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Differential Regulation of Vascular Endothelial Growth Factor (VEGF) in the Kidneys : Possible Mechanism for Gender Vulnerability of Progression of Renal Disease

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Background: Male gender is known to be associated with a more rapid progression of renal disease independent of blood pressure, dietary protein intake or serum levels of lipid. Despite several reports about possible mechanisms explaining gender-related difference in renal disease progression including the differences in renal structure, hemodynamics and renin-angiotensin system or direct effect of sex hormone, the mechanisms involved remain unclear. Recently, we have reported the key role of renal vasculopathy in progressive renal disease (JASN 13:806, 2002).

Method: To investigate the gender vulnerability in progressive renal disease and potential role of vasculopathy, we analyzed micro- and macrovascular changes in the 5/6 remnant kidney models (RK) both in male (n=8) and female (n=10) Sprague-Dawley rats up to 12 weeks after renal mass reduction.

Results: At 12 weeks, there was no significant difference in blood pressure between male and female. Glomerular tuft area as well as an increase in RK weight/body weight was also comparable. However, renal scarring assessed by % glomerulosclerosis and tubulointerstitial fibrosis was more severe with higher serum creatinine and more proteinuria in male RK rats. Endothelial cell proliferation of peritubular capillaries (PTC) and PTC density were higher in female RK at 4, 8, 12 weeks after renal mass reduction. Macrovascular changes in preglomerular vessels (smooth muscle cell proliferation, medial wall thickening and adventitial fibrosis) were also less prominent in female RK rats. Interestingly, the expressions of VEGF and VEGF type 2 receptor (flk-1) in renal cortex assessed by immunohistochemistry were higher in female RK. To dissect the mechanism of sex hormone-induced vascular remodeling and VEGF regulation, we investigated the in-vitro effect of 17β-estradiol (10 nM, 17E) on proliferation and VEGF expression of renal tubular cells (murine medullary thick ascending limb cells, mTAL) and vascular smooth muscle cells (VSMC). 17E inhibited serum-induced proliferation with down-regulation of hypoxia-induced VEGF mRNA expression in VSMC. In contrast, treatment of mTAL cells with 17E resulted in upregulation of VEGF mRNA and protein by RT-PCR and Western blotting.

Conclusion: More favorable outcome of renal disease progression in female RK rats was associated with preservation of PTC and less preglomerular arteriopathy. Our data suggest the potential possibility of direct protective effect of estrogen on progressive renal disease by altering VEGF regulation in renal tubular cell and VSMC, which may protect the kidneys from hypoxic damage by prevention of both endothelial loss and VSMC proliferation.