Feed My Heart or Eat It

miR-22 Decides*

Scot J. Matkovich, PhD, Gerald W. Dorn II, MD

If we live well, eat right, do not smoke, and by so doing avoid the usual diseases that end life prematurely, we will get old. More of us are doing so every year. Thus, for selfish and scientific reasons, the physical, biochemical, and molecular changes provoked by aging merit attention. A revolution in our understanding of how noncoding ribonucleic acid (RNA) species regulate cardiovascular function in health and disease makes the intersection between microribonucleic acid (miRNA) biology and aging fertile ground for investigation. In this issue of the Journal, Gupta et al. (1) described a miRNA that is increased in aging and suppresses a process whose dysfunction is postulated to contribute to aging phenotypes, autophagy.

Autophagy (“self-eating”) is an adaptive response to starvation and a compensatory response that promotes cell and tissue renewal in disease. However, autophagic activity decreases with age, and interruption of autophagy mimics aging, suggesting a pathophysiological relationship (2). Gupta et al. (1) developed and applied a screening system that identified miR-22 as a potent inhibitor of cardiac autophagy. They further discovered that miR-22 was increased in abundance in older mouse hearts, higher circulating levels of miR-22 were associated with adverse outcomes in clinical heart failure, and miR-22 inhibition using a specific anti-microribonucleic acid (anti-miR) enhanced cardiac autophagy and diminished adverse cardiac remodeling in an older mouse model of myocardial infarction (MI).

Messenger ribonucleic acids (mRNAs) that encode proteins and noncoding miRNAs that bind to coding mRNAs to regulate their translation are part of complex homeostatic mechanisms that protect cells from, or help them react appropriately to, environmental stresses. Accordingly, expression of both coding and noncoding RNAs varies with developmental and environmental context (3,4). Comprehensive mRNA and miRNA profiling reveals different transcriptional states evoked by developmental stage, reaction to injury, and response to chronic dysfunction. In short, tissue mRNA/miRNA profiling has identified biomarker signatures of health and disease. A logical next step in translating these basic findings to the clinic is to identify circulating serum RNAs with similar biomarker functions. Remarkably, aging tissue appears to have its own unique and evolutionarily conserved transcriptional signature (5,6). The question therefore arises: what transcriptional markers are disease effectors (i.e., potential therapeutic targets) versus beneficial or benign factors increased as adaptive or compensatory mechanisms? By answering this question for individual regulated RNAs and then using context-appropriate biological manipulations, it should be possible to enhance the intrinsic reactive response to disease, aging, and injury.

Dysregulated miRNAs are ideal candidates for therapeutic intervention because: 1) miRNAs can readily be targeted using engineered complementary RNAs, called anti-miRs; and 2) miRNAs bind to and suppress translation of multiple coding mRNAs within a given biological pathway, thereby resisting neutralization by classic endogenous counter-regulatory mechanisms (a limitation of single-target pharmacological therapies) (7,8). Examples of biological processes orchestrated in part by miRNAs...
include cardiac growth and development (9), cardiomyocyte apoptosis (10), myocardial fibrosis (11), and cardiac hypertrophy (3), to which we can now add autophagy (1).

Although a particular miRNA-mRNA interaction typically suppresses protein levels by only about one-half, this effect can be increased by the combined actions of several coregulated miRNAs that target the same mRNA. Moreover, miRNAs classically target multiple mRNA-encoded proteins within the same biological pathway, multiplying the overall effect due to serial suppression (50% × 50% × 50%, and so on). For these reasons, miRNA inhibition with anti-miRs is undergoing preclinical evaluation in a number of clinically relevant cardiac conditions: anti-miR-208a is being investigated to alleviate cardiac remodeling during heart failure in hypertensive rats (12), and there are ongoing efforts to restore cardiac function in murine heart failure induced by sustained pressure overload with anti-miR-25 (13).

Gupta et al. (1) developed a moderately high-throughput flow cytometry screening system to determine which of 380 different miRNAs increased or decreased autophagy in cultured immortalized HL-1 mouse cardiac cells (14). This type of functional screening approach previously identified miRNAs that favor cardiac regeneration (15) or modulate cardiac contractility (13). Here, the central miRNA that inhibited autophagy, miR-22, is also one of the most abundant miRNAs in the adult heart (16,17). It is notable that myocardial miR-22 abundance increases with aging, because a key finding of this study was that the efficacy of anti-miR-22 to enhance autophagy and improve cardiac outcomes after MI was greater in older than younger mice. Because aging-induced suppression of autophagy, aging-induced increase in miR-22 abundance, and miR-22 orchestration of autophagy converged upon autophagy-directed myocardial remodeling after infarction in older hearts, Gupta et al. (1) suggested that therapeutic miR-22 inhibition might prove particularly effective for managing the aftermath of MI in the elderly population.

A detailed mechanistic understanding of pathobiology can inform therapeutic initiatives. The most important miR-22 targets for regulating autophagy are not entirely clear. Computational modeling of miRNA targeting is a useful adjunct to experimentation in defining contextually (i.e., tissue- and disease-specific) important miRNA targets (17,18). Gupta et al. (1) classified previously described miR-22 targets according to whether or not they were likely to affect autophagy, and the mitochondrial biogenesis factor peroxisome proliferator-activated receptor alpha rose to the top of the list. This indeed represents an attractive target, as mitochondrial biogenesis and mitophagy comprise part of an integrated regulatory circuit that is imbalanced in several heart diseases (19). However, given that expression of both miR-22 and some coding miRNAs it can target are altered as part of the aging-related transcriptional signature (vide supra), context-specific transcriptome-wide examination of miR-22 targets might provide further mechanistic details underlying its effects. Genetic manipulation of miR-22 in mice previously suggested that both increases and decreases in its abundance are deleterious to the heart (20,21). A fairly narrow therapeutic window might therefore exist for anti-miR-22, and the proper goal of therapeutics may be to normalize miR-22 to levels observed in younger, normal hearts, thereby retaining its homeostatic functions.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Gerald W. Dorn II, Washington University Center for Pharmacogenomics, 660 South Euclid Avenue, Campus Box 8220, St. Louis, Missouri 63110. E-mail: gdorn@wustl.edu.

**REFERENCES**


KEY WORDS aging, autophagy, circulating miRNA, MiR-22, p62