### Editor SAURA C. SAHU

# microRNAs in Toxicology and Medicine





## microRNAs in Toxicology and Medicine

## 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

1 2014

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

## Contents

Lis	st of Contributors xw					
Pre	eface			xxi		
Ac	knowle	edgments		xxiii		
PA	RT I	microR	NAs AND TOXICOLOGY	1		
1	Intro Saur	duction		3		
	Refe	rences		4		
2	Envi <i>Kath</i>	ronment ryn A. B	al Toxicants and Perturbation of miRNA Signaling	5		
	2.1	Introdu	iction	5		
	2.2	miRNA	As: 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	Enviro	nmental Toxicant-Associated miRNA Perturbations	10		
		2.3.1 2.3.2	Toxicant Class 1: Carcinogenic Metals (Arsenic and Cadmium) Toxicant Class 2: Air Toxicants (Formaldehyde, Diesel Exhaust Particles,	10		
			Cigarette Smoke)	13		
		2.3.3 2.3.4	Toxicant Class 3: Polycyclic Aromatic Hydrocarbon (B( <i>a</i> )P) Toxicant Class 4: Endocrine Disruptors (BPA, DDT, Fludioxonil, Fenhexamid,	17		
			and Nonylphenol)	19		
	2.4	Conclu	sions and Future Directions	22		
	Acknowledgments			22		
	Refe	rences		22		
3	micr	oRNAs i	n Drug-Induced Liver Toxicity	33		
		ien, Jiek	un Xuan and Lei Guo	22		
	3.1 3.2	miDN	Ruon A Tissue Distribution and Abundance	33 34		
	3.2	321	miRNA in Solid Tissues	34 34		
		32.1	microRNA in Body Fluids	34		
	33	miRN4	A and Drug-Induced Liver Toxicity	35		
	5.5	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[ $a$ ]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
	Discla	aimer	44
	Refer	ences	44
4	Fishi	ng for microRNAs in Toxicology	49
	Jenni	fer L. Freeman, Gregory J. Weber and Maria S. Sepúlveda	
	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
	Ackn	owledgments	68
	Refer	ences	68
PA	RT II	microRNAs AND DISEASE STATES	77
5	micro	RNAs and Inflammation	79
	Yan F	luang, Samir N. Ghadiali and S. Patrick Nana-Sinkam	-
	5.1	Introduction	79
	5.2	miRNA Biogenesis and Functions	80
	5.5	miRNAs in Hematopoietic Systems	80
	5.4	miRNA and Inflammatory Diseases	81
	5.5	S 5 1 Acquired Immune System	86
		5.5.1 Acquired immunity	86
	56	3.3.2 Initiate Immunity	80
	3.0	Kegulation of miRNA Expression	/ ۲ د م
		5.0.1 Regulation of miDNA by Machanical Stimuli	/ ð / ەە
	57	Solect miDNA Degulation of Inflammation	00 00
	5.1	Scient mixing Regulation of milanination	09

		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	Conclu	ision	94	
	Refe	rences		94	
6	Regi	ılatorv l	Role of microRNAs in Mutagenesis	101	
-	Fans	cue Men	g. Yang Luan, Jian Yan and Tao Chen		
	6.1	Introdu	iction	101	
	6.2	miRN	A Roles in Xenobiotic Metabolism	102	
	63	miRN	A Roles in the Cell Cycle	105	
	6.4	miRN	A Roles in DNA Renair	105	
	65	Apont	neis	107	
	6.6	miRN	A Regulation and Mutation Formation	107	
	67	Conclu	isions	100	
	Disc	laimer	10113	109	
	Refe	rences		110	
	Reit	renees		110	
7 microRNAs and Cancer					
	Dong	gsheng I	an and Geir Skogerbø		
	7.1	Introdu	action	113	
	7.2	miRN	As are Deregulated in Cancer	114	
	7.3	miRN	As Function as Oncogenes and Tumor Suppressor Genes	116	
	7.4	miRN	As in Cancer Metastasis	117	
	7.5	miRN	As in Cancer Stem Cells	119	
	7.6	Mutati	ons in miRNA Loci	119	
	7.7	Mutati	ons in miRNA Target Genes	120	
	7.8	Prospe	ctive: miRNA as Biomarkers and Therapeutics	121	
	Acknowledgments				
	Refe	rences		121	
8	miR	NAs in (	Cancer Invasion and Metastasis	133	
	Broc	k Hump	hries and Chengfeng Yang		
	8.1	Introdu	action	133	
	8.2	miRN	As 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	
	83	miRN	As as Useful Cancer Prognostic Markers	146	
	8.4 Future Perspectives				
	Refe	rences	r	148	
				1.0	

