THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

# XUEMIN HE

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE
DEPARTMENT OF PHYSIOLOGY

Monday, December 12, 2016, 2:00 p.m.
Basic Sciences Education Building, Room 272, OUHSC

**INVESITIGATING THE ROLE OF PEDF AND LRP5 IN THE REGULATION OF RENAL FIBROSIS**

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Chronic kidney diseases and acute kidney injuries lead to renal fibrosis. Hitherto, there is no effective therapeutics to reverse the progression of fibrosis. Wnt signaling plays a key role in the renal fibrogenic process. The purpose of this study was to investigate the anti-fibrotic effects and mechanism of pigment epithelium-derived factor (PEDF), an endogenous inhibitor of Wnt signaling, and to characterize the functions of low-density lipoprotein receptor-related protein 5 (LRP5), a co-receptor of Wnt signaling, in the regulation of renal fibrosis and its mechanism of action.

We demonstrated that renal PEDF levels were significantly reduced in genetic models of type 1 and type 2 diabetes, and the model with ureteral obstruction. The kidneys of PEDF knock-out mice with ureteral obstruction displayed exacerbated expression of fibrotic and inflammatory factors, oxidative stress, tubulointerstitial fibrosis and tubule epithelial cell apoptosis, compared to the kidneys of wild-

type mice with obstruction. PEDF knock-out enhanced Wnt signaling activation induced by obstruction, while PEDF inhibited the Wnt pathway-mediated fibrosis in renal proximal tubule epithelial cells. Additionally, PEDF protected renal proximal tubules epithelial cells against oxidative stress and oxidation-induced apoptosis. The renoprotective effects of PEDF are mediated, at least partially, by inhibition of the Wnt pathway. We further shown that LRP5 was predominantly expressed in mouse renal tubules, and its levels were up-regulated in diabetic mouse kidneys and non-diabetic kidneys with ureteral obstruction, accompanied by elevated renal fibrosis. LRP5 knock-out kidneys with ureteral obstruction manifested significantly lower levels of fibrosis factors and TGF-β signaling components relative to wild-type kidneys with obstruction. LRP5 knock-out diminished Smad-dependent TGF-β signaling, while LRP5 over-expression potentiated Smad-dependent TGF-β signaling in renal tubule epithelial cells. LRP5 bound to TβRI independent of TGF-β1, and enhanced TGF-β signaling via the N-terminus. Moreover, LRP5 promoted the cell surface presentation, internalization and dimerization of TβRI and TβRII. Inhibition of TβRI abrogated LRP5-induced over-activation of TGF-β signaling. These findings indicate a novel role of LRP5 in regulating the TGF-β signaling pathway, independent of Wnt signaling. Thus our findings of the levels of PEDF and LRP5 could be used to for clinical assessment of fibrotic severity.