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Cardiac specific microRNA-125b deficiency impairs mitochondrial function in mouse neonatal and adult heart

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Background: We have previously reported that microRNA-125b, along with three other microRNAs, can promote structural and functional maturation of embryonic stem cell-derived cardiomyocytes. Given that the role of microRNA-125b regulation in cardiovascular biology in general is not well defined, we thus sought to investigate the effects of miRNA-125b deficiency in the murine heart during development.

Purpose: To investigate the role of microRNA-125b in the heart using knockout mice.

Methods and Results: Cardiac-specific microRNA-125b-1 knockout mice were generated using the Cre-Lox system (aMHC-Cre; miR-125b-1f/f). We found that cardiac-specific microRNA-125b deficiency resulted in a 60% perinatal death rate, with surviving mice possessing hearts with dilated ventricles. This was a surprising finding given that in most previous reports, induced microRNA deficiencies in mice do not cause severe effects. In neonatal mice, we observed greater TUNEL positivity and upregulation of stress markers Anp, Bnp and Acta1 in the myocardium. Mice that survived to adulthood displayed reduced ejection fraction, as well as greater interstitial fibrosis and cardiomyocyte hypertrophy. In both neonatal and adult mice, we observed that cardiomyocytes possessed mitochondria with abnormal morphology and an overall increase in activation of mitophagy in the myocardium. In neonatal myocardium we also observed that the respiratory complex proteins and mitochondrial transcription machinery were also impaired, with no significant alterations in the total number of mitochondria. When performing microRNA-125b knockdown in HL-1 cells we observed downregulation of oxygen consumption rate, as measured by seahorse assay. Thus, both our in vivo and in vitro data point towards microRNA-125b playing a crucial role in mitochondrial function in cardiomyocytes, especially during development. Mechanistically, using microarray data we found an upregulation of genes corresponding to the p53 pathway in microRNA-125b deficient mice. This suggests that the p53 network may be a downstream target of microRNA-125b regulation in the context of cardiovascular biology.

Conclusion: We conclude that microRNA-125b deficiency causes a high incidence of perinatal death, with surviving mice developing dilated cardiomyopathy with impaired ejection fraction. This was associated with mitochondrial dysfunction and dysregulation of mitophagy.