OMICS Group Conferences
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International Conference and Exhibition on
Nephrology & Therapeutics

August 20-22, 2012 Hilton Chicago/Northbrook, USA

Epithelial-mesenchymal communication: New paradigm in fibroblast activation and kidney fibrosis

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Renal fibrosis is the common final outcome of almost all progressive chronic kidney diseases (CKD). Because activated fibroblasts are the principal cells that are responsible for excessive production of extracellular matrix, elucidation of their origins, activation and regulation in injured kidney will be essential for providing mechanistic insights into the patho-mechanisms of CKD as well as for developing novel strategies for therapeutic intervention. As the major constituent of renal parenchyma, tubular epithelium is susceptible to a variety of metabolic, immunologic, ischemic and toxic insults, and is the primary target of kidney injury. Exactly how an injured tubular epithelium communicates with interstitial fibroblasts and causes them to undergo phenotypic activation is a central question. We recently uncovered a critical role for sonic hedgehog (Shh) and Wnt signaling in mediating such an epithelial-mesenchymal communication (EMC) in renal fibrogenesis. Shh was induced in tubular epithelium, but not in fibroblasts, in the fibrotic kidneys. However, Shh targeted fibroblasts, causing their proliferation and activation. Interestingly, upon stimulation by Shh, fibroblasts secreted a variety of Wnt ligands, which resulted in β-catenin activation in tubular epithelium. Furthermore, either inhibition of Shh signaling by cyclopamine or Wnt/β-catenin signaling by ICG-001 ameliorated renal fibrosis in obstructive nephropathy and adriamycin nephropathy. These results suggest that Shh and Wnt/β-catenin mediate a two-way communication between tubular epithelium and interstitial fibroblasts, thereby creating a vicious cycle that leads to uncontrolled fibroblast activation, matrix production and renal fibrosis.

Biography

Dr. Youhua Liu obtained his PhD in cell biology from the Peking Union Medical College in Beijing, China. After receiving his postdoctoral training at NIH and the University of Pittsburgh, he joined the faculty at Brown University as an Assistant Professor of Medicine. He is currently a Professor of Pathology at the University of Pittsburgh School of Medicine. Dr Liu's research is focused on dissecting the cellular and molecular pathways that lead to chronic kidney fibrosis, and exploring novel strategies for therapeutic intervention.

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