prognostic Markers	146
8.4	Future Perspectives	147
	References	148

9	The Role of microRNAs in Tumor Progression and Therapy	153
	<i>Azfar S. Ali, Aamir Ahmad, Shadan Ali, Philip A. Philip and Fazlul H. Sarkar</i>	
9.1	Introduction	153
9.2	Tumor Progression	154
9.3	Key Signaling Pathways	154
9.3.1	Angiogenesis	154
9.3.2	The Ras Pathway	155
9.3.3	The Epidermal Growth Factor Receptor Pathway	155
9.3.4	The PI3K/Akt Pathway	156
9.4	The miRNAs as Regulators of Tumor Progression	156
9.4.1	Current Therapies to Control Tumor Progression	157
9.4.2	Tumor Promoter miRNAs	158
9.4.3	Tumor Suppressor miRNAs	159
9.5	Regulation of miRNAs by Novel Anticancer Compounds	160
9.6	Conclusions and Perspectives	161
	References	162
10	Current Understanding of microRNAs as Therapeutic Targets in Cancer	167
	<i>Marion Gayral, Jérôme Torrisani and Pierre Cordelier</i>	
10.1	Introduction on the Rationale of Using miRNAs as Therapeutics in Cancer	167
10.2	Current Approaches to Target miRNAs	167
10.3	Evidence of Successful miRNA Targeting in Experimental Cancer Models	168
10.4	Open Question: Targeting miRNA Processing in Cancer Cells	170
10.5	Concluding Remarks	170
	References	170
11	microRNAs, New Players in Cancer Chemoprevention	173
	<i>Bin Yi and Yaguang Xi</i>	
11.1	Introduction	173
11.2	miRNA and the Natural Products	175
11.2.1	Vitamin A	175
11.2.2	Vitamin B	176
11.2.3	Vitamin D	176
11.2.4	Vitamin E	176
11.2.5	Fatty Acids	176
11.2.6	Curcumin	177
11.2.7	Resveratrol	177
11.2.8	Ellagitannin	177
11.2.9	Genistein	177
11.2.10	Catechins	178
11.2.11	Indoles	178
11.3	miRNA and Pharmaceuticals	178
11.3.1	Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	178
11.3.2	Estrogen Receptor Antagonist	181

11.4 Perspectives	182
Acknowledgments	183
References	183
12 microRNA and Neurodegenerative Diseases	189
<i>Josephine Malmeyik, Malin Åkerblom and Johan Jakobsson</i>	
12.1 Introduction	189
12.2 miRNAs and Parkinson's Disease	191
12.3 miRNAs and Alzheimer's Disease	193
12.4 miRNAs and Huntington's Disease	195
12.5 Outlook	195
Acknowledgments	196
References	196
13 Sleep and microRNAs (miRNAs) in Neurodegenerative Diseases	201
<i>Daniel B. Kay and Christopher J. Davis</i>	
13.1 Sleep and microRNAs (miRNAs) in Neurodegenerative Diseases	201
13.2 miRNAs and Sleep	202
13.3 Aging	203
13.4 Alzheimer's Disease	204
13.5 Parkinson's Disease	205
13.6 Creutzfeldt–Jakob Disease	206
13.7 Huntington's Disease	207
13.8 Multiple Sclerosis	208
13.9 Fronto-Temporal Dementia	208
13.10 Summary	208
Acknowledgments	209
References	209
14 Role of microRNAs in Autism Spectrum Disorder	215
<i>Tewarit Sarachana and Valerie W. Hu</i>	
14.1 Introduction	215
14.2 Epidemiology of ASD	216
14.3 Etiology of ASD: Genetic Associations	216
14.4 ASD as Multigenic Systemic Disorders	217
14.5 Evidence for Epigenetic Contributions	218
14.6 The Role of microRNAs in Neurodevelopment	218
14.7 microRNAs in Neurodevelopmental and Psychiatric Disorders: An Overview	219
14.8 microRNA Expression Profiles in Autism Spectrum Disorder	220
14.8.1 Evidence for Dysregulated miRNAs in Brain and Blood	220
14.8.2 Identification of Novel Gene Targets of Differentially Expressed miRNAs in ASD	220
14.8.3 Brain-Related miRNAs are Differentially Expressed in LCLs from Individuals with ASD	222

