Examining the Coding and Non-Coding Regions of Enhancer Landscapes in Vascular Smooth Muscle Cells (VSMCs) Stimulated with Angiotensin II

Mandi, Varun

Activation of aortic vascular smooth muscle cells (VSMCs) by the hormone Angiotensin II (Ang II) is a critical event in the development of atherosclerosis and hypertension. In addition, enhancers play crucial roles in cell-type-specific transcription and gene expression via interaction with transcription factors (TFs) and cooperation with long non-coding RNAs (lncRNAs). Ang II-induced gene expression in VSMC is unknown and was therefore examined in this study. Basal and Ang II-regulated enhancer repertoires were identified by ChIP-seq with antibodies to key enhancer marks (namely H3K4me1 and H3K27Ac), in rat VSMCs before and after Ang II stimulation. Data showed putative active enhancers were associated with the expression of 873 nearby genes in. I then: (i) validated the expression of nearby genes including lncRNAs regulated by Ang II by RT-qPCR, (ii) performed de novo motif analysis to identify transcription factor binding sites and (iii) cloned enhancer fragments into reporter plasmids to demonstrate their Ang II responsiveness in VSMC. Results showed altered activity states in several nearby genes and lncRNAs, in cultured VSMC (in vitro) and in rat aortas (ex vivo). Lnc-Ang26 and lnc-Ang184, which overlap with enhancer regions, showed a fold-over-control increase in gene expression of 20.94 and 8.42 in vitro, and 7.86 and 1.59 ex vivo. With the Jasper Database, it was found that active enhancers were enriched with binding sites for several key TFs including c-Fos and c-Jun (AP1), as well as ETS-1, both known to be involved in Ang II-mediated gene transcription. These results provide novel information about VSMC-specific enhancers, TF motifs in Ang II-regulated enhancers, and their functional roles in the regulation of genes relevant to cardiovascular disease.

Awards Won:
Second Award of $2,000