S7

The Mechanism of Vascular Injury in Diabetes
- Lessons from Cells, Organelles and Transgenic Animals -

Hiroshi Yamamoto, M.D., Ph.D.

Department of Biochemistry and Molecular Vascular Biology
Kanazawa University Graduate School of Medical Science, Japan

Microvessels are composed of endothelial cells and pericytes. They show peculiar changes in diabetes. Pericytes decrease (pericyte loss), while endothelial cells proliferate (angiogenesis) but with dysfunction (thrombogenesis). All of these changes were induced in vitro when each cell type was exposed to advanced glycation endproducts (AGE), non-enzymatically glycosylated protein derivatives which are formed at an accelerated rate during prolonged hyperglycemic exposure. And, those vascular cell responses were dependent on the presence of a cell surface receptor for AGE (RAGE).

Co-culture experiments revealed that loss of proximal interaction between the two cell types augments the microvascular derangement.

To evaluate in vivo the functional role of the AGE-RAGE system in diabetes-induced vascular injury, we then created a double transgenic mouse model in which RAGE is overexpressed in vascular cells and insulin-dependent diabetes develops early after birth. The RAGE-overexpressing animals exhibited advanced diabetic nephropathy exemplified by mesangial expansion and glomerulosclerosis, and this was prevented by the treatment with an inhibitor of AGE formation. Retinopathy indices were also exacerbated in the double transgenic model.

Lessons from the endothelial cell nucleus revealed that AGE ligands themselves, TNF-alpha and estradiol activate the transcription of RAGE gene, and that NF-kappa B mediates the induction by the former two, while the Sp-1

and estrogen receptor alpha complex mediates the estradiol induction.

Analysis of vascular cell-derived polysomal poly(A)+RNA led to the isolation of novel splice variants of RAGE mRNA coding for an N-terminally truncated protein and for a C-terminally truncated secretable form. The latter protein had an ability to capture AGE and to neutralize their action on endothelial cells, and was detected in human sera.

In conclusion, the AGE-RAGE system would seem to be a promising target for overcoming diabetic vascular complications. Circulating soluble RAGE could contribute to resistance against this life- and QOL-threatening disease.

References

1. Yamagishi, S. et al.: Advanced glycation endproducts-driven angiogenesis in vitro: Induction of the growth and tube formation of human microvascular endothelial cells through autocrine vascular endothelial growth factor. J. Biol. Chem. 272: 8723-30 (1997)
2. Yamagishi, S. et al.: Advanced glycation endproducts inhibit prostacyclin production and induce plasminogen activator inhibitor-1 in human microvascular endothelial cells. Diabetologia 41: 1435-41 (1998)
3. Tanaka, N. et al.: The receptor for advanced glycation endproducts is induced by the glycation products themselves and TNF-alpha through NF-kappa B, and by 17 beta-estradiol through Sp-1 in human vascular endothelial cells. J. Biol. Chem. 275: 25781-90 (2000)
4. Yamamoto, Y. et al.: Development and prevention of advanced diabetic nephropathy in RAGE-overexpressing mice. J. Clin. Invest. 108: 261-8 (2001)