Angiotensin-Converting Enzyme (ACE) Polymorphisms, Angiotensin II, ACE Inhibitors and Glomerulosclerosis – A Hypothesis

P.		Roy-Chaudhury ^a
I.H.	Izhar H.	Khan ^b

^aRenal Division, Beth Israel Hospital, Harvard Medical School, Boston, Mass., USA;

^bDepartment of Medicine and Therapeutics, University of Aberdeen, UK

P. Roy-Chaudhury, Renal Division, DA 517, Beth, Israel Hospital and Harvard Medical School, 330, Brookline Avenue, Boston, MA 02215 (USA)

Dear Sir,

Glomerulosclerosis (characterized by mesangial cell proliferation and matrix accumulation) is a final common pathway, which regardless of the initial pathology, often results in end-stage renal disease. An intriguing and as yet unanswered puzzle in clinical nephrology is the tremendous inter-individual variation in the rate of progression of glomerulosclerosis, even when the original disease is the same, and indeed in many instances has become quiescent. Recent information about a polymorphism of the angiotensin-converting enzyme (ACE) gene in humans, however, has allowed us to speculate about a possible mechanism to explain the above finding. Thus we know that: (a) Humans have a polymorphism for the ACE gene and that individuals with the DD (deletion) genotype have higher plasma (and possibly tissue) ACE levels as compared to individuals with the II (insertion) or ID (heterozygous) genotypes. These patients (DD genotype) are also at greater risk of having a myocardial infarction [1]. (b) ACE inhibitors have now been clearly shown to delay the progression of both clinical and experimental glomerulosclerosis more effectively than other antihypertensive agents [2].

The mechanisms responsible for the above effects remain unknown. Hemodynamic factors undoubtedly play a role but ACE inhibitors may also have direct inhibitory effects on the proliferation of mesangial cells and on the production of matrix proteins (both key features of glomerulosclerosis). This is because angiotensin II is a potent growth factor which induces mesangial cell hypertrophy/proliferation. Angiotensin II also increases collagen production, possibly by up-regulating TGF- β [3, 4].

How does one put all this information together? We suggest that individuals with the DD genotype have increased levels of plasma and tissue ACE which up-regulates production of angiotensin II and TGF- β . The net result is an increase in cellular hypertrophy and proliferation together with increased matrix synthesis. Individuals with the DD genotype would therefore be shifted towards a baseline pro-inflammatory, pro-sclerotic state and would be at greatest risk of progressive glomerulosclerosis (or athero-genesis [1]). A natural corollary is that these patients would benefit most from ACE inhibitor therapy. For example, it is possible that the decreased rate of progression of renal failure in diabetics treated with an

ACE inhibitor in the recent Collaborative Study [2] occurred mainly in patients with the DD genotype.

Finally, the above hypothesis suggests a number of fascinating avenues for future laboratory and clinical investigation. These include: (a) The relative risk for individuals with the DD genotype to develop glomerulosclerosis, and the rate of progression of glomerulosclerosis in these patients as compared to those with the ID and II genotypes.

Identification of a possible etiologic role for the DD genotype with regard to the aggressive glomerulosclerosis that occurs in African Americans in the United States.

The importance of the DD genotype in other chronic inflammatory disorders characterized by cellular hypertrophy/proliferation and matrix production (rheumatoid arthritis, interstitial lung diseases, uveitis, chronic transplant rejection).

References

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