Risk factors, biomarkers and patho-mechanisms of chronic kidney disease

Supported by the National Natural Science Foundation of China, the research team led by Prof. Hou Fanfan (侯凡凡) and Liu Youhua at the State Key Laboratory of Organ Failure Research, Southern Medical University, has made remarkable progress in identifying the risk factors and biomarkers and elucidating the patho-mechanisms of chronic kidney disease (CKD). Four papers describing these findings were published in the *Journal of the American Society of Nephrology* (2016), a premier journal of nephrology in the world.

Air pollution and membranous nephropathy in China. Air pollution has become a serious problem in many cities in China, but the extent of its impact on individuals' health remains unknown. A new study, led by Hou Fanfan, MD, PhD indicates that air pollution also likely causes damage to the kidneys. The team analyzed data on kidney biopsies taken over 11 years from 71,151 patients from 938 hospitals in 282 cities across China, encompassing all age groups. On average, the risk of developing membranous nephropathy, an immune disorder of the kidneys that can lead to kidney failure, increased 13% annually over the 11-year study period, whereas the proportions of other major kidney conditions remained stable. Each 10 mg/m^3 increase in PM2.5 concentration associated with 14% higher odds for membranous nephropathy in regions with PM2.5 concentration >70 mg/m^3. The frequency of membranous nephropathy has doubled over the last decade in China. This study is the first to link that increase to the regional distribution of particulate air pollution, and calls for attention on the role of air pollution in the development of kidney disease.

AKI to CKD progression. Acute kidney injury (AKI) is responsible for about 2 million deaths each year worldwide. There is growing evidence that patients who survive an episode of AKI will have a significant risk of developing CKD. Following AKI, the kidney sometimes fully recovers its structure and function via an adaptive repair and regeneration, or undergoes maladaptive responses in other circumstances. Exactly what factors dictate such divergent outcomes of AKI, however, remains a mystery. In a recent study, the team led by Liu Youhua and Hou Fanfan demonstrated that sustained activation of Wnt/β-catenin signaling plays a decisive role in driving CKD progression after AKI. As transient activation of Wnt/β-catenin, a developmental signaling essential for kidney formation during embryonic development, has been previously shown to be instrumental in facilitating kidney repair after injury, these findings suggest that a sustained and exaggerated Wnt signaling actually leads to renal maladaptation and drives AKI to CKD progression.

Urinary MMP-7 is a non-invasive biomarker. CKD is manifested by persistent functional decline and progressive tissue fibrosis. While kidney function can be evaluated by an estimated glomerular filtration rate (GFR), direct assessment of renal fibrosis is only achievable with kidney biopsy, which is an invasive procedure. Therefore, developing a noninvasive, surrogate biomarker that can detect and monitor the progression of renal fibrotic lesions is urgently needed. In a study recently published online, a team led by Liu Youhua and Hou Fanfan, has reported that urinary matrix metalloproteinase-7 (MMP-7) can be utilized as a noninvasive biomarker for kidney fibrosis in CKD patients. The levels of urinary MMP-7 were closely correlated with the severity of kidney dysfunction. Of the 30 CKD patients who had biopsy specimen, there was a close correlation between urinary MMP-7 levels and kidney fibrotic score. Similarly, urinary MMP-7 levels were also associated with serum creatinine, as well as serum levels of cystatin C. These findings suggest that urinary MMP-7 can serve as a noninvasive biomarker for estimating the severity of kidney fibrosis and renal dysfunction in humans.

Molecular dissection of the fibrogenic microenvironment. Kidney fibrosis is the final common outcome of a wide variety of progressive CKD. However, it typically initiates at certain focal sites, in which interstitial fibroblasts become activated, proliferate and produce a large amount of ECM components. The molecular identities and composition of such a niche are poorly characterized. A new study from the group led by Liu Youhua has initiated the efforts to molecular characterization of the fibrogenic niche in kidney fibrosis. They demonstrated that tenascin C (TNC), an evolutionarily conserved, multi-modular glycoprotein of the extracellular matrix, is a key component of the fibrogenic niche, which provides the specialized microenvironment for fibroblast proliferation and expansion. The study is the first to demonstrate that TNC is a major player in organizing the fibrogenic niche that provides a favorable environment for fibroblast activation and proliferation in kidney fibrosis.