More Than Just an Engine
The Heart Regulates Body Weight

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A Cardiac MicroRNA Governs Systemic Energy Homeostasis by Regulation of MED13
Grueter et al

A recent study published in Cell may represent a paradigm shift in the way we look at cardiac metabolism: The study identifies the heart as an endocrine organ that regulates body weight. It raises two important questions: What would be the “slimming factor” released by the heart that regulates fuel homeostasis in distant organs? What are the possible mechanisms directing metabolic energy to either storage or dissipation?

Traditional reasoning goes as follows: The heart uses much energy to pump even more energy into the rest of the body. Alternatively stated, the heart is an efficient engine that both consumes and provides energy. Yet until now it seemed improbable that the heart should also control body weight and energy homeostasis. However, in the April 27, 2012 issue of Cell,1 Eric Olson and his group report on a serendipitous observation made in the context of pharmacological inhibition of miR-208a with locked nucleic acid-modified antisense nucleotides. They show that the heart regulates systemic energy homeostasis via MED13, a subunit of the mediator complex, which controls gene transcription by thyroid hormone and other nuclear hormone receptors. MED13, in turn, is suppressed by a cardiac-specific miR-208/499-family member, miR-208a. The surprising results of the study show that cardiac-specific over-expression of MED13, or pharmacological inhibition of miR-208a, in mice confers resistance to diet-induced obesity and improves insulin responsiveness. Vice versa, deletion of MED13 in heart muscle enhances obesity in response to high-fat diet and exacerbates features of the metabolic syndrome (Figure). Interestingly MED13 was previously linked to adiposity in Drosophila, suggesting an ancient role of this gene in metabolism.2 The experimental strategies very elegantly reveal that the heart plays an important role in systemic metabolic control. The readers of Circulation Research may enjoy the following comments.

First, this study is an example of the power of molecular biology, which has now reached a level of complexity beyond imagination only a few years ago. Specifically, during the last decade, miRNAs have come front and center as major players in cardiac disease.3-4 Previous studies revealed a key role of miR-208a as a master organizer of cardiac remodeling to pathological stress.3 The initial discovery of miR-208a in 2007 has spawned a small cottage industry of miRNA-based therapeutics involving the use of antimiRNA oligonucleotides as drugs in the cardiovascular system.5

In our view the study by Grueter et al represents a paradigm shift in our understanding of cardiac metabolism, which until now was considered solely to liberate the energy stored in organic compounds to support cardiac function. The concept that the heart may regulate whole body metabolism has recently been proposed6 and received credence when it was shown that atrial and ventricular peptides (atrial natriuretic factor and brain natriuretic peptide) influence mitochondrial biogenesis, uncoupling, and respiration.7 The authors propose that the heart may be a central regulator of adipose tissue biology. Of course, there is a possibility that miR-208a may be a regulator of cardiac peptides such as atrial natriuretic factor and brain natriuretic peptide. Whatever the mechanism, we now know that the heart does more than pump blood. It is tempting to liken this paradigm shift to other great discoveries in the history of the medical sciences. The discoveries that diabetes ensues after pancreatectomy,8 that a blood pressure raising substance is formed in the kidneys and passed on into the blood stream,9 that the heart humorally controls its workload through the activities of atrial natriuretic factor and brain natriuretic peptide,10 that a hormone released from fat cells controls satiety,11 and, most
recently, that a hormone released from muscle during exercise drives brown-fat–like development of white fat.\textsuperscript{12}

The work raises 2 important questions, both of which have yet to be answered. First, what would be the “slimming factor” released by the heart that regulates fuel homeostasis in distant organs such as fat and muscle tissue? Secondly, what are the possible mechanisms directing metabolic energy to storage or dissipation in the end-organs? And, what is the target tissue(s) of the cardiac factor? Might this signal be delivered initially to the brain as a relay system to the other organs or do fat and muscle respond directly to the cardiac-derived signal? Hypothetical answers are shown in the Figure.

For 30 years, the heart has been recognized as an endocrine organ that produces peptides, such as atrial natriuretic factor and brain natriuretic peptide (for review, see de Bold 2011).\textsuperscript{10} and cytokines such as TNFα.\textsuperscript{11} However, these previous studies set out to test for a known or suspected compound of physiological significance, whereas the present study portends the existence of a new class of cardiac-specific circulatory molecules with hormone-like activities. In the wake of the discovery of miRNAs with metabolic actions\textsuperscript{14} circulating in the blood stream, the molecule could be another miRNA. More likely, and given the powerful analytic tools now used in discovery-driven research, we can expect a search for an interesting new peptide molecule with a fitting Greek name in the line of renin, leptin, or irisin. Or, perhaps it is a thyroid hormone analog? The search for such a “slimming factor” (Figure), we are sure, must be already on its way.