14.8.4	Functional Associations of Confirmed Differentially Expressed miRNAs	225
14.9	Conclusions	226
	Acknowledgments	227
	References	227
15	The Emerging Function of Natural Products as Regulators of miRNAs in Human Diseases	237
	<i>Keitaro Hagiwara, Luc Gailhouste, Nobuyoshi Kosaka and Takahiro Ochiya</i>	
15.1	Introduction	237
15.2	History of Natural Products as Drugs	238
15.3	Functions of miRNAs in Human Diseases	238
15.4	Regulation of miRNAs using Natural Products	239
15.5	Resveratrol and miRNAs	239
15.6	EGCG and miRNAs	241
15.7	Curcumin and miRNAs	242
15.8	Isoflavone and miRNAs	242
15.9	Metformin miRNA	242
15.10	Traditional Herbs and miRNAs	243
15.11	Polyphenol and miRNAs	243
15.12	Rice and miRNA	243
15.13	Human Breast Milk and miRNAs	244
15.14	Conclusion	245
	Acknowledgments	245
	References	245
PART III	microRNAs AND STEM CELLS	249
16	Pluripotency and Early Cell Fate Decisions are Orchestrated by microRNAs	251
	<i>Matthias Jung and Insa S. Schroeder</i>	
16.1	Importance of microRNAs in ES and iPS Cells	251
16.2	Biogenesis and Function of microRNAs	252
16.3	microRNAs Mark ES Cell Identity	254
16.3.1	ES Cell Identity is Characterized by Distinct miRs	254
16.3.2	Mouse ES Cell-Specific miRs	254
16.3.3	Human ES Cell-Specific miRs	255
16.3.4	Self-Renewal of ES Cells is Regulated by Cell Cycle Regulating miRs	255
16.3.5	Differentiation Capacity of ES Cells is Maintained by miRs	256
16.3.6	Isoforms and 3' Variability in ES Cell-Specific miRs	256
16.4	microRNAs Guide Induced Pluripotency	257
16.4.1	Reprogramming Factors Regulate ES Cell-Associated miRs	257
16.4.2	Differentiation of ES and iPS Cells is Prevented by miRs	258
16.4.3	Reprogramming Requires ES Cell-Specific miRs	258
16.5	microRNAs Manipulate Cell Fate Decisions	259
16.5.1	Induction of Early Differentiation is Regulated by miRs	259
16.5.2	Major Signaling Pathways in ES Cells Regulated by miRs	260
16.5.3	Differentiation of ES Cells Can be Manipulated by miRs	260

16.5.4	Cell Fate Decisions are Influenced by miRs and RNA Binding Proteins (RBPs)	261
	References	262
17	microRNAs in Cancer Stem Cells: Micromanagers of Malignancy	269
	<i>Arun Bhardwaj, Sumit Arora, Seema Singh, and Ajay P. Singh</i>	
17.1	Introduction	269
17.2	Cancer Stem Cells	270
17.2.1	Origin of Cancer Stem Cells	270
17.2.2	Characteristics and Pathological Significance of Cancer Stem Cells	271
17.3	microRNAs: Biology and Mechanism	273
17.4	Role of microRNAs in the Regulation of Genes and Signaling Pathways Associated with Cancer Stem Cells	273
17.4.1	HMGA2	275
17.4.2	Bcl-2	275
17.4.3	Bmi-1	276
17.4.4	Wnt/ β -Catenin	276
17.4.5	Notch	277
17.4.6	Hedgehog	277
17.4.7	TGF- β	278
17.5	Translational Implications and Future Perspectives	279
	References	279
PART IV	microRNAs AND GENOMICS	285
18	microRNAs: Tiny Regulators of Great Potential for Gene Regulation	287
	<i>Nahid Akhtar and Tariq M. Haqqi</i>	
18.1	Introduction	287
18.2	microRNAs: Biogenesis and Expression Criteria	288
18.3	Mechanism of miRNA Mediated Regulation of Genes	288
18.4	Complexities of miRNA Regulation	290
18.5	microRNA and Epigenetics	291
18.6	Role of miRNAs in Biological Processes	295
18.7	microRNAs: Association with Disease Pathogenesis	296
18.8	microRNAs: Another Way to Unravel Disease Pathogenesis	297
18.9	microRNAs as Novel Therapeutic Targets	298
18.10	Concluding Remarks	299
	Competing Interests	300
	Conflict of Interest Statement	300
	Acknowledgments	300
	References	300
19	Exploration of microRNA Genomic Variation Associated with Common Human Diseases	309
	<i>Joel Fontanarosa and Yang Dai</i>	
19.1	Introduction	309