

ADVANCES IN TRANSLATIONAL MEDICINE

TRANSLATING MicroRNAs TO THE CLINIC

EDITED BY:

JEFFREY LAURENCE

GUEST EDITOR:

MARY VAN BEUSEKOM



TRANSLATING MicroRNAs TO THE CLINIC

Edited by

JEFFREY LAURENCE

Division of Hematology-Medical Oncology, Weill Cornell
Medical College and New York Presbyterian Hospital,
New York, NY, United States

Guest Editor

MARY VAN BEUSEKOM

Health Partners Institute for Education and Research and
Synapse Writing and Editing, Exelsior, MN, United States



Amsterdam • Boston • Heidelberg • London
New York • Oxford • Paris • San Diego
San Francisco • Singapore • Sydney • Tokyo

Academic Press is an imprint of Elsevier



Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1800, San Diego, CA 92101-4495, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

Copyright © 2017 Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers may always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data

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

ISBN: 978-0-12-800553-8

For information on all Academic Press publications
visit our website at <https://www.elsevier.com>



**Working together
to grow libraries in
developing countries**

www.elsevier.com • www.bookaid.org

Publisher: Mica Haley

Acquisitions Editor: Mica Haley

Editorial Project Manager: Sam W. Young

Production Project Manager: Chris Wortley

Designer: Mark Rogers

Typeset by TNQ Books and Journals

TRANSLATING MicroRNAs TO THE CLINIC

LIST OF CONTRIBUTORS

S. Akkina

University of Illinois at Chicago, Chicago, IL, United States

S. Ansar Ahmed

Virginia Tech, Blacksburg, VA, United States

B.N. Becker

University of Chicago, Chicago, IL, United States

C. Bime

The University of Arizona, Tucson, AZ, United States

D.M. Brown

Ohio State University Medical Center, Columbus, OH, United States

E.E. Creemers

University of Amsterdam, Amsterdam, The Netherlands

C. Croce

Ohio State University Medical Center, Columbus, OH, United States

R. Dai

Virginia Tech, Blacksburg, VA, United States

A.A. Desai

The University of Arizona, Tucson, AZ, United States

A. Esquela-Kerscher

Eastern Virginia Medical School, Norfolk, VA, United States

J.G.N. Garcia

The University of Arizona, Tucson, AZ, United States

C.I. Gurguis

The University of Arizona, Tucson, AZ, United States

T. Hasegawa

Eastern Virginia Medical School, Norfolk, VA, United States

L. Hecker

The University of Arizona, Tucson, AZ, United States

C.D. Hoang

National Institutes of Health, Bethesda, MD, United States

N. Kaminski

Yale University, New Haven, CT, United States

T.A. Kerr

University of Texas Southwestern Medical Center, Dallas, TX, United States

R.A. Kratzke

University of Minnesota, Minneapolis, MN, United States

H. Lewis

Eastern Virginia Medical School, Norfolk, VA, United States

B.B. Madison

Washington University, Saint Louis, MO, United States

M.A. Montano

Harvard Medical School, Boston, MA, United States

S.P. Nana-Sinkam

Ohio State University Medical Center, Columbus, OH, United States

K. Ono

Kyoto University, Kyoto, Japan

K.V. Pandit

University of Pittsburgh, Pittsburgh, PA, United States

Y.M. Pinto

University of Amsterdam, Amsterdam, The Netherlands

G. Song

University of Minnesota, Minneapolis, MN, United States

A.J. Tijssen

Technion-Israel Institute of Technology, Haifa, Israel; University of Amsterdam, Amsterdam, The Netherlands

