ABSTRACT

Coxsackievirus B3 (CVB3) induced viral myocarditis, characterized by inflammation and cell death in the myocardium, is one of the leading causes of sudden unexpected death in infants and young adults. Both direct virus- and immune-mediated injuries contribute to the damage in the infected organs. A clear understanding of the virus-induced host cell signaling alterations would be key to elucidating the pathogenesis of viral myocarditis and to improve therapeutic strategies. Recently discovered microRNAs (miRNAs) are small endogenous non-coding RNAs widely involved in gene regulation controlling developmental processes and disease pathogenesis including cardiac diseases and viral infections. In this dissertation, the main objective is to investigate the roles of miRNAs in CVB3 replication and pathogenesis of myocarditis. I hypothesize that 1) CVB3 infection alters host miRNA expression profiles to benefit its own replication; and 2) the dysregulated miRNAs contributes to the damage and dysfunction of cardiomyocytes. I used in vitro (cultured cells) and in vivo (mouse) models to explore the changes of host miRNAs' expression during CVB3 infection. miRNA microarray and quantitative-reverse transcription-PCR (q-RT-PCR) revealed that miR-126, miR-203 and miR-21 were upregulated by CVB3 infection. Further studies on these three miRNAs demonstrated their unique roles in regulating viral replication and cellular pathology in the myocardium. miR-126 was induced by CVB3 infection through the ERK1/2-ETS1/2 signal pathway. I found that increased miR-126 in turn enhanced activation of ERK1/2 and degradation of β-catenin through targeting SPRED1, LRP6 and WRCH1. This targeting benefited CVB3 replication and promoted virus-induced cell death. miR-203 was upregulated by the activation of the PKC/AP-1 cascade during CVB3 infection. I showed that miR-203 targeted ZFP-148 and supported cell survival and growth, which provided favorable environment for CVB3 replication. I further conducted the first investigation on the role of miR-21 in cell-cell connections among cardiomyocytes during CVB3 infection. I proved that miR-21 upregulation induced desmin degradation and desmosome disorganization via ubiquitin-proteasome pathway by targeting YOD1 and that miR-21 directly targeted VCL and disrupts fascia adherens. Together, my findings have shed light on the host-virus interactions in signal transduction pathways and provided new therapeutic strategies against CVB3-induced heart diseases.