Glomerular sclerosis and activation of intraglomerular renin-angiotensin system (An experimental model of glomerular sclerosis induced by *in vivo* transfection of genes for renin and angiotensinogen and gene therapy by *in vivo* transfection of antisense oligonucleotide)

Yoshihiro Fujiwara, Naohiko Ueda, Yasufumi Kaneda, Enyu Imai,
Satoshi Ochi, Akira Wada, Takenobu Kamada
(First Department of Medicine, Osaka University
Institute for Molecular and Cellular Biology, Osaka University)

Summary

We introduced human genes for renin and angiotensinogen into the rat kidney by hemagglutinating virus of Japan(HVJ)-liposome method to elucidate the local effect of overexpressed angiotensin II in the glomerulus *in situ*. Three days after transfection human renin was detected in the glomeruli by immunohistochemistry. Seven days after transfection extracellular matrix(ECM) was expanded in the glomeruli and α-smooth muscle actin was expressed in the mesangial cells. These results suggest that locally activated renin-angiotensin system induces glomerular sclerosis and a phenotypic change in mesangial cells.

The intraglomerular expression of TGB-β has been raported to increase in experimental and clinical glomerular diseases and there is a possibility that angiotensin II exerts its action on the glomeruli at least in part by inducing mesangial cells to produce TGF-β. We tried to suppress the glomerular lesion of an experimental glomerulonephritis by introducing antisense oligodeoxynucleotide(ODN) for TGF-β into the mesangial cells. Intravenus infusion of anti-Thy-1 antibody(OX-7) into rats causes mesangioproliferative glomerulonephritis characterized by glomerular hypercellularity and ECM expansion in glomeruli. Two days after infusion of OX-7 antisense ODN for TGF-β was introduced into the left kidney by HVJ-liposome method. Nine days after infusion of OX-7 rats were sacrificed and their kidneys were examined histologically. Intraglomerular accumulation of ECM was suppressed in the left kidney compared with the right kidney of the same rat. In addition expression of α-smooth muscle actin was also suppressed by the introduction of antisense ODN for TGF-β. In conclusion, inhibition of TGF-β expression by antisense ODN can suppress the glomerular lesion of an experimental glomerulonephritis.