T.H. Tran

Harvard Medical School, Boston, MA, United States

H. Vollbrecht

University of Minnesota, Minneapolis, MN, United States

T. Wang

The University of Arizona, Tucson, AZ, United States

CONTENTS

List of Contributors

xi

1. MicroRNAs: Mirrors of Health and Disease 1

T.H. Tran and M.A. Montano

Key Concepts	1
1. Introduction	1
2. Knocking Out MicroRNA: Small RNAs With Big Effects	2
3. Genetic Organization, Variation in MicroRNAs, and Tissue-Specific Expression of MicroRNAs	3
4. MicroRNA Regulatory Complexity: Feedback Loops and Environmental Sensing	5
5. Organ Diseases and MicroRNAs	6
6. Cancer and MicroRNAs	7
7. Aging and MicroRNAs	8
8. MicroRNA Therapeutics and Target Prediction: Successes and Challenges	10
9. Circulating MicroRNA as Biomarkers	11
10. Concluding Remarks	13
References	13

2. Clinical and Therapeutic Applications of MicroRNA in Cancer 17

D.M. Brown, C. Croce and S.P. Nana-Sinkam

Key Concepts	17
1. Introduction	18
2. MicroRNA Processing	19
3. Circulating MicroRNA as Biomarkers	21
4. MicroRNA Isolation and Amplification Methodologies	21
5. Packaging and Delivery Mechanisms	22
6. MicroRNA Dysregulation in Cancer	22
7. Role of MicroRNA in Cancer Diagnosis, Prognostication, and Treatment	24
8. MicroRNA in Clinical Trials	31
9. Future Directions for MicroRNA Research	32
List of Acronyms and Abbreviations	33
References	33

3. MicroRNAs in Kidney Function and Disease	39
S. Akkina and B.N. Becker	
Key Concepts	39
1. Introduction	39
2. Kidney Physiology	40
3. Blood Pressure Regulation	41
4. Kidney Disease	42
5. Kidney Transplantation	47
6. Biomarkers	48
7. Clinical Implications	48
8. Summary	49
References	49
 4. MicroRNAs in the Pathogenesis, Diagnosis, and Treatment of Liver Disease	 55
B.B. Madison and T.A. Kerr	
Key Concepts	55
1. Introduction	56
2. MicroRNA Biogenesis	56
3. MicroRNA Analysis and Bioinformatics	57
4. Hepatic MicroRNAs as Metabolic Modulators and Their Importance in NAFLD	58
5. MicroRNAs and Hepatitis C Virus	66
6. MicroRNAs and Hepatitis B Virus	71
7. MicroRNAs and Hepatocellular Carcinoma	73
8. MicroRNAs as Biomarkers of Liver Injury	82
List of Acronyms and Abbreviations	84
Acknowledgments	85
References	85
 5. Clinical Application of MicroRNAs in Liver Diseases	 93
G. Song and H. Vollbrecht	
Key Concepts	93
1. Introduction	93
2. Role of MicroRNAs in Liver Pathology and Pathophysiology	94
3. MicroRNAs as Diagnostic and Prognostic Markers in Liver Disease	110
4. MicroRNA-Based Therapeutics for Liver Disease	114
List of Acronyms and Abbreviations	124
References	124

6. MicroRNAs in Inflammatory Lung Disease	135
C. Bime, C.I. Gurguis, L. Hecker, A.A. Desai, T. Wang and J.G.N. Garcia	
Key Concepts	135
1. Introduction	135
2. MicroRNAs in Asthma	136
3. Acute Respiratory Distress Syndrome	143
4. Chronic Obstructive Pulmonary Disease	147
5. Cystic Fibrosis	149
6. Sarcoidosis	169
7. Summary and Conclusion	171
Acknowledgment	171
References	171
7. MicroRNAs in Idiopathic Pulmonary Fibrosis: Partners in Health and Disease	179
K.V. Pandit and N. Kaminski	
Key Concepts	179
1. MicroRNAs	179
2. Idiopathic Pulmonary Fibrosis	180
3. MicroRNA Studies in Idiopathic Pulmonary Fibrosis	182
4. Laboratory Techniques	188
5. Limitations	191
6. MicroRNA Therapeutics	192
7. MicroRNA–Long Noncoding RNA Interaction	193
8. Conclusions and Future Directions	195
List of Acronyms and Abbreviations	195
References	196
8. MicroRNA as Biomarkers of Malignant Mesothelioma	203
C.D. Hoang and R.A. Kratzke	
Key Concepts	203
1. Clinical Problem: Mesothelioma	203
2. Molecular Pathology	204
3. MicroRNAs as Oncogenes and Tumor Suppressors	204
4. Translational Applications of MicroRNA in Mesothelioma	205
5. Conclusions and Future Directions	217
List of Acronyms and Abbreviations	217
Acknowledgments	218
References	218

