Title: Modeling microRNA Regulatory Network Changes in the Brainstem during Hypertension Development

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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. Multi-scale cell-type and tissue-type specific correlational models were constructed based on miRNA, mRNA and transcription factor expression data for two different regions of the brainstem: the nucleus tractus solitarius (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 6 miRNAs of the NTS, a key nucleus in the brainstem capable of modulating blood pressure, and 17 miRNAs of the RVLM. miRNA downstream targets were predicted using the MirWALK database and validated using high-throughput qPCR of 150 targets corresponding to catecholaminergic processes and neuromodulation. Transcription factors implicated in the regulation of the miRNAs and their respective targets were evaluated via chromatin immunoprecipitation. DAVID pathway analysis tool, in conjunction with an extensive literature search for prior network knowledge, and the above expression data was used to determine processes specific to three main cell types--astrocytes, microglia and neurons 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, target gene expression and transcription factor expression, implicating these miRNAs as players in the aberrant dynamics of regulatory networks contributing to hypertension. Future work includes obtaining a more-refined time course of data to incorporate into the model as well as validating model simulations of hypertension development and refining the network to emphasize the key mediators of blood pressure regulation. Finally, we hope to be able to integrate these three cell-type specific models to simulate the overall effect of miRNA changes in the brainstem contributing to hypertension development.

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