COMMENTARY

microRNAs: What the Clinician Should Know About This New Frontier

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As clinicians, we are often overwhelmed by the explosion of new discoveries in technology. When investigators of various aspects of obesity and diabetes moved from physiologic studies of β-cell function and insulin action in metabolic tissues, they moved into the realm of gene expression, gene array, and other laboratory techniques. These techniques were readily included in our understanding of the disorders. For example, enhanced hepatic glucose production secondary to impaired insulin release from the pancreas and hepatic insulin resistance was often associated with increased expression of important regulatory enzymes, such as glucose-6-phosphatase and PEPCK. The exquisite regulation of their gene expression is commonly measured as mRNA, a step before translation into the protein. More recently, we have had to come to grips with large-scale genome-wide association studies that relate the disease with single nucleotide polymorphisms—often only associations without definitive or identifiable causal relationships. Thus, while we could readily understand genetic mutations resulting in disease states, it was often less apparent how single nucleotide polymorphisms could explain diseases in the absence of genetic mutations (1).

If that wasn't enough, we now are becoming overwhelmed by new physiologic and pathologic processes discovered more recently as the sequence of the whole genome is no longer a mystery! Many types of small RNAs initially discovered in more primitive organisms are now found widespread throughout the various kingdoms, including animals, plants, and fungi. Two species of regulatory RNAs that are critical are endogenous small interfering RNAs (siRNAs) and microRNAs (miRNAs). A major difference is actually the mechanism whereby each is generated. miRNAs are small (~22 nucleotides) and are usually negative regulators of gene expression (1). They bind to specific regions of the mRNA and block translation, resulting in a reduction in protein levels of their targets (Fig. 1). Alternatively, if the expression of miRNAs is inhibited, then increased protein expression may be seen. In animal species, there are now hundreds of miRNAs that have identified target proteins, and many have already been shown to have causal relationships with various physiologic processes and disease conditions. Given the excitement that this process and technology has generated, it is not surprising that to date over 25,000 publications are indexed since their initial discovery in the year 2000.

While initially the expression and functional role of miRNAs were studied in cells and tissues, more recently it has also been established that they can be identified in the circulation. Exosomes are small membranous vesicles that are released from the vascular endothelial cells and contain molecules like miRNAs that are protected from degrading RNases (2). They are also released into other body fluids including saliva, urine, and milk. When released into the circulation they are hypothesized to communicate with other tissues, probably through miRNAs. The extracellular miRNAs thus form a newly identified intercellular communication system capable of regulating immune function, differentiation, cell migration, and other important functions. On the other hand, they may also be useful as biomarkers (3).

What is the function of miRNAs in disease states? It is rapidly becoming apparent that they play an important regulatory role in disease states, mostly commonly studied in development, cancer, and cardiovascular disease, to name a few examples (3). More recently, their role in diabetes has been studied both in relation to the changes in metabolic tissues, control of pancreatic islet mass and β-cell function, such as insulin secretion, and their roles in diabetes complications (4,5).

In this issue, Ortega et al. (6) performed a study comparing individuals with normal glucose tolerance (NGT) with patients with type 2 diabetes. They showed a significant increase of miR-140-5p, miR-142-3p, and miR-222, and a

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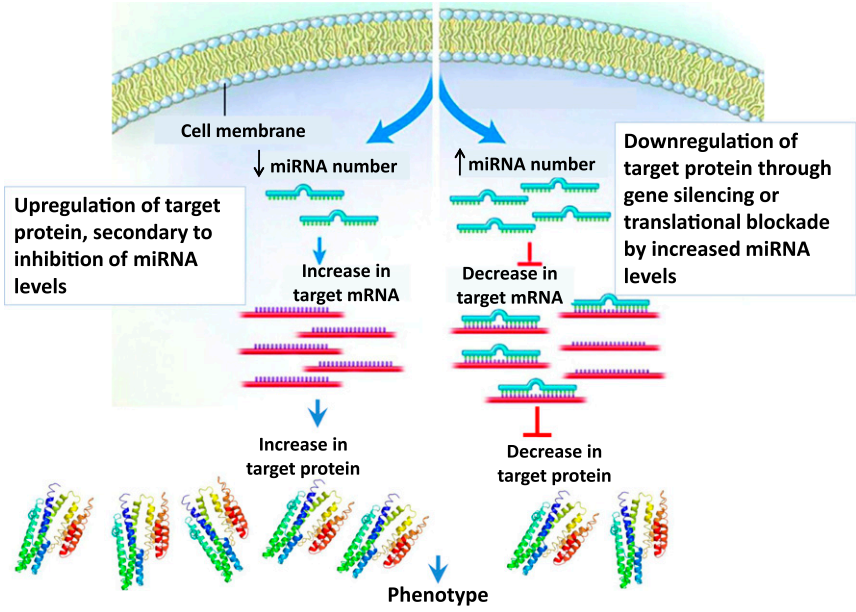