9. MicroRNA, an Important Epigenetic Regulator of Immunity and Autoimmunity	223
R. Dai and S. Ansar Ahmed	
Key Concepts	223
1. Introduction	224
2. MicroRNA Biogenesis	224
3. MicroRNA in Normal Immune System Development and Function	225
4. MicroRNA in the Development and Prevention of Autoimmunity	234
5. MicroRNA in Systemic Lupus Erythematosus	235
6. Cell-Free Circulating MicroRNAs as Biomarkers in Systemic Lupus Erythematosus	243
7. Regulation of MicroRNA Expression in Systemic Lupus Erythematosus	244
8. Conclusion and Perspective	247
Glossary	248
List of Acronyms and Abbreviations	250
Acknowledgments	251
References	251
10. MicroRNA-Linked Heart Disease and Therapeutic Potential	259
K. Ono	
Key Concepts	259
1. Introduction	259
2. Cardiac Hypertrophy	261
3. Cardiac Fibrosis	263
4. Myocardial Ischemia and Cell Death	266
5. Vascular Diseases	267
6. Heart Failure	269
7. Circulating MicroRNAs	271
8. Therapeutic Strategies to Modulate the Functions of MicroRNAs	273
9. Summary and Conclusions	275
List of Acronyms and Abbreviations	275
References	276
11. The Clinical Potential of Heart Failure–Related miRNAs	283
A.J. Tijssen, Y.M. Pinto and E.E. Creemers	
Key Concepts	283
1. Introduction	283
2. MicroRNAs as Therapeutics	288
3. MicroRNAs in Cardiac Remodeling	296

4. Circulating MicroRNAs as Biomarker	309
5. Conclusions and Future Directions	317
Glossary	321
List of Acronyms and Abbreviations	322
References	323
12. The Role of Noncoding RNAs in Prostate Cancer	329
T. Hasegawa, H. Lewis and A. Esquela-Kerscher	
Key Concepts	329
1. Introduction	329
2. Prostate Cancer and MicroRNAs	331
3. MicroRNAs as Prostate Cancer Biomarkers	349
4. Conclusions and Future Directions for MicroRNAs in the Clinic	358
List of Acronyms and Abbreviations	361
Conflict of Interest	363
References	363
<i>Index</i>	371

CHAPTER 1

MicroRNAs: Mirrors of Health and Disease

T.H. Tran, M.A. Montano

Key Concepts

This chapter gives examples of tissue and cell type-specific knockdown of components of the microRNA machinery and their deleterious effects. It discusses the genetic organization of microRNAs and how that architecture is designed to regulate multiple targets within regulatory pathways, and their role in adaptive regulation in response to changes in the microenvironment. It looks at the role of MicroRNA networks in specific tissue and organ diseases, including lung, heart, and skeletal muscle, as well as in modulating cancers in those tissues. Newer research is introduced linking shifts in microRNA expression with biological aging and diseases associated with aging. The potential role for MicroRNAs as therapeutic tools to modulate target RNA sequences implicated in disease states is explored. Finally, the utility of MicroRNAs as circulating biomarkers for disease risk and severity, as well as in the therapeutic response to candidate drug interventions is discussed.

1. INTRODUCTION

Since their discovery as a novel class of small noncoding RNAs capable of regulating protein translation and/or messenger RNA (mRNA) stability, microRNAs (miRNAs) have been implicated as key regulators in the homeostasis of multiple biological systems that include organs such as heart, lung, and skeletal muscle, as well as modulation of the pathobiology processes such as cancer and aging. Experimental loss of key regulators of miRNA biogenesis has revealed the crucial role for the control of posttranscriptional gene expression. The genetic organization, the variability of their loci, and the tissue specificity of their expression further illustrate an adaptive capacity of the miRNA machinery to modify and fine-tune the transcriptome and translated protein targets in response to physiologic environmental cues, as well as their vulnerability to becoming co-opted in diseases such as cancer, fibrosis, sepsis, aging, and autoimmune disease. Current efforts to leverage knowledge of the miRNA regulatory system to

diagnose, track, and attenuate disease progression, represent a major new research opportunity, and challenge in this rapidly growing area of translational medicine.

