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MicroRNA-205: a novel epicardial regulator of cell cycle and cardiac growth in the perinatal heart.

Patrick G. Burgon[1,2*], Jonathon J. Weldrick[2,3], Rui Yi[4], and Lynn A. Megeney[2,5]

[1]Department of Chemistry & Earth Sciences, College of Arts and Sciences, Qatar University, Qatar
[2]Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ontario, Canada
[3]University of Ottawa Heart Institute, Ottawa, Ontario, Canada
[4]Department of Pathology, Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago,USA
[5]Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

Fetal heart development is a complicated multistep morphogenetic process coordinated through the sequential and succinct spatiotemporal control of gene expression. During fetal development, the mammalian myocardium undergoes a period of hyperplastic growth. After birth, cardiomyocytes proceed through a final round of cell division in the absence cytokinesis that results in binucleation of a majority of adult cardiomyocytes. Nearly all subsequent increase in myocardial mass is due to cardiomyocyte hypertrophy, with extremely low number of new cardiomyocytes being produced throughout post-natal life. Moreover, mice with a heart specific deletion of Dicer, a key enzyme that is required for microRNA maturation, die by postnatal day five despite displaying no abnormal heart morphology-function at birth. In spite of the importance of this phenomenon, little is known about the molecular/genetic basis, especially with regard to the role of micro-RNAs, for the transition from hyperplastic to hypertrophic-based myocardial growth.

We hypothesize a specific perinatal heart micro-RNA-mediated gene program is necessary for the normal transition from a fetal heart to an adult heart gene program.

To identify the molecular mechanisms and genetic pathways involved in cardiac myocyte differentiation, RNA was isolated from E19, and 1, 3, 5, 7, 10 and 35-day old mouse hearts (n=9 hearts/time point pooled). Cardiomyocyte micro-RNA profiles (n=3 arrays/time point) were measured and bioinformatic analysis was used to identify genes that are transiently and significantly changing ($p<0.05$, fold change >1.5) during the perinatal period.

Our analysis identified microRNA-205 as a candidate for playing a role in the cardiac transitional program. Previous studies have shown a global knockout of miR-205 to be neonatally lethal. We observe a transient 20-fold increase in miR-205 expression between day 1 and day 5 of post-natal life, with levels returning to baseline by day 10. In-situ hybridization revealed miR-205 expression to be restricted to the epicardium of the heart.

Mice harbouring a cardiomyocyte-specific deletion of miR-205 using αMHC-Cre are born healthy with expected Mendelian ratios and develop through the neonatal period normally. Hearts collected from adult mice show signs of abnormal growth and hypertrophy, up to 50% larger than controls. Cardiac-specific miR-205 over-expression mouse model expedited more cardiomyocytes present five days after birth with no difference in cardiomyocyte number at 14 days after birth. Both of the heart models present with altered Hippo signaling kinetics after birth. Previous studies demonstrated that miR-205 directly targets YAP within the evolutionarily conserved hippo pathway that controls organ size. Hearts lacking miR-205 exhibit a substantial increase in YAP protein expression. Increased cardiac size has been demonstrated in a constitutively active YAP transgenic mouse model. We conclude that miR-205 plays a direct role in regulating post-natal heart size through direct modulation of the Hippo pathway.