x Contents
------------

9	The l	Role of microRNAs in Tumor Progression and Therapy	153			
	Azfur S. Ali, Aamir Ahmad, Shadan Ali, Philip A. Philip and Fazlul H. Sarkar					
	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			
	Refer	ences	162			
10	Curr	ent Understanding of microRNAs as Therapeutic Targets in Cancer	167			
	Maru	on Gayral, Jerome Torrisani and Pierre Cordelier	167			
	10.1	Introduction on the Rationale of Using miRNAs as Therapeutics in Cancer	167			
	10.2	Current Approaches to Target miRNAs	16/			
	10.3	Evidence of Successful miRNA largeting in Experimental Cancer Models	108			
	10.4	Open Question: Targeting miRNA Processing in Cancer Cells	170			
	10.5 Defen	Concluding Remarks	170			
	Refer	ences	170			
11	micro	DRNAs, New Players in Cancer Chemoprevention	Cancer Chemoprevention 173			
	Bin Y	i and Yaguang Xi	1.50			
	11.1	Introduction	1/3			
	11.2	miRNA and the Natural Products	1/5			
		11.2.1 Vitamin A	1/3			
		11.2.2 Vitamin B	1/0			
		11.2.5 Vitamin D	1/0			
		11.2.4 Vitamin E	176			
		11.2.5 Fatty Acids	1/6			
		11.2.0 Curcumin	1//			
		11.2.7 Resveratroi	1//			
		11.2.0 Conjetajn	1//			
		11.2.9 Utilistem	1//			
		11.2.10 Catecillis	1/8			
	11.2	11.2.11 Indoles	1/8			
	11.5	IIIKINA and Pharmaceuticals	1/8			
		11.5.1 INOUSTERIOIDAI ANTI-INHAMMATORY DRUgs (INSAIDS)	1/8			
		11.3.2 Estrogen Receptor Antagonist	181			

	11.4	Perspec	ctives	182		
	Ackn	owledgn	nents	183		
	Refer	References				
12	microRNA and Neurodegenerative Diseases Josephine Malmevik, Malin Åkerblom and Johan Jakobsson					
	12.1	Introdu	uction	189		
	12.2	miRNA	As and Parkinson's Disease	191		
	12.3	miRNA	As and Alzheimer's Disease	193		
	12.4	miRNA	As and Huntington's Disease	195		
	12.5	Outloo	k	195		
	Ackn	owledgn	nents	196		
	Refer	ences		196		
13	Sleen	and mi	croRNAs (miRNAs) in Neurodegenerative Diseases	201		
	Daniel B. Kay and Christonher I. Davis					
	13.1	Sleep a	and microRNAs (miRNAs) in Neurodegenerative Diseases	201		
	13.2	miRNA	As and Sleep	202		
	13.3	Aging		203		
	13.4	Alzheii	mer's Disease	204		
	13.5	Parkins	son's Disease	205		
	13.6	Creutz	feldt–Jakob Disease	206		
	13.7	Huntin	gton's Disease	207		
	13.8	Multip	le Sclerosis	208		
	13.9	Fronto-	Temporal Dementia	208		
	13.10	Summa	arv	208		
	Ackn	Acknowledgments				
	References					
14	Role	of micro	oRNAs in Autism Spectrum Disorder	215		
	Tewa	rit Sarac	chana and Valerie W. Hu			
	14.1	Introdu	iction	215		
	14.2	Epiden	niology of ASD	216		
	14.3	Etiolog	y of ASD: Genetic Associations	216		
	14.4	ASD a	s Multigenic Systemic Disorders	217		
	14.5	Eviden	ce for Epigenetic Contributions	218		
	14.6	The Ro	ble of microRNAs in Neurodevelopment	218		
	14.7	microR	NAs in Neurodevelopmental and Psychiatric Disorders: An Overview	219		
	14.8	microR	NA 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		