2. KNOCKING OUT MICRORNA: SMALL RNAs WITH BIG EFFECTS

As our understanding of miRNA biogenesis and downstream regulatory activities unfold, so too does our appreciation for the extent and scope of influence these small RNAs have on multiple biological processes across human health and disease. The endonuclease Dicer is an obligatory first step in the RNA interference pathway and formation of the RNA-inducing silencing complex (RISC). Without RISC formation, argonaute-mediated degradation of target mRNA is lost [1,2]. Therefore, Dicer knockdown, in effect, disables the processing of miRNA from precursors of miRNA, ie, premiRNA. This can have deleterious effects. In murine models of cancer, global gene-disruption of Dicer can enhance tumor susceptibility [3]. Tissue- and cell type-specific knockdown of Dicer can also lead to deleterious effects. For example, cardiomyocyte-specific ablation of Dicer can result in cardiomyopathy [4]. Kidney podocyte-specific knockdown of Dicer can lead to systemic proteinuria and glomeruli abnormalities in mice [5]. Moreover, conditional knockdown of Dicer in the kidney impairs its normal development, further emphasizing the normal and dysregulatory potential in miRNA processing. Dicer deletion in skeletal muscle can result in increased myocyte apoptosis, skeletal muscle hypoplasia, and eventually perinatal death [6]. Hepatocytes obtained from Dicer-null mice exhibit abnormal lipid buildup and eventual renal steatosis [7]. Liver-specific Dicer deletion at 3 weeks leads to progressive hepatic steatosis [8]. This phenotype, however, has not been universally observed. While unlikely to change the overall conclusion that miRNAs clearly play a significant role in regulating multiple pathways, the subtleties or disparities in observation of distinct phenotypes in these conditional knockdowns may hinge upon the buildup of precursor miRNAs that activate other RNA surveillance pathways, such as RNA editing, which would then introduce an additional variable [9,10]. Comparative transcriptome profiling with high throughput RNA sequencing will likely provide more insight into the global regulatory profile of these knockdowns.

3. GENETIC ORGANIZATION, VARIATION IN MICRORNAs, AND TISSUE-SPECIFIC EXPRESSION OF MICRORNAs

MicroRNAs (miRNAs) undergo multiple processing events to reach their functional 21–23 ribonucleotide RNA sequence. Canonical miRNAs are generated from protein-coding transcriptional units; whereas, other miRNAs (ie, noncanonical miRNAs) are generated from nonprotein-coding transcriptional units. In both cases, the miRNAs can be located either within intronic or exonic regions. A noteworthy mechanistic distinction in canonical versus noncanonical miRNAs is that canonical intronic miRNAs are Drosha dependent and are thus processed cotranscriptionally with protein-coding transcripts in the nucleus. The premiRNA then enters the miRNA pathway, whereas the rest of the transcript undergoes premRNA splicing to produce mature mRNA which will then direct protein synthesis. Noncanonical intronic small RNAs (also called mirtrons) can derive from small introns that resemble premiRNAs, and bypass the Drosha-processing step [11]. miRNAs tend to be organized in a related cluster and also tend to target multiple mRNA transcripts within common cellular response pathways (eg, proliferation, apoptosis). This organizational thematic provides miR clusters with a capacity for coordinate regulation of multiple steps within a pathway, providing an opportunity for complex and adaptive regulatory control of entire pathways. An interesting class of miRNAs is myomiRs—so-called because they are coded within myosin heavy chain (MYH) genes. myomiRs are transcribed in the same precursor mRNA as the parental MYH gene [4]. Of special note is the myomiR-499, which despite the absence of a parent mRNA, is one of the most highly expressed miRNAs in heart tissue. In an apparently novel evolutionary phenomenon, alternative splicing in the heart uncouples production of mature miR-499 from expression of parent MYH7b mRNA, meaning that the mRNA has perhaps evolved into a non-functional host mRNA for its intronic miR (ie, miR-499).

