Genetics of Human Hypertension

Ashok Kumar
Department of Pathology, New York Medical College, Valhalla, USA

Genome wide association studies (GWAS) have established a link between hypertension and a plethora of single nucleotide polymorphisms in the renin angiotensin aldosterone system (RAAS axis). However, majority of these SNPs are in the regulatory, non-coding part of the RAAS genes. Over the past several years we have tried to understand the role of haplotypes, formed by linkage disequilibrium amongst various SNPs, in bringing about variable transcriptional regulations of RAAS genes including, the hAGT, the hAT1R, and the hCYP11B2. These haplotypes, and not the individual SNPs, are the principal determinants of inter-individual variability in gene transcription and are closely linked to hypertension in humans. We have generated novel "humanized" transgenic mice to study the precise role of these gene-haplotypes in affecting transcriptional regulation under basal and various pathophysiological settings including, age, gender, and diet. Double transgenic mice with -6A and +1164 A/G polymorphism have been used to study the role of introns in hAGT gene-regulation; this paradigm-shifting model has, for the first time, gave insight into the mechanisms behind recently reported GWAS association of +1164A with human hypertension. As role of introns in gene-regulation is largely unknown, our unique models are crucial to the development and advancement of this field. Additionally, hAGT gene has an A/C SNP at -20 and -20A allele creates an estrogen response element that binds differentially to estrogen receptor and USF. This could explain the inter-individual variability amongst pre-menopausal and post-menopausal women. Double transgenic mice with -20 A/C containing hAGT haplotypes will be used to elaborate genetics of female hypertension. This too is an important arm of our project as both, systolic and diastolic blood pressures are higher in postmenopausal women that are further increased by hormone replacement therapy (HRT). Finally, our humanized mice with different haplotypes of hCYP11B2 gene are key to understand the effects of diet and age on the transcriptional regulation of this gene, which is central to regulation of sodium balance and blood pressure. In this regard, -344T containing haplotype of the hCYP11B2 is associated with human hypertension and significantly increases blood pressure in transgenic mice when compared to mice with -344C haplotype. We have examined the role of both of the risk alleles of AGT and Cyp11B2 genes on blood pressure regulation. Thus, not only will these humanized mice help us understand variable transcriptional regulation of hAGT and hCYP11B2 under altered pathophysiological settings like, high-salt diet, aging, and gender differences; but also, they can usher in personalized medicine where physicians can fine-tune patient therapy with the knowledge of their risk haplotype. These transgenic mice can also be used to understand pharmacogenomics and find new anti-hypertensive therapies.