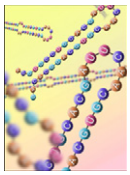

microRNAs: small regulators with a big impact on lipid metabolism

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Although the completion of the Human Genome Project in 2001 gave us a comprehensive readout of our DNA, our understanding of how to interpret this blueprint was far from complete. Over the last decade, our understanding of the complexity of the genome has been further advanced by the Encyclopedia of DNA Elements (ENCODE) project, a multi-center effort whose goal was to generate a comprehensive list of functional elements in the human genome by sequencing RNA from a diverse range of sources. Using comparative genomics, integrative bioinformatic methods, and human curation, the ENCODE investigators identified such elements as binding sites for proteins that influence gene activity, RNA species with numerous roles, and chemical modifications that serve to silence stretches of our chromosomes (1). From this annotation, it is now estimated that over 90% of the human genome serves some biochemical purpose, prompting scientists to reassess stretches of DNA that were previously disregarded as "Junk DNA."

In particular, noncoding RNA has emerged as an important class of regulatory molecules that modulate gene expression, including those that mediate pre-, co-, and post-transcriptional regulatory processes. These include long noncoding RNA (lncRNA, <200 nucleotides), which facilitate chromatin remodeling; small nuclear RNA (snRNA ~150 nucleotides), which mediate splicing; and cytoplasmic microRNA (miRNA, ~22 nucleotides), which destabilize RNA and/or inhibit protein translation. miRNAs are currently the most widely studied and can simultaneously repress hundreds of genes to directly influence the output of interconnected biological networks (2). Numerous reports have now shown these small RNAs to be potent posttranscriptional regulators of gene networks controlling lipid homeostasis. In the last several years, miRNAs have been proven to be: *i*) regulators of plasma levels of lipoproteins (3, 4), *ii*) novel intercellular signaling molecules (5), *iii*) plasma biomarkers of physiological status (6, 7), *iv*) etiological factors in complex diseases (8), and *v*) promising therapeutic targets (9, 10). These various roles are highlighted in this Thematic Review series in the current issue of the *Journal of Lipid Research*.

The human genome encodes over 1,000 miRNAs, approximately one-third of which are organized in polycistronic clusters. While most miRNAs are located within intergenic regions of the genome, others are located within protein-coding genes. One such example is miR-33, which is cotranscribed with the SREBF family of genes and is a critical regulator of lipoprotein metabolism and fatty acid oxidation (11). In a review of the roles of miRNAs in regulating HDL, Mireille Ouimet and Kathryn Moore of New York University School of Medicine discuss the functional relevance of miR-33 to lipid homeostasis, how this and other recently identified microRNAs regulate components of the reverse cholesterol transport pathway, and their potential as therapeutic targets for the treatment of atherosclerosis.

While miR-33 was one of the first miRNAs shown to have a role in lipid biology, the number of genes in the complex network that controls lipid homeostasis identified to be under miRNA control is rapidly growing and includes those involved in sensing and effector pathways, lipoproteins, and extracellular enzymes. It thus follows that natural genetic variation in the compendium of elements that regulate miRNA expression (transcriptional control elements and premiRNAs) or miRNA activity (target sites) will contribute to interindividual variability in lipid phenotypes. This is the topic of a review by Praveen Sethupathy of the University of North Carolina, who describes the evidence for miRNA-related genetic variation as etiological factors in lipid disorders and the use of systems approaches to uncover miRNA-related genetic associations, thereby illuminating the "needles in the genetic haystack" that control lipid phenotypes.

The exciting discovery that miRNAs can be exported into the extracellular space and be stably delivered to adjacent cells and/or distal tissues has unearthed new potential roles for miRNAs. Extracellular miRNAs are now recognized as a novel class of signaling molecules that mediate cell-to-cell communication, and distinct circulating miRNA signatures have been identified in health and disease. This is the topic of a review by Katey Rayner and

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colleagues of the University of Ottawa Heart Institute, who highlight the various routes of export of miRNAs into the extracellular space, their transport by membrane-derived vesicles (exosomes and microparticles) and lipoproteins, and how miRNAs in the circulation may give us hints of the underlying biology of certain disease states.

As the tools to study miRNAs have been developed, our appreciation of the complexity of miRNA gene regulation has continued to expand. Recent advances in high-throughput small RNA sequencing technology have revealed an unexpected dynamic repertoire of miRNAs generated by a single genomic locus. In the final review of the series, Kasey Vickers and colleagues summarize the mechanisms through which multiple functionally distinct isoforms can arise from a miRNA coding sequence, the resulting plasticity of miRNA control, and the biological relevance of such isomiRs in regulating lipid metabolism.

As scientists continue to unravel the miRNA networks that regulate hepatic and systemic lipid homeostasis, exciting discoveries in the field of lipid metabolism are likely to proceed at an unprecedented pace. This will no doubt be paralleled by the rapid identification of novel disease biomarkers and targets for therapeutic intervention. Preclinical studies of miR-33 inhibitors in mice and nonhuman primates have revealed the potential for miRNA inhibitors in the treatment of dyslipidemias and atherosclerosis, and further studies in humans are eagerly awaited. The recent FDA approval of Mipomersen, a first-in-class antisense oligonucleotide inhibitor that targets apolipoprotein B-100 to reduce LDL cholesterol for the treatment of homozygous familial hypercholesterolemia (12), opens the door to other oligonucleotide-based therapies, bringing miRNA therapeutics one step closer to reality.

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