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. 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 pharmacologic reductions in blood pressure have been shown to decrease the incidence of these adverse consequences, large numbers of hypertensive patients go undiagnosed, undertreated, or are nonresponsive to lifestyle modifications and medical therapy. 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 (monogenic traits) of hypertension. Although rare, these mutations which mainly involve altered renal salt handling, provide a molecular basis for understanding the critical role of the kidney during normal blood pressure regulation. By contrast, our understanding of the relative contributions of kidney, heart, CNS, and blood vessel function to blood pressure variations in the general population is complicated by the fact that spontaneous hypertension typically arises as a complex quantitative trait affected by differing combinations of genetic and environmental factors. A number of quantitative trait loci (QTL) associated with hypertension have been identified in both animal disease models and human patients, however the affected gene(s) at these sites have remained elusive owing to the large size and complexity of the regions identified. The use of congenic rodent strains to reduce the genomic size of QTLs is an important advance in the field (Reviewed in ). Indeed, an article in this issue of Circulation Research highlights the potential of this strategy.

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. It may be of further relevance to human hypertension that a similar blood pressure QTL is found on arm of chromosome 1 by combining phenotypic and genetic analyses of reciprocal intercrosses between SHR and WKY rat strains. Substrain analysis allowed dissection of the original blood pressure QTL region into smaller blood pressure QTL regions named BP1 and BP2. In the current study, a congenic SHR substrain 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 substrain 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, the prototypical member of a group of nonthrombospondin members of the thrombospondin type I repeat (TSR) superfamilly of proteins. It is a multifunctional protein containing 6 TSRs in its carboxyl terminus and 2 unique domains in its amino terminus. In the case of thrombospondin, the TSR domains can attract multiple different cells types through their ability to bind extracellular components including laminin, fibronectin, heparin, heparin sulfate proteoglycan, and CD36. In the case of the F-spondin TSR domains, the relevant extracellular binding partners have not been rigorously determined despite strong data supporting its role as an attachment factor for different cells.

F-spondin was originally 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. F-spondin is not highly expressed in adult nerve tissue, but it is highly expressed in developing 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 pathophysiologic 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...
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 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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