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Editorial

Rodent models of chronic kidney disease for studies of early renal tubulointerstitial fibrosis

Chronic kidney disease (CKD) is the progressive decline of renal function resulting from renal fibrosis because of several causes [1]. CKD is an important health care problem that impacts upon the global economy because of the need for long-term renal replacement therapy at the final stage, referred to as "end stage renal disease" or "ESRD". Interestingly, similar clinical manifestations, such as anemia, nausea and vomiting, are present in patients with ESRD regardless of the initial causes of renal injury. CKD could be unofficially differentiated into chronic glomerular disease (CGD) and chronic tubulointerstitial disease (CTID). Because of the progressive natural history of CKD, biomarkers for the early diagnosis and monitoring of CKD are essential. The diagnosis of CKD is currently based on the levels of serum creatinine (Scr) and proteinuria (urine albumin or urine total proteins), which has several limitations in the early detection of CKD. Scr levels in CKD are confounded by several nonrenal factors (e.g. muscle mass and liver function) [2] and often increase after the presence of proteinuria. By contrast, proteinuria levels are influenced by diet and the diurnal variation [3]. Therefore, new sensitive and reliable biomarkers for CKD are needed. Exosomes, nano-sized vesicles containing cytosolic and membrane proteins secreted from a wide variety of cell types, are new and interesting sources of urine biomarkers, because exosomes can be detected in urine and the analysis of exosomes resembles a random biopsy of the cell [4]. Thus, a new noninvasive method of so-called "liquid biopsy" through isolation of exosomes in urine should open up more opportunity for biomarker discovery.

Most of the current rodent models of CKD are models of CGD, such as 5/6 nephrectomy, puromycin, and Heymann nephritis induced models [5], which show a significant proteinuria. Animal models of CTID have been mentioned only in a few reports [6, 7]. In this issue, there are 2 rodent models of CTID proposed for urine biomarker studies via urine exosome analyses. In the description of a rat model of CKD by Rattanasinganchan et al. [8], intraperitoneal injection of folic acid could induce tubulointerstitial fibrosis just 2 weeks after the injection with a renal pathology compatible with CTID in patients. Moreover, at 1 week after the injection, there was already inflammatory cell infiltration in the kidney without fibrosis. Importantly, for practical purposes, the amount of urinary exosomes collected from this folic acid-induced rat model of renal injury was adequate for high-throughput proteomic analysis. Urinary exosomes at 1 week and 2 weeks after folic acid treatment were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) to identify urinary biomarkers for acute and chronic tubulointerstitial injury, respectively. Many proteins specific to inflammation (1 week) or fibrosis (2 weeks) were demonstrated in this study. To simulate the CTID seen in patients more closely, it will be useful to analyze urinary exosomes at 2 weeks after folic acid treatment.

In a parallel study by Leelahavanichkul et al. [9], a mouse model of tubulointerstitial fibrosis was generated by an ischemia–reperfusion injury coupled with contralateral nephrectomy (Chr IR injury). Renal fibrosis cannot be induced by ischemia–reperfusion injury alone. The nephrectomy in this mouse model increases the burden on the injured kidney, thus propelling a progressive decline in renal function. In this mouse model of CKD, tubulointerstitial fibrosis was demonstrated at 12 weeks after the initiation of Chr IR. Although the renal histopathology of mice in this model induced by Chr IR is not obviously different from that of the folic acid-induced model in rats, the mouse model appears to resemble patients with CTID more closely, in that clinical features of progressive kidney injury, such as anemia, poor weight gain, and increased Scr are demonstrated, whereas these features were not observed in the rat model. However, the mice in the model induced by Chr IR take a longer time to produce renal fibrosis and produce less urine volume compared rats in the model induced by folic acid treatment. Nevertheless, the authors took advantage of the CKD-induced diuresis to obtain sufficient 24 h volumes of urine for exosome isolation to investigate urinary biomarkers. Despite the limitation in urine volume, the greater availability of

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genetically manipulated mice over rats allows the Chr IR-induced model to be a versatile tool for pathophysiological studies of CTID.

Both rodent models of tubulointerstitial fibrosis reported in this issue of *Asian Biomedicine* are apparently useful for the studies of the pathophysiology of and urine biomarkers for CTID. Such studies may ultimately lead to improvement in the clinical management of CTID.

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