

# **Experientia Supplementum**

Volume 106

More information about this series at <http://www.springer.com/series/4822>

Peter Igaz

Editor

# Circulating microRNAs in Disease Diagnostics and their Potential Biological Relevance

 Springer

*Editor*  
Peter Igaz  
2nd Department of Medicine  
Semmelweis University  
Budapest, Hungary

ISSN 1023-294X  
Experientia Supplementum  
ISBN 978-3-0348-0953-5      ISBN 978-3-0348-0955-9 (eBook)  
DOI 10.1007/978-3-0348-0955-9

Library of Congress Control Number: 2015957587

Springer Basel Heidelberg New York Dordrecht London

© Springer International Publishing Switzerland 2015

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made.

Printed on acid-free paper

Springer Basel AG is part of Springer Science+Business Media ([www.springer.com](http://www.springer.com))

# Preface

The discovery of RNA interference and their endogenous mediators, microRNAs, has revolutionized molecular biology in the past two decades. Beside their obvious biological relevance, microRNAs can also be exploited as biomarkers and even as potential therapeutic targets. One of the most recent developments of microRNA research was the recognition of secreted microRNA that can be detected in body fluids, most importantly in the blood. Circulating blood-borne microRNAs might represent a novel, minimally invasive diagnostic tool that might be exploited in many diseases. However, there are major technical difficulties to be conquered, and standardization of analytical methods is needed for their successful clinical introduction. The biological relevance of circulating microRNAs is intriguing as this might represent a form of paracrine or even endocrine (hormonal) communication that would convey epigenetic information to cells or tissues distant from the microRNA-secreting source.

This book focuses on this fascinating and rapidly developing research field. Both researchers and students of biology or medicine could find this topic interesting.

This book comprises 3 parts including 14 chapters altogether. The first part composed of three chapters presents the molecular features and biological relevance of both tissue and circulating microRNAs, and the technical difficulties of circulating microRNA analysis are also discussed. The second, largest part attempts to present an overview of the potential diagnostic relevance of circulating microRNAs as minimally invasive biomarkers in various diseases such as solid and hematologic tumors, cardiovascular diseases, systemic autoimmune diseases, inflammatory bowel disease, and diabetes. The third part deals with potential biological effects of circulating microRNAs including experimental findings and also hypotheses on their potential relevance. Due to the vast number of recent research papers published on circulating microRNAs, it is impossible to include all findings in a book. We have therefore tried to select the most relevant or most interesting aspects of circulating microRNA research focusing on potential biomedical relevance.

I hope that the reader will find this topic exciting and interesting, and the pieces of information included in the book would be helpful to anyone trying to be taken up with this fascinating field of biomedicine.

Budapest, Hungary

Peter Igaz

# List of the Most Commonly Used Abbreviations

AD	Alzheimer's disease
AGO	Argonate protein
ALL	Acute lymphocytic leukemia
ALS	Amyotrophic lateral sclerosis
AML	Acute myeloid leukemia
ATL	Adult T cell leukemia
AUC	Area under the curve
bp	Base pair
BC	Breast cancer
BE	Barrett's esophagus
BM-MSC	Bone marrow mesenchymal stem cell
BPH	Benign prostatic hyperplasia
CC	Cervical cancer
CD	Crohn's disease
CEA	Carcinoembryonic antigen
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CP	Chronic pancreatitis
CR	Complete remission
CRC	Colorectal cancer
CSCC	Cervical squamous cell carcinoma
CSF	Cerebrospinal fluid
DFS	Disease-free survival
DLBCL	Diffuse large B cell lymphoma
DNA	Deoxyribonucleic acid
dpc	Days post-coitum
dsRNA	Double-stranded RNA
e	Embryonic day
EAC	Esophageal adenocarcinoma
EC	Endometrial cancer

EDTA	Ethylenediaminetetraacetic acid
EMT	Epithelial to mesenchymal transition
EOC	Epithelial ovarian cancer
ESCC	Esophageal squamous cell carcinoma
EV	Extracellular vesicle
ex-miRNA	Extracellular miRNA
FL	Follicular lymphoma
GBM	Glioblastoma multiforme
GC	Gastric cancer
G-C	Guanine-cytosine
GWAS	Genome-wide association study
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HDL	High-density lipoprotein
HCV	Hepatitis C virus
HD	Huntington's disease
HL	Hodgkin's lymphoma
IBD	Inflammatory bowel disease
IFN	Interferon
IL	Interleukin
LADA	Latent autoimmune diabetes of adults
LDL	Low-density lipoprotein
LNA	Locked nucleic acid
miR	microRNA
miRISC	miRNA-induced silencing complex
miRNA	microRNA
MM	Multiple myeloma
MaM	Malignant melanoma
MCI	Mild cognitive impairment
MCTD	Mixed connective tissue disease
MET	Mesenchymal to epithelial transition
MoDC	Monocyte-derived dendritic cells
MDS	Myelodysplastic syndrome
MODY	Maturity onset diabetes of the young
MSC	Mesenchymal stem cell
mTOR	Mammalian target of rapamycin
MVB	Multivesicular body
NGS	Next-generation sequencing
NHL	Non-Hodgkin's lymphoma
NK	Natural killer cell
NSCLC	Non-small cell lung cancer
nt	Nucleotide
OS	Overall survival
OSCC	Oral squamous cell carcinoma