Comparative studies evaluating the organizational structure of the mammalian genome have identified a wealth of chromosomal insertion-deletions, copy number variants, and single nucleotide polymorphisms (SNPs) that, depending on the environmental context, contribute to the genetic variation that can underlay phenotypic diversity. This diversity is evident in nearly every aspect of human health and disease that has been investigated. Perhaps not surprisingly, there is now a growing recognition that variation in miRNAs and their target genes also contribute to this phenotypic variability. Several

solid and hematologic malignancies can be linked to miRNAs located at amplified, deleted, or translocated chromosomal regions in the mammalian genome [12]. Variation in gene expression and regulation is likely influenced by genetic variants in *cis*- and *trans*-acting SNPs (also known as expression quantitative trait loci) [13]. An interesting observation of miRNA binding is their ability to recognize binding site polymorphism (miRSNPs) in transcribed functional genes. For example, miR-24 appears to be deregulated in human colorectal tumor through a target site polymorphism in the dihydrofolate reductase gene. In another example, a polymorphism within the myostatin gene creates a target site for miR-1 and miR-206, which are highly expressed in skeletal muscle. The binding of these miRs to the polymorphism in myostatin causes translational inhibition of myostatin transcripts and can phenocopy the observed muscle hypertrophy that is observed with genetic knockouts of the myostatin gene [14]. Given the significant differences in gene expression and genetic variation across human populations, analysis of the role of miRNAs in contributing to population differences in gene expression is likely to provide substantial insights in population based health disparities and physical functionalities [13]. Indeed, comparative genomic studies indicate that the target mRNA sequences for miRNAs: untranslated regions (UTRs) on mRNAs often display sequence diversity. This may suggest adaptive evolution of coexpressed miRNAs and cognate mRNAs with these UTR variants. Depending on whether the dampening of protein output is beneficial, inconsequential, or harmful, the UTR sites may be selectively conserved, neutral, or avoided during miRNA:mRNA coevolution [1].

Studies evaluating the tissue-specific expression of miRNAs illustrate a “cross-regulation” feature of miRNAs that contributes to cell fate specification by repressing alternate cell fates to facilitate commitment to one cell fate and to maintain stability of a differentiated phenotype [15]. For example the myomiRs miR-1, miR-133, miR-206, miR-208, miR-486, and miR-499 are enriched in skeletal muscle and play crucial roles in the development, growth, and maintenance of skeletal muscle [16]. Notably, miR-133 prevents osteogenic cell lineage differentiation by repressing Runx2, a factor essential for bone formation [15]. MiR-7, miR-24, miR-128, miR-134, miR-219, and others are highly expressed in the mammalian brain and regulate neurite outgrowth, neuronal differentiation, and dendritic spine size [17]. Regionally enriched miRNAs in specific tissues can exert specialized function. For example, miR-7 and miR-24 are highly expressed in the hypothalamus and fine-tuning expression of Fos and oxytocin which play vital roles in the control of water, lactation, and parturition [18].

