Unravelling The Molecular Network in Cardiomyocyte Maturation

Yibin Wang, PhD

Abstract

Cardiomyocyte maturation occurs in the postnatal period where cardiomyocytes undergo drastic fetal-to-adult transition at structural, molecular, metabolic, and functional levels to accommodate major changes in circulatory pattern and hemodynamic workload after birth. In recent years, cardiomyocyte maturation has gained more attention due to the realization that cardiomyocytes derived from human pluripotent stem cells (hPSC-CMs) are immature, and this limitation impedes the applications of hPSC-CMs in drug discovery, disease modeling, and cell-based therapies for heart failure. Most of the efforts to promote maturation focused on extrinsic measures, however, the intrinsic regulatory molecular network that drives cardiomyocyte maturation remains to elucidated.

We compared the global transcriptome profiles between neonatal and adult rat hearts. Gene ontology (GO) analysis of differentially expressed genes (DEG) identified mRNA splicing as one of the top enriched DEG pathways associated with cardiac maturation. We found expression of a muscle-specific RNA splicing regulator, RNA Binding Fox-1 Homolog 1 (Rbfox1) is markedly induced during the postnatal period in the heart. Using immunofluorescence, qRT-PCR, and electrophysiological assessment, we have demonstrated that ectopic Rbfox1 expression is sufficient to promote maturation in human pluripotent stem cells-derived cardiomyocytes (iPSCs-CMs) and rat neonatal myocytes (NRNM) at functional, morphological and molecular levels. Furthermore, we identified a

putative enhancer of Rbfox1 (MyoM-En) which also confers with the postnatal temporal expression of Rbfox1. We also found the presence of super-enhancer markers such as enhancer RNA (eRNA), H3K27ac, and H3K4me associated with MyoM-En.

In conclusion, we uncovered the splicing factor Rbfox1, a part of the molecular drivers for cardiomyocyte maturation. By dissecting the functional regulation of the fetal-to-adult splicing events during maturation may also provide a better understanding of the pathogenesis of heart diseases, since a failing heart shows fetal-like features in the transcriptome. Modulating the Rbfox1 and its downstream activities could serve as a molecular target to promote cardiomyocyte maturation for disease modelling and cell-based therapy, as well as heart failure.