	14.9 Ackne Refer	14.8.4 Functional Associations of Confirmed Differentially Expressed miRNAs Conclusions owledgments ences	225 226 227 227		
15	The l Disea	Emerging Function of Natural Products as Regulators of miRNAs in Human ses	237		
	Keita	ro Hagiwara, Luc Gailhouste, Nobuyoshi Kosaka and Takahiro Ochiya			
	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				
	Ackn	owledgments	245		
	Refer	ences	245		
PA	RT III	microRNAs AND STEM CELLS	249		
16	Pluri	potency and Early Cell Fate Decisions are Orchestrated by microRNAs	251		
	Matth	uas Jung and Insa S. Schroeder	251		
	10.1	Importance of microRNAs in ES and IPS Cells	251		
	16.2	Biogenesis and Function of microkinAs	252		
	10.3	16.2.1 ES Cell Identity is Characterized by Distinct miDs	254		
		16.3.1 ES Cell Identity is Characterized by Distinct miks	254		
		16.3.2 Human ES Cell-Specific miRs	254		
		16.3.4 Solf Donouvel of ES Colls is Dogulated by Coll Cycle Dogulating miDs	255		
		16.3.5 Differentiation Canacity of ES Calls is Mointained by miRs	255		
		16.3.6 Jooforms and 2' Variability in ES Cell Specific miPs	250		
	16.4	microDNAs Guide Induced Divinotency	250		
	10.4	16.4.1 Penrogramming Easters Degulate ES Cell Associated miDs	257		
		16.4.2 Differentiation of ES and iDS Calls is Dravanted by miDs	257		
		16.4.3 Reprogramming Requires ES Call Specific miDs	230 250		
	16.5	nicroPNAs Manipulate Cell Fate Decisions	250		
	10.5	16.5.1 Induction of Early Differentiation is Regulated by miRs	259		
		16.5.2 Major Signaling Pathways in FS Cells Regulated by miRs	259		
		16.5.2 Differentiation of FS Cells Can be Manipulated by miRs	200		
		10.5.5 Differentiation of LS cens can be manipulated by miles	200		

		16.5.4	Cell Fate Decisions are Influenced by miRs and RNA Binding	
			Proteins (RBPs)	261
	Refer	ences		262
17	micro	RNAs i	n Cancer Stem Cells: Micromanagers of Malignancy	269
	Arun	Bhardw	aj, Sumit Arora, Seema Singh, and Ajay P. Singh	
	17.1	Introdu	ction	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	microR	NAs: Biology and Mechanism	273
	17.4	Role of	microRNAs in the Regulation of Genes and Signaling Pathways Associated	
		with Ca	ancer 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
	175	1/.4./	IGF-p	278
	1/.J	Transla	tional implications and Future Perspectives	279
	Refer	ences		219
PA	RT IV	micro	RNAs AND GENOMICS	285
18	micro	RNAs:	Tiny Regulators of Great Potential for Gene Regulation	287
	Nahid	d Akhtar	and Tariq M. Haqqi	
	18.1	Introdu	ction	287
	18.2	microR	NAs: Biogenesis and Expression Criteria	288
	18.3	Mechar	nism of miRNA Mediated Regulation of Genes	288
	18.4	Comple	exities of miRNA Regulation	290
	18.5	microR	NA and Epigenetics	291
	18.6	Role of	miRNAs in Biological Processes	295
	18.7	microR	NAs: Association with Disease Pathogenesis	296
	18.8	microR	NAs: Another Way to Unravel Disease Pathogenesis	297
	18.9	microR	NAs as Novel Therapeutic Targets	298
	18.10	Conclu	ding Remarks	299
	Comp	beting Int	rerests	300
	Conff	ict of Int	erest Statement	300
	ACKN	owledgm	ents	300
	Kefer	ences		300
19	Explo	oration o	of microRNA Genomic Variation Associated with Common Human Diseases	309
	<b>Joel</b> 19,1	F <i>ontanai</i> Introdu	<i>rosa and Yang Dai</i>	309
				/

