A pathogenetic role for microRNAs in essential hypertension at last?

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As a complex (or polygenic) genetic trait, essential hypertension is determined by the interplay between many genetic variants and several environmental factors. Despite an enormous and continuous effort from the clinical and research communities, much of the genetics of essential hypertension remains elusive. The classic approach for identifying disease-causing genes, that is, linkage analyses, brought to the identification of genes responsible for genetic—and thus rare—forms of hypertension; in contrast, the candidate gene approach has led to results that are subject to controversy and definitely less straightforward than those from linkage analysis. As a matter of fact, essential hypertension is a multifactorial and multigene disease, and thus the study of its etiology must be approached with complex bioinformatic and biostatistic techniques for studying gene-environment interaction and synergism among many hypertension-associated single nucleotide polymorphisms (SNPs). Given its multifactorial nature, a single SNP may be able to modify the disease phenotype only together with other SNPs and in an appropriate environmental context.

MicroRNAs (or miRs) are now considered fundamental components of the regulatory system of eukaryotic gene expression. They act posttranscriptionally through cis-regulatory sites, located typically in 3′-untranslated regions (UTRs) of mRNAs, usually significantly reducing protein expression without completely inhibiting the targeted mRNAs. Interestingly, more than 20,000 SNPs of miRNA target sites have been catalogued thus far and, over the last few years, several independent studies have claimed to associate some of them with genetic disorders ranging from cancer to Parkinson disease and hypertension. For example, it was shown that rs5186—an SNP in the 3′-UTR of the human angiotensin II type 1 receptor (AGTR1) messenger RNA, and previously associated with hypertension—mediates allele-specific targeting of miR-155 to AGTR1, thereby modulating its protein level. Other SNPs residing on the 3′-UTRs of renin-angiotensin system genes have been described, leaving room for speculation on their potential role as causal variants of essential hypertension.

Following up their previous results from a genetic linkage study, Wei and colleagues reveal in the current issue of Circulation: Cardiovascular Genetics that the ATP6V0A1 3′-UTR common variant T3246C alters gene expression through differential binding to the microRNA miR-637. The ATP6V0A1 gene, located in chromosome 17q21, encodes the α1 subunit of vacuolar H+-translocating ATPase, a heteromultimeric complex responsible for acidification of the secretory pathway compartment that includes secretory granules, such as the catecholamine storage vesicles of the adrenal medulla. A main component of chromaffin granules is chromogranin A (CHGA), the hormonal precursor of at least 4 different bioactive peptides, including the catecholamine release inhibitor catestatin. The same authors previously established that alterations in the level and/or activity of this integral membrane complex correlate with an impaired vesicular acidification process that can ultimately lead to an altered formation and an incorrect trafficking of the chromaffin granules. At the clinical level, “granins” have been shown to be important in patients with essential hypertension in which an increased plasma level of the prohormone CHGA and a reduced hematic concentration of the CHGA-derived peptide catestatin have been assessed. Interestingly, the above-mentioned allelic variation of ATP6V0A1 (rs9386761) was found to be associated with plasma catestatin concentration, chromogranin A:catestatin ratio, and systemic blood pressure in the population. The ATP6V0A1 3′-UTR variant T3246C could thus influence the levels of both CHGA and catestatin subsequent to the alteration of vacular pH by modulating either proteolysis of the precursor or its exocytotic secretion.

To test this hypothesis, Wei et al first demonstrated that compared with the wild-type T3246 allele, the risk haplotype carrying the C allele in the ATP6V0A1 3′-UTR significantly reduced the luminescence of a luciferase reporter gene. This result was confirmed by an in vitro translation assay, in which protein expression of the blood pressure–associated variant was found to be clearly reduced. Then, using an elegant approach with fluorescent chimeric proteins, the authors demonstrated how the expression of the T3246C variant alone was responsible for granular pH perturbation (ie, alkalization) in rodent pheochromocytoma (PC12) cells treated with a selective inhibitor of the V-ATPase complex. As hypothesized, this disruption of secretory granule core acidification significantly increased CHGA processing while reducing its regulated secretion. As suggested by the same authors, this result could theoretically explain why plasma
concentrations of CHGA and catestatin are usually lower in the population harboring the T3246C variant. Finally, to clarify the molecular mechanism whereby the presence of T3246C could be causal to the alteration of granule acidification, the authors investigated whether a microRNA binding site was located in that region. Computational analysis of the sequences flanking the T3246 locus identified a motif complementary to miR-637, with a higher match for the C variant, raising the possibility of a more efficient translational repression for messengers bearing the C allele. Both overexpression (miR mimic) and inhibition (antagomiR) approaches in PC12 cells supported the evidence of differential miR-637–mediated regulation of ATP6V0A1, with the blood pressure–associated (C allele) haplotype showing a higher affinity for the microRNA compared with the wild-type (T allele) one.

Data presented by Wey et al\(^{12}\) are fascinating and support the hypothesis that a “better” miR-637 binding site within the ATP6V0A1 3′ UTR contributes to the association of this region with plasma catestatin concentration and CHGA:catestatin ratio and, ultimately, with systemic blood pressure in the population. Although very interesting, more definitive and compelling evidence is needed to conclusively link T3246C to a mechanism in human cells.

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None.

**References**


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