The dark matter of the genome and blood pressure regulation – modeling non-coding genetic mechanisms in cellular models and rats

Aron M. Geurts[1], Hong Xue[1], Manoj Mishra[2], Rajan Pandey[2], Bhavika Therani[2], Michael Grzybowski[1], Mark Vanden-Avond[1], Yong Liu[2], Andrew S. Greene[3], Sridhar Rao[4], Pengyuan Liu[2], Allen W. Cowley, Jr.[1], & Mingyu Liang[2]

[1]Department of Physiology, Medical College of Wisconsin, Milwaukee, WI, USA. [2] Department of Physiology, University of Arizona, Tucson, AZ, USA. [3]The Jackson Laboratory, Bar Harbor, ME, USA. [4]Versiti Blood Research Institute, Milwaukee, WI, USA.

Most single nucleotide polymorphisms (SNPs) associated with complex human complex traits such as blood pressure (BP) are located noncoding regions of the genome and have small effect sizes in the general population. Many SNPs have no apparent linkage with protein-coding variants and therefore must exert their effects through other mechanisms. Functional studies in controlled model systems are essential to ascertain the effect of these noncoding loci on gene expression and phenotypes, but such direct testing is challenging and largely absent, contributing to a critical gap between genetic discoveries and physiological understanding. A collaborative multi-laboratory effort has taken on this challenge of modeling BP-associated non-coding genetic variation through precise CRISPR-Cas9 engineering in contextually relevant human iPSC-derived cell models and orthologous sequences in a rat model of human hypertension, the Dahl salt-sensitive rat. We highlight examples of SNPs and loci which have tissue-specific and or sex-specific effects on local gene expression and intermediate physiological mechanisms to ultimately modify the blood pressure response to a high salt diet challenge. These remarkable effects indicate that noncoding genomic segments may have profound impact on phenotypes which can be effectively modeled in permissive genomic backgrounds with informative stressors to uncover novel genetic mechanisms.