MicroRNA-34a
A New Piece in the Cardiac Aging Puzzle

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How Was the Hypothesis Tested?
Boon et al performed microarray profiling of miRNAs to compare miRNA expression in young and aged hearts and discovered an upregulation of miR-34a in aged hearts. They inhibited miR-34a in vivo by antisense oligonucleotides (Ant-34a) to study its effect on cardiomyocyte cell death. They generated a miR-34a knockout mouse model to further investigate the roles of miR-34a in cardiac aging. Myocardial infarction (MI) induces similar but more robust responses (eg, fibrosis and cardiomyocyte apoptosis) compared with cardiac aging, and aging exacerbates cardiac dysfunction after MI. The interaction between cardiac aging and MI hints that the underlying mechanisms of the 2 conditions may interact and augment each other. Boon et al observed upregulation of miR-34a after MI and assessed the involvement of miR-34a in cardiac dysfunction after MI. They identified a novel target of miR-34a by microRNA target prediction tools and genome-wide microarray, validated by luciferase reporter assay, and investigated its role in cardiac dysfunction by adeno-associated virus-mediated overexpression after MI.

Principal Findings
Boon et al showed that expression of miR-34a increased in the aged mouse heart and positively correlated with age in human hearts. They demonstrated that miR-34a was predominantly expressed by cardiomyocytes, and in vivo silencing of miR-34a by Ant-34a for 1 week could rescue the increase in cardiomyocyte cell death in aged mice. They showed that genetic deletion of miR-34a can attenuate the decline in contractile function and prevent cardiac hypertrophy in aged mice. Similar improvements in contractile function by inhibition of miR-34a were also demonstrated in Ku80 knockout mice (a mouse model of accelerated aging). These findings support the notion that cardiac aging is regulated by miR-34a. Parallel to its roles in cardiac aging, miR-34a was upregulated in the border zone of infarcted heart, and miR-34a inhibition by Ant-34a improved remodeling after MI.

The authors identified phosphatase 1 nuclear targeting subunit (PNUTS) as a novel direct target of miR-34a and detected downregulation of PNUTS in the aged heart. PNUTS interacts with telomeric repeat binding factor 2 (TRF2) and has been implicated in DNA damage response. Boon et al demonstrated that overexpression of PNUTS reduced telomere shortening, attenuated DNA damage caused by doxorubicin or 4-nitroquinoline 1-oxide, and prevented H2O2-induced cardiomyocyte apoptosis in vitro. Furthermore, they demonstrated the role of PNUTS in vivo after MI by showing that adeno-associated virus-mediated cardiac PNUTS overexpression ameliorated remodeling and contractile dysfunction after MI.

Implications
The study by Boon et al identified miR-34a as a regulator of cardiac aging and MI and suggested the potential of miR-34a as a therapeutic target. Although miR-34a deletion or inhibition of miR-34a can prevent cardiac contractile dysfunction
in aged mice or Ku80 knockout mice, respectively, the inhibition of miR-34a was initiated before the occurrence of cardiac dysfunction in both cases. Whether miR-34a inhibition in aged mice with established cardiac aging can reverse cardiac aging phenotypes remains uncertain. Compared with contractile function, diastolic function is more severely impaired with aging. The effect of miR-34a inhibition on the age-related decline in diastolic function is still awaiting investigation. In addition to miR-34a, Boon et al detected altered expression of other miRNAs in aged hearts. The involvement of these miRNAs in cardiac aging deserves further study. miR-34a inhibition or overexpression of its novel target PNUTS attenuated contractile dysfunction after MI, suggesting the role of miR-34a-PNUTS axis in remodeling after MI. However, whether the cardiac aging regulation by miR-34a is mediated by PNUTS or other miR-34a targets (eg, silent information regulator 1 [SIRT1]) has not been addressed. Mild-to-moderate overexpression of SIRT1 reduces cardiac hypertrophy and cardiomyocyte apoptosis and improves contractile function in aged mice. The similar cardiac benefits observed by miR-34a inhibition could, in part, be mediated by increased SIRT1 expression under miR-34a inhibition. Further studies will be required to determine the relative contributions of PNUTS and SIRT1 in miR-34a regulation of cardiac aging.

The first months of 2013 were tremendously productive of publications that describe novel interventions that may retard or regress cardiac aging in animal models. It remains to be seen whether these different interventions have common underlying mechanisms; however, it is already clear that the prospects for interventions in cardiac aging are looking much brighter than they did just a short time ago.

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Disclosures

None.

References


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