PaC	Pancreatic cancer
PBMC	Peripheral blood mononuclear cell
PC	Prostate cancer
PCR	Polymerase chain reaction
PD	Parkinson's disease
PDAC	Pancreatic ductal adenocarcinoma
PSA	Prostate-specific antigen
qRT-PCR	Quantitative reverse transcription polymerase chain reaction
RA	Rheumatoid arthritis
RBC	Red blood cell
RCC	Renal cell carcinoma
RISC	RNA-induced silencing complex
RNA	Ribonucleic acid
RNAi	RNA interference
ROC	Receiver operator characteristics
SCA	Spinocerebellar ataxia
siRNA	Small interfering RNA
SCLC	Small-cell lung cancer
SEC	Size-exclusion chromatography
SLE	Systemic lupus erythematosus
snoRNA	Small nucleolar RNA
SPN	Solitary pulmonary nodule
SSc	Systemic sclerosis
ssRNA	Single-stranded RNA
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
TF	Transcription factor
TGF	Transforming growth factor
Th	T helper cell
TNF	Tumor necrosis factor
tRNA	Transfer RNA
Treg	Regulatory T cell
UC	Ultracentrifugation
UF	Ultrafiltration
UrC	Urothelial carcinoma
UIC	Ulcerative colitis
UTR	Untranslated region
WHO	World Health Organization



# Contents

## **Part I General Features and Technical Issues Related to Circulating microRNA**

- 1 Introduction to microRNAs: Biogenesis, Action, Relevance of Tissue microRNAs in Disease Pathogenesis, Diagnosis and Therapy—The Concept of Circulating microRNAs . . . . .** 3  
Zoltán Nagy and Peter Igaz
- 2 Extracellular microRNAs in Membrane Vesicles and Non-vesicular Carriers . . . . .** 31  
Anna M.L. Coenen-Stass, Imre Mäger, and Mathew J.A. Wood
- 3 Technical Aspects Related to the Analysis of Circulating microRNAs . . . . .** 55  
Henriett Butz and Attila Patócs

## **Part II Diagnostic Relevance of Circulating microRNAs**

- 4 Circulating Blood-Borne microRNAs as Biomarkers in Solid Tumors . . . . .** 75  
Petra Vychytilova-Faltejskova and Ondrej Slaby
- 5 Circulating microRNA as Biomarkers in Hematological Malignancies . . . . .** 123  
Monika Stankova, Veronika Kubackova, Lenka Sedlarikova, and Sabina Sevcikova
- 6 Circulating microRNAs as Biomarkers in Cardiovascular Diseases . . . . .** 139  
Salvatore De Rosa and Ciro Indolfi
- 7 Circulating microRNAs in Neurodegenerative Diseases . . . . .** 151  
Margherita Grasso, Paola Piscopo, Alessio Crestini, Annamaria Confaloni, and Michela A. Denti

**8 Circulating Extracellular microRNA in Systemic Autoimmunity . . . 171**  
 Niels H.H. Heegaard, Anting Liu Carlsen, Kerstin Skovgaard,  
 and Peter M.H. Heegaard

**9 Circulating microRNAs in Inflammatory Bowel Diseases . . . . . 197**  
 Maria Gazouli

**10 Circulating microRNAs in Diabetes Progression: Discovery,  
 Validation, and Research Translation . . . . . 215**  
 Ryan J. Farr, Mugdha V. Joglekar, and Anandwardhan A. Hardikar

**11 Diagnostic Relevance of microRNAs in Other Body Fluids  
 Including Urine, Feces, and Saliva . . . . . 245**  
 Ivan Igaz and Peter Igaz

**Part III Potential Biological Relevance of Circulating microRNA**

**12 Circulating microRNAs as Hormones: Intercellular and  
 Inter-organ Conveyors of Epigenetic Information? . . . . . 255**  
 Yusuke Yoshioka, Takeshi Katsuda, and Takahiro Ochiya

**13 Are Circulating microRNAs Involved in Tumor Surveillance? . . . . 269**  
 Ivan Igaz and Peter Igaz

**14 Hypothetic Interindividual and Interspecies Relevance  
 of microRNAs Released in Body Fluids . . . . . 281**  
 Ivan Igaz and Peter Igaz