

In the 1920s a vasodepressor was discovered in urine; later called kallikrein, it is a protease which liberates the vasodilator lysyl-bradykinin from its kininogen precursor (1). By the 1930s, diminished urinary kallikrein excretion was noted in human hypertensives, a finding rediscovered in the 1970s (2). Diminished kallikrein excretion is an early trait in people at genetic risk of hypertension (3, 4), and pedigree studies suggest that a gene for high urinary kallikrein may protect against hypertension (5).

Parallel work on rodents found diminished kallikrein excretion in the spontaneously hypertensive rat (SHR) (6), and genetic linkage between a kallikrein locus and blood pressure (7).

In this issue, Wang et al. (8) report exploratory work on somatic cell gene therapy as treatment for hereditary hypertension, initially in the SHR. Their strategy was remarkably simple: they intravenously infused naked DNA encoding human renal kallikrein into SHRs, and noted a prolonged fall in blood pressure. The SHRs expressed human kallikrein, and reversal of the blood pressure fall after kallikrein inhibition documented the role of expressed kallikrein in blood pressure reduction.

Do these results suggest that somatic cell gene therapy for complex disorders, such as hypertension, might be as simple as a plasmid preparation? Like all innovative science, the work of Wang et al. (8) raises perhaps even more questions than it answers, such as:

Is intravenous injection of naked DNA an efficient or long-lasting form of gene therapy? Intravenous DNA injections can give rise to extended systemic expression in rodents (9). Improved methods of gene delivery, such as incorporation of the gene into a retroviral vector for dividing cells (10), an adenoviral vector for non-dividing cells, or a fusogenic liposome (11), might improve the process. However, unless a population of progenitor or "stem" cells for the target tissue can be identified and transduced, somatic cell gene therapeutic strategies face the prospect of repeated administration of the gene.

Where did the expressed kallikrein act to lower blood pressure? Renal kallikrein-like enzymatic activities are normally found not just in kidney, but also in vascular wall (12). Improved cell-type-specific expression might be accomplished by a variety of means, including use of tissue-specific promoters, vector envelope-targeting towards appropriate cell surfaces (13), or catheter-delivery to specific vascular segments or organs.

Human essential hypertension is a complex trait, with both genetic and environmental determinants (14), and the genetic component is likely to be polygenic (14). In such an etiologically heterogeneous process, how might one select organisms best suited for somatic cell gene therapy with a very specific gene, such as kallikrein?

How will the recipient immunologically tolerate the gene product or vector? Although Wang et al. (8) showed that mouse

recipients of the human kallikrein gene did not mount a humoral immune response, recipient inflammatory responses against gene transfer vectors have been an impediment to successful gene therapy (15).

In light of widespread expression of intravenous DNA (8, 9), does such DNA gain access to the germ line?

Nonetheless, the results of Wang et al. (8) are bold, provocative, and elegant in their simplicity. Such studies point the way toward the possibility of fundamentally new therapeutic options in the very complex traits which constitute many (if not most) human diseases.

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## References

- Wehrle, E. 1970. Discovery of the most important kallikreins and kallikrein inhibitors. Chapter 1, in: *Handbook of Experimental Pharmacology*. Volume 25. Bradykinin, kallidin and kallikrein. Springer-Verlag, New York. 1-6.
- Margolius, H. S., R. Geller, J. de Jong, J. J. Pisano, and A. Sjoerdsma. 1971. Altered urinary kallikrein excretion in human hypertension. *Lancet*. 2:1063-1065.
- Zinner, S. H., H. S. Margolius, B. Rosner, and E. H. Kass. 1978. Stability of blood pressure rank and urinary kallikrein concentration in childhood: an eight-year followup. *Circulation*. 58:908-915.
- Martinez, J. A., T. T. Dao, M. T. Kailasam, R. J. Parmer, and D. T. O'Connor. 1995. Renal kallikrein excretion: early changes in subjects at genetic risk for essential hypertension. *J. Investigative Med.* 43(Suppl 1):166A. *Clin. Res.* In press.
- Berry, T. D., S. J. Hasstedt, S. C. Hunt, L. L. Wu, J. B. Smith, K. O. Ash, H. Kuida, and R. R. Williams. 1989. A gene for high urinary kallikrein may protect against hypertension in Utah kindreds. *Hypertension*. 13:3-8.
- Geller, R. G., H. S. Margolius, J. J. Pisano, and H. R. Keiser. 1975. Urinary kallikrein excretion in spontaneously hypertensive rats. *Circ. Res.* 36(6 Suppl 1):103-106.
- Pravenec, M., V. Kren, J. Kunes, A. G. Scicli, O. A. Carretero, L. Simonet, and T. W. Kurtz. 1991. Cosegregation of blood pressure with a kallikrein gene family polymorphism. *Hypertension*. 17:242-246.
- Wang, C., L. Chao, and J. Chao. 1995. Direct gene delivery of human tissue kallikrein reduces blood pressure in spontaneously hypertensive rats. *J. Clin. Invest.* 95:1710-1716.
- Zhu, N., D. Liggitt, Y. Liu, and R. Debs. 1993. Systemic gene expression after intravenous DNA delivery into adult mice. *Science (Wash. DC)*. 261:209-211.
- Anderson, W. F. 1992. Human gene therapy. *Science (Wash. DC)*. 256:808-813.
- Morishita, R., G. H. Gibbons, K. E. Ellison, M. Nakajima, H. von der Leyen, L. Zhang, Y. Kaneda, T. Ogihara, and V. J. Dzau. 1994. Intimal hyperplasia after vascular injury is inhibited by antisense cdk 2 kinase oligonucleotides. *J. Clin. Invest.* 93:1458-1464.
- Maddedu, P., T. Gherli, P. P. Bacciu, M. Maioli, and N. Glorioso. 1993. A kallikrein-like enzyme in human vascular tissue. *Am. J. Hypertension*. 6:344-348.
- Kasahara, N., A. M. Dozy, and Y. W. Kan. 1994. Tissue-specific targeting of retroviral vectors through ligand-receptor interactions. *Science (Wash. DC)*. 266:1373-1376.
- Ward, R. 1990. Familial aggregation and genetic epidemiology of blood pressure. In *Hypertension: Pathophysiology, Diagnosis and Management*. J. H. Laragh and B. M. Brenner, editors. Raven Press, NY. 81-100.
- Simon, R. H., J. F. Engelhardt, Y. Yang, M. Zepeda, S. Weber-Pendleton, M. Grosman, and J. M. Wilson. 1993. Adenovirus-mediated transfer of the CFTR gene to lung of nonhuman primates: toxicity study. *Human Gene Ther.* 4:771-780.