see original article on page 1920

Nuclear receptors link gender dimorphism of renal disease progression

Y Guan[1,2]

Profound gender differences in the progression of chronic kidney disease (CKD) remain poorly understood. Differential expression of the genes for male- and female-specific proteins in the kidney has been proposed to account for this clinical phenomenon. Lu and colleagues provide evidence that the signaling pathways of the nuclear receptors ERα, AR and PPARα are associated with gender differences in CKD progression.

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Chronic kidney disease (CKD) represents a major social, economic, and health problem in the world. Current pharmacological agents, including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, benefit only a sub-population of CKD patients. Novel therapeutic approaches based on mechanistic elucidation of renal function loss are therefore urgently needed.

It has long been known that in female CKD patients, deterioration of renal function is much slower than in male patients, which suggests that male- and female-specific genes may play an important role in modulating the function of the kidney. A 2.2-year follow-up of the 840 participants in the Modification of Diet in Renal Disease study revealed that female patients displayed less proteinuria and lower serum creatinine levels for given glomerular filtration rates than male patients, and the rate of decline in glomerular filtration rate was significantly slower in women. A metaanalysis involving 11 345 CKD patients further confirmed that women with non-diabetic CKD of various etiologies show a much slower decline in renal function over time than do men.[1] Also, this protective effect in females is markedly lost after menopause.[2] In various animal models of CKD, males display accelerated progression of renal damage as compared with females. In 5/6 nephrectomized rats, castration protected against the development of proteinuria, tubulointerstitial damage, and renal fibronectin accumulation in males but not in females.[3] Administration of estrogen to aging male rats or spontaneously hyperlipidemic rats ameliorated proteinuria and glomerular fibrosis.[4] Collectively, these observations clearly point to a gender difference in progression of renal injury in subjects with CKD. However, whether the presence of androgen or the absence of estrogen, or both factors combined, account for this disparity in renal disease progression is debatable. The mechanisms by which sex hormones regulate renal homeostasis are not yet fully understood.

The sex hormones estrogen and testosterone exert biological actions mainly via their corresponding nuclear receptors — estrogen receptor (ER) and androgen receptor (AR). Both ER and AR belong to the superfamily of nuclear receptor transcription factors, consisting of 49 transcription factors. Nuclear receptors govern the expression of genes involved in a diversity of biological processes, including reproduction, energy metabolism, lipid homeostasis, inflammation, and cell proliferation and differentiation.[5] AR and ERα are expressed in the kidney, where activation of both may mediate the effect of androgen and estrogen on renal function. Previous studies involving a transgenic model of renin-dependent hypertension (mRen2 transgenic rats) clearly demonstrated a role for AR in accelerating renal injury.[4] An AR-selective antagonist, flutamide, not only modestly attenuated hypertension but also completely reversed renal histological changes and albuminuria in this model. Consistently, mutation of AR (testicular feminization mutation (*tfm*)) resulted in lower blood pressure and reduced proteinuria in mRen2 transgenic rats.[4] Lu *et al.*[6] (this issue) now provide the first evidence of renal induction of AR expression in 5/6 nephrectomized male rats, which may account for the rapid deterioration of renal function that they observed. AR may therefore represent a promising therapeutic target for CKD treatment.

Although estrogens clearly confer significant renal protection in CKD subjects,[1,2] the underlying mechanism remains largely unknown. Several elegant studies at the cellular level showed that estradiol reverses transforming growth factor-β1-stimulated mesangial collagen IV expression and collagen I production via a casein kinase 2/Sp1 mechanism and a mitogen-activated protein kinase/AP1 signaling pathway, respectively.[4] Furthermore, estrogen treatment also results in enhanced metalloproteinase-2 activity in a mitogen-activated protein kinase/AP2-dependent manner.[4] These effects of female sex hormones on mesangial cells may suppress extracellular matrix accumulation and promote extracellular matrix degradation, thereby improving glomerulosclerosis. In light of these results, ER may repre-

[1]*Department of Physiology and Pathophysiology, Peking (Beijing) University Health Science Center, Beijing, China; and* [2]*Division of Nephrology, Vanderbilt University Medical Center, Nashville, Tennessee, USA.*

Correspondence: *Y Guan, Department of Physiology and Pathophysiology, 38 Xueyuan Road, Peking (Beijing) University Health Science Center, Beijing, China 100083.*
E-mail: youfeiguan@bjmu.edu.cn

sent a molecular basis for the renoprotective effect seen in females, although an ER-independent mechanism(s) cannot be excluded.