Next, the metabolic effects of the “slimming factor” are so striking that they need an explanation. Here we remember the First Law of Thermodynamics, ie, energy can neither be created nor be destroyed. In his famous 1847 treatise “On the Conservation of Force” the young army physician Herman Helmholtz expressed the implications of the principle. “Animals,” he wrote, “take up oxygen and the complicated oxidizable compounds which are produced in plants and give these out again mainly burned to carbonic acid and water…They consume, therefore, a certain quantity of chemical potential energy and produce from it heat and mechanical energy” (cited by Holmes, 1992).\textsuperscript{15} Therefore, the second important question arising from this study is how is it that the miR-208a:MED13 pathway in the heart can elicit a lean body phenotype in the absence of overt changes in caloric intake and activity-dependent energy expenditure? In other words, how is it possible that for the same amounts of food intake, physical movement, and nonexercise activity, the genetically manipulated mice can be either lean or fat?

What come to mind first are the mitochondria—the organelles that convert fuel to carbon dioxide, water, and ATP. Mitochondria are also the site of energy dissipation via uncoupling proteins and adaptive thermogenesis.\textsuperscript{16} More work is needed to pinpoint energy wastage in various tissues, especially the brown adipose tissue. Another, perhaps simpler explanation would be that of substrate cycles in metabolic control. In normal cells, including heart muscle cells, energy transfer occurs through a series of moieties conserved cycles.\textsuperscript{17} Cycles improve the efficiency of energy transfer.\textsuperscript{18} The sensitivity of linear metabolic pathways is improved by “futile” substrate cycles in which the activity of the key enzyme in the metabolic pathway is opposed by a reverse reaction catalyzed by a different enzyme.\textsuperscript{19} (Figure). According to Newsholme, energy loss through substrate cycling can amount to as much as 50% of the daily caloric intake, keeps the system “revved up,” and is under humoral control. It would be of considerable interest to know whether MED13 (and the resulting release of a proposed “slimming factor”) changes the capacity of substrate cycles in different tissues. And, if so, how? A useful mind experiment is depicted in the lower panels of the Figure in the form of a short pathway from A (substrate) to D (product) with cycling of the 2 intermediates B and C.

The role of substrate cycling in metabolic regulation involves an enzyme-catalyzed reaction that is nonequilibrium in the forward reaction to be opposed by a reaction that is nonequilibrium in the reverse direction of a metabolic pathway, which effectively dissipates energy.\textsuperscript{20,21} According to Newsholme and Crabtree, the covalent modification of an enzyme via the interconversion of an inactive to an active form and vice versa is a logical extension of the substrate cycle.\textsuperscript{22} Although the cycling between active and inactive forms of enzymes may be lower than that of the metabolic intermediates in a substrate cycle, the rate of heat fluctuation will be considerably less. Another cycle of considerable energy cost is the cycle of amino acids in and out of proteins.

The possibilities are tantalizing. The biggest question here is: Does what works in mice, work in humans too? Is the heart the seat of the long elusive “thrifty gene”? The search for the “thrifty gene” began exactly 50 years ago when James Neel, at the time a professor of human genetics at the University of Michigan, proposed that genes that predispose to diabetes (“thrifty genes”) were evolutionary advantages for survival of a species, but they became detrimental in the modern world.\textsuperscript{23} We think that the Olson group has created a fitting model for the “thrifty gene” hypothesis. Consider also that the pharmaceutical treatment of obesity is still unsatisfactory and fraught with either failures or unwanted side effects. Would the miR-208a inhibitor offer new hope for curbing the obesity epidemic? Would the antimiR restore insulin responsiveness and provide a cure for type 2 diabetes? Would the antimiR reverse or prevent the consequences of lipotoxicity prevalent in the failing human heart?\textsuperscript{24} In reality, targeting miRNAs for a therapeutic purpose may not be without challenges. \textit{miR-122} was the first miRNA implicated in metabolic control, specifically in hepatic cholesterol and lipid metabolism.\textsuperscript{25} Antisense inhibitors using locked nucleic acid chemistry proved to be safe and raised the exciting possibility of a new therapeutic strategy for lowering cholesterol. However, \textit{miR-122} antagonism not only lowered LDL but also HDL cholesterol levels which raised concerns about long-term effects,\textsuperscript{14} illustrating uncertainties about the range of actions of microRNAs in vivo. Nevertheless, preliminary reports of a phase II clinical trial of the locked nucleic acid-modified \textit{miR-122} inhibitor in humans have shown efficacy in cholesterol lowering, as well as suppression of hepatitis C viremia, without overt toxicity.\textsuperscript{26}
Hans Krebs wrote in his autobiography that the primary aim of research must not just be accumulation of more and more facts, but more facts of strategic value. The paper by Grueter et al is a case in point. Research into small noncoding RNAs, including miRNAs, is rapidly transforming the understanding of how entire metabolic networks are regulated. Lastly, the paper is also a fitting illustration for the powerful symbiosis between academic research and industry. Without serendipity in the process of drug screening, this discovery would not have been possible. Metabolism may no longer be the lost child of cardiology, but no one can raise the child alone anymore. Given the new challenges of transcriptional control of metabolism, strong collaborative efforts between academia and industry will continue to benefit the whole field.

Acknowledgments
We thank Roxy A. Tate, Truong Lam, and Henry Wu for their assistance with the preparation of this manuscript.

Sources of Funding
Research funding is from the National Institutes of Health (H.T.) and the American Heart Association (A.R.).

Disclosures
None.

References
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Circ Res. 2012;111:513-515
doi: 10.1161/CIRCRESAHA.112.276063

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