19.2 Methods	310
19.3 Results	311
19.4 Discussion	313
Acknowledgment	315
References	315

#### PART V microRNAs AND EPIGENOMICS

317

20	Cross Zhen	stalk between microRNAs and Epigenetics: From the Nutritional Perspective hua Liu, Stephanie A. Tammen, Simonetta Friso and Sang-Woon Choi	319			
	20.1	Introduction	319			
	20.2	Epigenetic Regulation of microRNA Expression	321			
		20.2.1 microRNA Biogenesis and Epigenetic Regulation	321			
		20.2.2 Epigenetically-Regulated microRNAs	323			
	20.3	Regulation of Epigenetic Machinery by microRNAs	326			
		20.3.1 Epigenetic Machinery and its Regulation by microRNA	326			
		20.3.2 epi-miRNAs	327			
	20.4	microRNA and Epigenetics: Regulation by Nutrition	329			
		20.4.1 Nutrition and Epigenetics	329			
		20.4.2 Nutrition and microRNA	331			
		20.4.3 Nutritional Modulation of the Epigenetics-microRNA Inter-Regulatory				
		Network	332			
	20.5	Summary	333			
	References		334			
PA	RT VI	microRNAs AND BIOMARKERS	341			
21	Body	Fluid microRNAs as Toxicological Biomarkers	343			
	Zhish	an Wang and Chengfeng Yang				
	21.1	microRNA History, Biogenesis and Functions	343			
	21.2	Differential Expression of miRNAs During Development and Diseases	344			
	21.3	Alterations of miRNA Expressions by Toxicant Exposures	345			
	21.4	Discovery of Body Fluid miRNAs	346			
	21.5	Body Fluid miRNAs as Toxicological Biomarkers	347			
		21.5.1 Plasma or Serum miRNAs as Toxicological Biomarkers	347			
		21.5.2 Urinary miRNAs as Toxicological Biomarkers	353			
		21.5.3 Other Body Fluid miRNAs as Toxicological Biomarkers	355			
	21.6	21.6 Challenges and the Future of Body Fluid miRNAs as Biomarkers				
	Refer	ences	358			
22	Cell-	Cell-free microRNAs as Biomarkers in Human Diseases				
	Xi Ya	ng, William B. Mattes, Oiang Shi, Zuquan Weng and William F. Salminen				
	22.1	Introduction	363			
	22.2	Secretion and Transportation of Cell-Free miRNAs in Body Fluids	365			
	22.3	Technical Challenges in the Analysis of Cell-Free miRNAs	367			

	22.4	Cell-Free miRNAs as Novel Potential Biomarkers for Cancers and Tissue In	juries 369				
		22.4.1 Acute Myeloid Leukemia and B-Cell Lymphoma	370				
		22.4.2 Bladder Cancer	370				
		22.4.3 Breast Cancer	370				
		22.4.4 Colorectal Cancer	373				
		22.4.5 Gastric Cancer	373				
		22.4.6 Hepatocellular Carcinoma	374				
		22.4.7 Lung Cancer	374				
		22.4.8 Melanoma	375				
		22.4.9 Oral and Squamous Cell Carcinoma	375				
		22.4.10 Ovarian Cancer	376				
		22.4.11 Pancreatic Cancer	376				
		22.4.12 Prostate Cancer	377				
		22.4.13 Cardiovascular Diseases	377				
		22.4.14 Drug-Induced Liver Injury	379				
		22.4.15 Kidney Injury	380				
	22.5	Conclusion and Perspectives	380				
	Discl	aimer	380				
	Refer	rences	381				
23	Plasma microRNAs as Biomarkers of Human Diseases						
	Katar	rina Cuk, Dharanija Madhavan, Andrey Turchinovich and Barbara Burwink	cel				
	23.1	Introduction	389				
	23.2	Cancer	390				
		23.2.1 Breast Cancer	390				
		23.2.2 Prostate Cancer	391				
		23.2.3 Lung Cancer	406				
		23.2.4 Colorectal Cancer	407				
	23.3	Cardiovascular Diseases and Disorders	408				
		23.3.1 Acute Myocardial Infarction	408				
		23.3.2 Other Cardiovascular Diseases	410				
	23.4	Neurological Diseases and Disorders	411				
	23.5	Diabetes Mellitus	412				
	23.6	Infectious Diseases	413				
	23.7	Standardization of Circulating miRNA Analysis	413				
		23.7.1 Sample Processing and Handling	413				
		23.7.2 Data Normalization	415				
	23.8	Discovery, Origins and Functions of Circulating miRNAs	416				
	Refer	rences	418				
24	Circu	ulating microRNAs as Biomarkers of Drug-Induced Pancreatitis	425				
	Rodn	ney L. Rouse, Barry A. Rosenzweig and Karol L. Thompson					
	24.1	Introduction	425				
	24.2	Pancreatic Injury and Serum Biomarkers	426				
	24.3	Amylase and Lipase: Sensitivity and Specificity as Biomarkers of Pancreatic	Injury 427				
	24.4	Pancreas Selective microRNAs as Circulating Biomarkers	428				

		24.4.1	Pancreas Selective Expression of microRNAs in Tissue	428
		24.4.2	Circulating microRNAs in Models of Pancreatitis	429
		24.4.3	Mouse Model of Acute Pancreatic Injury	430
		24.4.4	Time Course of Pancreas-Selective microRNAs in the Serum of Mice Treated with Caerulein	430
		24.4.5	Dose Response of Pancreas-Selective microRNAs in the Serum of Mice	132
		24.4.6	Serum Linese and Amulase in Mice Treated with Coerulein	432
		24.4.7	Receiver Operating Characteristic (ROC) Analysis of Serum microRNAs.	455
			Lipase, and Amylase	433
	24.5	Conclu	sions	433
	24.6	Future	Directions	434
	Ackn	owledgn	nents	434
	Discl	aimer		434
	Refer	ences		435
25	micro	RNA P	rofiling: Strategies and Challenges	437
	Jieku	n Xuan,	Leming Shi and Lei Guo	
	25.1	miRNA	A Biogenesis	437
	25.2	Challer	ages of miRNA Profiling	437
	25.3	miRNA	A Profiling Methodologies	438
		25.3.1	Northern Blotting	438
		25.3.2	Quantitative Reverse Transcription PCR	440
		25.3.3	Microarray	441
		25.3.4	Next Generation Sequencing	441
	25.4	Technic	cal Challenges of Circulating miRNA Profiling	446
	25.5	Quality	Assessment and Data Normalization	446
	25.6	Conclu	ding Remarks	448
	Discl	aimer		449
	Refer	ences		449
Au	thor I	ndex		457