4. MICRORNA REGULATORY COMPLEXITY: FEEDBACK LOOPS AND ENVIRONMENTAL SENSING

Perhaps one of the most salient and unexpected features of miRNA is the role for miRNA in amplifying or tempering cell signaling. The modulatory capacity provides an adaptive tool that allows the initiation of cellular signaling to be calibrated to accommodate cues from the microenvironment, as well as to potentially buffer signaling. This buffering function has been proposed to function as a network stabilizing effect in the context of dynamic and interlocking feedback loops [19]. In the lung, miR-21 promotes transforming growth factor (TGF- β) amplification and fibrosis in a feed-forward loop by relieving the repression of the inhibitor Smad 7 through targeting the mRNA [20]. Interestingly, TGF- β both inhibits miR-let-7 and upregulates miR-21. These two miRNAs appear to be functionally opposed in lung tissue from human subjects with idiopathic pulmonary lungs (let-7 acts as a negative regulator and miR-21 as a positive regulator) that in effect can balance the fibrotic phenotype. In the context of sepsis, monocyte expression of miR-146 and miR-155 are rapidly upregulated during endotoxin/LPS exposure, representing an innate response regulatory role for these miRNAs [11,13]. MiR-146a appears to function as a negative feedback regulator by targeting IL-1 receptor-associated kinase 1 (IRAK-1) and TNF receptor-associated factor 6 (TRAF6). A reciprocal negative feedback is achieved through MAP kinase phosphatase-1 (MKP-1)-mediated suppression of miR-155, which in turn targets suppressor of cytokine signaling-1. Thus, MKP-1 appears to function as a derepressor of miR-155-mediated suppression to modulate LPS response in monocyte/macrophages. In the context of skeletal muscle, C2C12, a skeletal muscle precursor cell line, miR-1 targets mRNAs for the insulin growth factor-1 (IGF-1) and the IGF-1 receptor. In a familiar theme of regulatory loops, IGF-1 reciprocally regulates miR-1 via the transcription factor Foxo3a, apparently through an enhancer-binding element within the miR-1 promoter. Interestingly, skeletal muscle response to endurance or resistance exercise stimuli has been linked to changes in miRNA levels [21,22]. However, such changes are depending on the age of the subjects, the mode of exercise, and the duration of exercise. For example, when anabolic response is dichotomized into so-called “low responders” versus “high responders” to resistance exercise-induced muscle hypertrophy, the former, but not the latter, exhibit a decrease in miR-26a, miR-29, and miR-378. Since miR-29 has been implicated as positive regulator of myogenesis, its reduction in

“low responders” may contribute to the attenuated response in muscle hypertrophy. Interestingly, physical inactivity such as prolonged bed rest (10 days) leads to muscle atrophy and a reduction in the levels miR-206, miR-23a, and several members of let-7 family of miRNAs [23]. These miRNAs contribute to a wide array of functions in that influence muscle function and maintenance, insulin response, growth and atrophy, cell cycle, differentiation, and glucose homeostasis. Other anabolic modulators such as estrogen and androgen also alter miRNA levels [11].

5. ORGAN DISEASES AND MICRORNAs

A potentially important and therapeutically exploitable distinction between disease and healthy states in tissue homeostasis may reside in the regulatory miRNA networks that reflect healthy and disease states. There is a growing recognition that miRNA networks are often associated with tissue dysfunction and are likely to be a key source of altered gene expression that underlays and distinguishes healthy versus disease states. A better understanding of the key perturbations that lead to these alternative regulatory network states may help to inform therapeutics. A reduction in Dicer expression has been implicated in cardiac disease. In skeletal muscle, a reduction of miR-29 expression has been associated with decreased muscle regeneration and Duchenne’s muscular dystrophy, but also chronic kidney disease, pointing to the complexity of miRNA control networks [21]. To add to this complexity, miR-29 expression increases with age and this induction may inhibit muscle regeneration by affecting overall protein translation via modulating IGF-1 and p85 α . In the context of lung biology, profiling studies of bronchial airway epithelia reveal an array of changes, wherein multiple miRNAs were downregulated in smokers that could be correlated with mRNA target expression in vivo [24]. In the kidney, miR-155 is differentially expressed in different tissue compartments (ie, kidney cortex versus kidney medulla regions) [5]. In individuals with trisomy 21, the chromosomal disorder also known as Down’s syndrome, fibroblasts display higher levels of miR-155. In kidney, the expression of miR-192 is dysregulated in diabetic nephropathy, with a suggestive role in mediating TGF- β -induced collagen expression. In that study, deletion of the inhibitory Smad 7 promoted miR-192 expression, in a model for obstructive kidney disease. In diabetes, mRNA profiles are altered based on the observation that there is an apparent discordance between proteomic profiles and their respective mRNA levels, suggesting a potential role for miRNAs [7]. Interestingly, insulin-secreting cells exposed