Figure 1—miRNAs regulated protein expression by binding to mRNAs. Adapted from Divakaran and Mann (8).

significant decrease of miR-423-5p, miR-125b, miR-192, miR-195, miR-130b, miR-532-5p, and miR-126 in the patients with type 2 diabetes.

Insulin/intralipid infusions raised the circulating levels of miR-222 and miR-140-5p in parallel, with a worsening of the insulin resistance. Other studies have confirmed an association, for example, with the miR-140 species, with morbid obesity and particularly fat mass, with a reduction in levels after bariatric surgery. Interestingly, in the current study metformin therapy led to reductions in miR-140-5p and an increase in miR-192—changes that paralleled an improvement in insulin resistance and an improvement in fasting glucose and HbA_{1c}.

In extending these types of studies, investigators have identified specific circulating miRNAs in diabetic cardiovascular disease and retinopathy and other diabetes complications. These findings add to the accumulating evidence of multiple miRNAs involved in pancreatic β-cell development, regeneration, and function (4,5).

The strength of the study by Ortega et al. (6) lies in identifying miRNAs that are associated with obesity, insulin resistance, and type 2 diabetes, as well as a response to metformin therapy. Weaknesses relate to the relatively small sample size with some aspects of their study and the absence of effects of other medications that would be of interest to the readers.

Remaining questions that need to be addressed in detail by the investigators to move the field forward include:

1. Do circulating miRNAs represent biomarkers for various disorders (7)?
2. Do miRNAs truly function as intercellular regulators?
3. How are miRNA levels controlled at the cell of origin?
4. How do lifestyle and other pharmaceutical agents affect miRNA expression and levels in the circulation?

While the story will take years to unfold, the decision of the editors to publish this small study in *Diabetes Care* was intended to recognize the importance of this emerging field as contributing to the understanding of the pathophysiology and development of diabetes and to inform our readers of new cellular factors that will dictate clinical presentation. Clearly, it is our prediction that miRNAs will be shown to be important regulators in diabetes-related conditions, as with other diseases such as cancer.

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References

1. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell 2009;136:215–233
2. EL Andaloussi S, Mäger I, Breakefield XO, Wood MJ. Extracellular vesicles: biology and emerging therapeutic opportunities. Nat Rev Drug Discov 2013;12:347–357
3. Zhu H, Fan GC. Extracellular/circulating microRNAs and their potential role in cardiovascular disease. Am J Cardiovasc Dis 2011;1:138–149
4. Lynn FC. Meta-regulation: microRNA regulation of glucose and lipid metabolism. Trends Endocrinol Metab 2009;20:452–459
5. Kredo-Russo S, Mandelbaum AD, Ness A, et al. Pancreas-enriched miRNA refines endocrine cell differentiation. Development 2012;139:3021–3031
6. Ortega FJ, Mercader JM, Moreno-Navarrete JM, et al. Profiling of circulating microRNAs reveals common microRNAs linked to type 2 diabetes that change with insulin sensitization. Diabetes Care 2014;37:1375–1383
7. Guay C, Regazzi R. Circulating microRNAs as novel biomarkers for diabetes mellitus. Nat Rev Endocrinol 2013;9:513–521
8. Divakaran V, Mann DL. The emerging role of microRNAs in cardiac remodeling and heart failure. Circ Res 2008;103:1072–1083