Lu and colleagues[6] contribute a novel and important study of sexual differences in CKD with potential clinical implications. In comparing the expression levels of ERα in male and female remnant kidneys, the authors found, for the first time, that female kidneys showed much less of a decrease in ERα gene expression than male kidneys. Furthermore, the authors present the first evidence in male remnant kidneys that renal ERα expression levels, rather than circulating 17β-estradiol concentrations, are associated with multiple markers of CKD progression, including glomerular filtration rate, creatinine clearance, and proteinuria. These observations support the idea that ER may be a critical determinant of CKD severity, and they provide a convincing explanation for why the male kidney rather than the female kidney has greater susceptibility to progressive renal injury. Although the authors' study did not delineate the underlying mechanisms mediating ERα suppression in CKD kidneys, the findings suggest that selective activation of renal ERα might represent a rational maneuver to treat CKD in men and postmenopausal women.

Peroxisome proliferator-activated receptors (PPARs) form a subfamily of the nuclear receptor superfamily. Three PPAR isoforms exist, designated PPARα, PPARβ/δ, and PPARγ.[7] The expression of each subtype of PPARs is tissue specific. PPARα is predominantly expressed in tissues with high energy demand, including liver, heart, and kidney. In the kidney, PPARα is selectively abundant in proximal tubule cells, where its activation is essential in fatty acid metabolism, energy homeostasis, and anti-inflammatory regulation. PPARα agonists significantly improve but PPARα gene deficiency markedly accelerates renal injury in many kidney diseases, including diabetic nephropathy, cisplatin-induced acute renal failure, and the 5/6 nephrectomy model of chronic renal disease.[8,9] These observations suggest that PPARα could serve as an important renoprotective factor contributing to gender dimorphism of renal disease progression. To test this hypothesis, Lu and colleagues[6] examined the expression of PPARα in normal and nephrectomized rat kidneys of both sexes. Renal PPARα expression was decreased in both male and female remnant kidneys but was much lower in male than in female kidneys. Importantly, the authors showed a tight negative correlation between the level of PPARα and its target gene acyl-CoA oxidase and multiple markers of CKD in both sexes. These findings provide the first line of evidence that renal PPARα transcriptional activity may be one of the key renoprotective factors involved in disease progression of CKD. The lower level of PPARα expression in male than in female remnant kidneys may therefore imply that PPARα may be another nuclear receptor determining the greater susceptibility of the male kidney than the female kidney to accelerated decline of renal function.

To study further the role of PPARα in gender dimorphism of CKD, Lu and colleagues[6] focused on the role of cytochrome P450 4a1 (Cyp4a1), another well-documented PPARα target gene. Consistently, they found a higher Cyp4a1 expression in nephrectomized females than in males. Furthermore, they observed a negative correlation between the expression of renal Cyp4a1 and that of various inflammatory and apoptotic markers, especially in nephrectomized females. These findings significantly extend our understanding of the role of Cyp4a1 in the kidney. In addition to its previously reported hemodynamic effect,[10] Cyp4a1 may be a potent anti-inflammatory and antiapoptotic factor downstream of the PPARα receptor in the diseased kidney.

In conclusion, Lu and co-workers[6] have provided valuable evidence that nuclear receptors may play a key role in gender differences in CKD progression. The alteration of ERα, AR, and PPARα pathways, together with changes in other transcription factors, including aryl hydrocarbon receptor and Wilms tumor 1, demonstrated in this study, may exert renoprotective effects on the female kidney during CKD. Although the article by Lu and colleagues[6] represents an excellent first step toward understanding sexual dimorphism of renal disease progression, several basic questions remain: Do ERα, AR, and PPARα function independently or in concert? Do other nuclear receptors also contribute to the marked gender disparity in CKD? And what biological actions do these nuclear receptor signaling pathways mediate in the kidney? Further studies are required to compare the expression profiles of all 49 nuclear receptors in the male and female kidney and uncover the molecular events determined by each nuclear receptor in renal tissue. Such study will offer a simple but powerful way to obtain highly relational information about the roles of these receptors in gender dimorphism of renal disease progression.

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