microRNA regulatory networks in the brainstem underlie hypertension development

Danielle DeCicco

Hypertension affects ~50 million adults in the U.S. with 90-95% of cases having no known medical cause. This study aims to elucidate and model the mechanisms by which microRNAs (miRNAs) regulate autonomic control networks driving hypertension development. Correlational models were constructed based on miRNA and mRNA data for two different regions of the brainstem: the nucleus tractus solitaries (NTS) and the rostral ventrolateral medulla (RVLM) in the Spontaneous Hypertensive Rat (SHR) compared to Wistar Kyoto (WKY) controls. Using a high-throughput assay for 419 miRNAs in the SHR and WKY at three key stages of hypertension development, significant differences appear in 7 miRNAs of the NTS, a key nucleus in the brainstem capable of modulating blood pressure, and 7 miRNAs of the RVLM. miRNA downstream targets were predicted using the MirWALK database and validated using high-throughput qPCR of 144 targets corresponding to catecholaminergic processes and neuromodulation. DAVID pathway analysis tool, in conjunction with an extensive literature search for prior network knowledge, and the above expression data were used to determine processes specific to three main cell types—neurons, microglia and endothelial cells involved in blood pressure regulation. These networks impact hypertension by modulating the pathways, such as angiotensin II signaling and leukotriene-based inflammation known to have physiological effects. Network alterations were stage- and region-dependent. Results show a broad concordance between the miRNA dynamics and target gene expression and transcription factor expression, implicating these miRNAs as players in the aberrant dynamics of regulatory networks contributing to hypertension.