Subject Index

459

#### **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
- Azfur 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 Gailhouste 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 Skogerbø 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
- Jérome 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

## Part I microRNAs and Toxicology

## 1 Introduction

#### Saura C. Sahu

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

The microRNA, found in eukaryotic cells, belongs to a family of small, single-stranded noncoding regulatory ribonucleic acid (RNA) molecules with an average of 22 nucleotides conserved by evolution (Christodoulou *et al.*, 2010). Discovered in 1993 (Lee *et al.*, 1993), they regulate gene expressions, and control many developmental and cellular processes in eukaryotic organisms. The physiological function of the majority of microRNAs is unknown. However, recent studies strongly suggest that they likely to play important roles in a wide range of human diseases, including cancer. As a result they have become an important component to study in the molecular mechanisms of disease processes. However, challenges remain in the understanding of their involvement in various disease processes. Therefore, microRNA research has become a hot new discipline in biology and medicine: microRNAs are promising important biomarkers of diseases.

The microRNAs have attracted great interest in toxicology. Published reports provide evidence that toxic exposures and cellular stress can affect microRNAs (Lema and Cunningham, 2010). Therefore, they are expected to play an important role in cellular responses to xenobiotic exposure. They bind to target messenger RNAs (mRNA) and suppress their translation into proteins. Exposure of cells to xenobiotics leads to altered microRNA expressions, as do other genes that play important roles in toxicology. Altered microRNA expression affects protein translation, which alters cellular physiology leading to adverse biological effects. Also cellular stress affects expression of microRNAs as a mechanism of adaptation (Lema and Cunningham, 2010). Thus microRNAs play an important role in toxicogenomics. Their potential as biomarkers of toxicity appears to be promising.

It is becoming increasingly clear from the rate of published literature that developments in microRNA research are moving rapidly. Therefore, new means are needed to report the current status of this new developing area of research. The purpose of this book, *microRNAs in Toxicology and Medicine*, is the timely dissemination of information on current interests in this emerging field of science. As the Editor, it gives me great pride to introduce this unique book which encompasses many aspects of microRNA research never

microRNAs in Toxicology and Medicine, First Edition. Edited by Saura C. Sahu.

© 2014 John Wiley & Sons, Ltd. Published 2014 by John Wiley & Sons, Ltd.

#### 4 microRNAs in Toxicology and Medicine

published together before. It is only recently that this exciting area of research has attracted the attention of toxicologists. This book deals with information on microRNAs at a level designated to take the reader to the borderline of research in this newly developing scientific discipline. The microRNA research work, actively pursued throughout the world, will lead to major discoveries of fundamental importance and of great clinical significance. This book brings together the ideas and work of investigators of international reputation who have pioneered this exciting area of research in toxicology and medicine. The book provides up-to-date information as well as new challenges in this exciting research area, and reflects the remarkable blossoming of this research in recent years. New ideas and new approaches are brought to bear on exploration of the role played by microRNAs in toxicology and medicine. Therefore, exciting times are ahead for future research. The up-to-date techniques, ideas, applications, and bibliographies are presented in this book in sufficient detail to enable newcomers to this scientific discipline to apply them in their studies and pursue them to any depth. I sincerely hope that the book will provide authoritative information as well as new ideas and challenges on microRNA research for stimulating the creativity of graduate students and investigators who are actively engaged in this rapidly developing field. The extensive collection of current information presented here will make it a valuable reference source for all scientists working in the microRNA area.

#### References

Christodoulou F, Raible F, Tomer R, Simakov O, Trachana K, Klaus S, *et al.* 2010. Ancient animal microRNAs and the evolution of tissue identity. *Nature* **463**, 1084–1088.

- Lee RC, Feinbaum RL, Ambros V. 1993. The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* **75**(5):843–854.
- Lema C and Cunningham MJ. 2010. MicroRNAs and their implications in toxicological research. *Toxicol Lett.* **198**(2):100–105.