A Candidate Hypertension Gene
Will SPON1 Hold Salt and Water?

Scott Heximer, Mansoor Husain

Hypertension affects >20% of the general population, and yet its etiologic basis remains unknown in the vast proportion of those affected.1 Hypertension greatly increases the risk of stroke, myocardial infarction, congestive heart failure and renal dysfunction thus making it an important focus of clinical research. Although pharmacological reductions in blood pressure have been shown to decrease the incidence of these adverse consequences,2 large numbers of hypertensive patients go undiagnosed, undertreated, or are nonresponsive to lifestyle modifications and medical therapy.1 As such, there remains a pressing need for an improved understanding of the mechanisms underlying hypertension.

Recent advances in genomic and proteomic analyses have led to the discovery of Mendelian forms (monogenetic traits) of hypertension.3,4 Although rare, these mutations which led to the discovery of Mendelian forms (monogenetic traits) of hypertension greatly increases the risk of stroke, myocardial infarction, congestive heart failure and renal dysfunction thus making it an important focus of clinical research. Although pharmacological reductions in blood pressure have been shown to decrease the incidence of these adverse consequences,2 large numbers of hypertensive patients go undiagnosed, undertreated, or are nonresponsive to lifestyle modifications and medical therapy.1 As such, there remains a pressing need for an improved understanding of the mechanisms underlying hypertension.

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Using this approach, Clemitson and colleagues have identified SPON1 as a novel candidate hypertension gene from within a region of rat chromosome 1 containing a blood pressure QTL.8 It may be of further relevance to human hypertension that a similar blood pressure QTL is found on chromosome 1 by combining phenotypic and genetic analyses of reciprocal intercrosses between SHR and WKY rat strains.11 Substrain analysis allowed dissection of the original blood pressure QTL region into smaller blood pressure QTL regions named BP1 and BP2.12 In the current study, a congenic SHR strain containing WKY sequences at the BP1 QTL is bred against SHR (Figure, A) to reduce the genomic size of the WKY region to a point where targeted sequencing and expression profiling become feasible. The region identified contained 18 known and 3 novel genes. Following sequence and expression profile comparisons between numerous parental and congenic strain combinations, the authors show that increased SPON1 mRNA and protein expression is consistently observed in animals from which BP1 genomic region is derived from the SHR rather than WKY strain. Accordingly, they contend that these studies warrant investigation of this gene as a novel positional candidate gene in the control of blood pressure in rats and humans (Figure, B).

The SPON1 gene product is F-spondin, a protein identified as a candidate floor plate-derived adhesion protein that was highly expressed during development of the nervous system. Early work on this protein indicated that it could promote neurite attachment and outgrowth in the cultured spinal cord and sensory neurons.17 F-spondin is not highly expressed in adult nerve tissue, but it is highly expressed in developing17–19 and damaged nerve tissue leading to the hypothesis that upregulation of F-spondin promotes sensory nerve regeneration. The specific TSR domains that are required for this effect, and the extent to which F-spondin acts as an anchor protein relative to a trophic factor, remain to be established. It is tempting to speculate that F-spondin may also regulate sensory nerve guidance in the developing kidney or during pathophysiological stress and that this may modulate kidney function. The authors point to the interesting possibility that higher SPON1 expression in the vasculature of the developing kidney or during pathophysiological stress and that this may modulate kidney function. The authors point to the interesting possibility that higher SPON1 expression in the vasculature of the developing kidney or during pathophysiological stress and that this may modulate kidney function. The authors point to the interesting possibility that higher SPON1 expression in the vasculature of the developing kidney or during pathophysiological stress and that this may modulate kidney function.
kidneys contributes to the hypertensive phenotype in SHR rats, and that this may mediate strain-dependent morphological changes in the distal afferent arterioles. In support of the notion that F-spondin is involved in blood vessel development, F-spondin can promote vascular smooth muscle cell (VSMC) growth and exert antiangiogenic effects by inhibiting integrin signaling on endothelial cells. Alternatively, F-spondin may regulate blood pressure by direct modulation of VSMC signaling. Recent evidence suggests that the TSRs in the thrombospondin family prototype TSP-1 activate CD36 on the surface of VSMCs and endothelial cells to effect reduced NO-mediated accumulation of cGMP. If F-spondin TSRs had a similar inhibiting effect on NO-induced cGMP signaling, the attenuation of NO-mediated vasodilation may affect both renal and peripheral resistance vessels.

A more definitive strategy will be required to evaluate the functional significance of altered SPON1 expression. Organism-wide or tissue-specific transgenic strategies to overexpress or delete SPON1 will be required to evaluate whether simply changing its expression in the absence of additional genomic differences within the BP1 QTL is sufficient to modulate blood pressure in rats or mice. Such strategies will also provide the animal models in which more specific biological mechanisms underlying the pathogenesis of SPON1-related hypertension will need to be elucidated.

The current study represents a significant advance in the strategies used to identify positional candidate genes in QTLs for blood pressure and other physiologic traits. The absence of a molecular explanation for the observed increase in SPON1 expression thus proving it is not simply a consequence of changes in pathophysiologic status of the kidneys or other tissues.

Dissection of a blood pressure QTL on rat chromosome 1 leads to identification of SPON1 as a novel candidate gene for hypertension. A, Shown is the breeding strategy used to reduce the size of the genomic region on chromosome 1 containing a blood pressure QTL. WKY-derived (black) sequences are shown on a SHR (white) genetic background. Recombination within the WKY-derived region produced 2 mutually exclusive congenic substrains, 1 of which showed differences in blood pressure regulation compared with SHR. Position of the candidate blood pressure regulation locus (shaded) is shown in relation to the original QTL and to WKY-derived sequences in the new congenic sub-strains. B, Expression profiling revealed increased expression of SPON1 and its gene product F-spondin in SHR-expressed compared with WKY-derived sequences. It is hypothesized that the higher level of F-spondin produced from SHR-derived sequences affects developing kidneys, blood vessels, but possibly also other cardiovascular tissues to produce increased blood pressure levels.

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None.

References

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