Aging is a major factor in many cardiovascular diseases. The molecular factors that regulate age-related changes in cardiac physiology and contribute to the increased cardiovascular risk in the elderly are not fully understood. A study recently published in *Nature* suggests a specific role for microRNAs (miRNAs) in regulating cardiac aging and function, challenging the concept that aging is an inevitable process in the heart.

Aging is an evolutionarily conserved yet poorly understood process that leads to deterioration of many physiological functions during the lifespan of an organism. Aging increases the risk of cardiovascular diseases and leads to worse clinical outcomes. Elderly patients have an increased risk of acute myocardial infarction (MI) and an increase in both in-hospital and postdischarge mortality. The capability of the adult mammalian heart to replenish its cardiomyocyte pool both during physiological aging and in response to injury has now been definitively established. However, cardiomyocyte refreshment occurs at a low rate (<1%/y) even in youth and seems to slow with advancing age. Recent evidence suggests that some of the aging hallmarks, like age-related cardiac hypertrophy, are regulated by hormones and can be reversed. The molecular mechanisms that regulate cardiac aging are complex and not yet completely understood.

In the March 31, 2013, issue of *Nature*, Boon et al describe a new molecular pathway that regulates cardiac aging. Using a microarray approach, the authors identified several miRNAs, including miR-34a, that change with age. miR-34a increases with age and acts as a regulator of telomere shortening, DNA damage, and apoptosis in cardiomyocytes, whereas its inhibition improves functional recovery after acute MI (Figure). miRNAs are endogenous noncoding single-stranded small regulatory RNA molecules, ~22 nucleotides in length, and these RNAs play an important role in the regulation of gene expression. miRNAs can silence the expression of multiple genes with an average miRNA having >100 targets, and thus miRNAs have the potential to regulate at least a third of the human genes. miRNAs participate in many cardiovascular biological processes by regulating heart development, cardiac regeneration, and aging and by modulating gene expression.

In this new study, Boon et al compared groups of young and old mice and unsurprisingly found the hearts of aged mice exhibited increased fibrosis, cardiac hypertrophy, shorter telomeres, and increased cardiomyocyte apoptosis. To identify factors that are dysregulated with age and can contribute to the development of the aging cardiac phenotype, the authors performed miRNA microarray profiling. They identified miRNAs that are differentially expressed in the 2 experimental populations, and they discovered that the miRNA family is upregulated in an age-dependent manner. This miRNA family contains 3 members: miR-34a, miR-34b, and miR-34c, and the authors showed that miR-34a expression is upregulated in aging hearts and specifically in cardiomyocytes. miR-34a plays a crucial role in p53-induced cell cycle arrest, cell senescence, and apoptosis; and miR-34a is also known to induce apoptosis in cancer cell lines. The authors also showed that miR-34a expression increases in human hearts with age, suggesting that a similar pathway might regulate cardiac aging in humans.

Inhibition of miR-34a in rat neonatal cardiomyocytes reduced H₂O₂-induced apoptosis, and overexpression of miR-34a increased apoptosis, suggesting a specific role of miR-34a in regulation of apoptosis in cardiomyocytes. In line with this intriguing in vitro finding, Boon et al showed that by inhibiting miR-34a via administration of an antisense antagonist in vivo, cardiomyocyte apoptosis in aging mice was significantly reduced after 1 week of treatment. To further study the impact of miR-34a on cardiac function, the authors developed miR-34a knockout (miR-34a−/−) mice. The miR-34a−/− mice line showed no increase in mortality or specific phenotype and will be published by the authors in a follow-up article. Interestingly, aged miR-34a−/− mice have reduced cardiac hypertrophy compared with miR-34a+/− mice. The effect of miR-34a was further confirmed by showing that pharmacological inhibition of miR-34a by locked nucleic acid–based anti-miRs can rescue the expected reduction in cardiac contractile function in the Ku80−/− genetic model for accelerated aging.

The findings of this study support the hypothesis that miR-34a could be involved in the pathophysiology of MI, where apoptosis and fibrosis are important hallmarks. The authors found that miR-34a is indeed upregulated in border zone after MI in mice. Furthermore, pharmacological inhibition of miR-34a for 2 weeks after MI results in improved cardiac contractile function, reduced cell death, and a reduction in scar area. It
is not yet clear whether this effect is a result of regulation of fibrosis, apoptosis, or both.

miR-34a targets the class III histone deacetylase SIRT1 in endothelial and endothelial progenitor cells19 and induces apoptosis in cancer cells17; SIRT1 is essential for neovascularization after ischemia18 and its suppression by miR-34a negatively affects endothelial cells function.19 In line with this, the authors observed that inhibition of miR-34a resulted in a reduction in rates of cell death in noncardiomyocytes after infarction. In particular, they observed increased neovascularization in mice that were treated with the inhibitors, suggesting that the overall positive effect on cardiac function after infarction can be multifactorial, including inducing resistance to programmed cell death and improving regional perfusion.

Study of the mechanistic role of miR-34a in regulating cardiac function as a function of age unveiled a novel and SIRT1-independent pathway that underlies senescence in cardiomyocytes. Using multiple miRNA prediction tools, Boon et al7 were able to narrow the pool of potential targets to a single gene, Ppp1r10 (also known as protein phosphatase 1 nuclear–targeting subunit [PNUTS]) that was predicted as a target of miR-34a and was also downregulated with age. PNUTS has emerged as a component of the DNA damage response that is recruited to the DNA damage sites and in-


Keep PNUTS in Your Heart
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