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Circulating proteasome activity in Plasma as a Potential Biomarker of Chronic Kidney Disease

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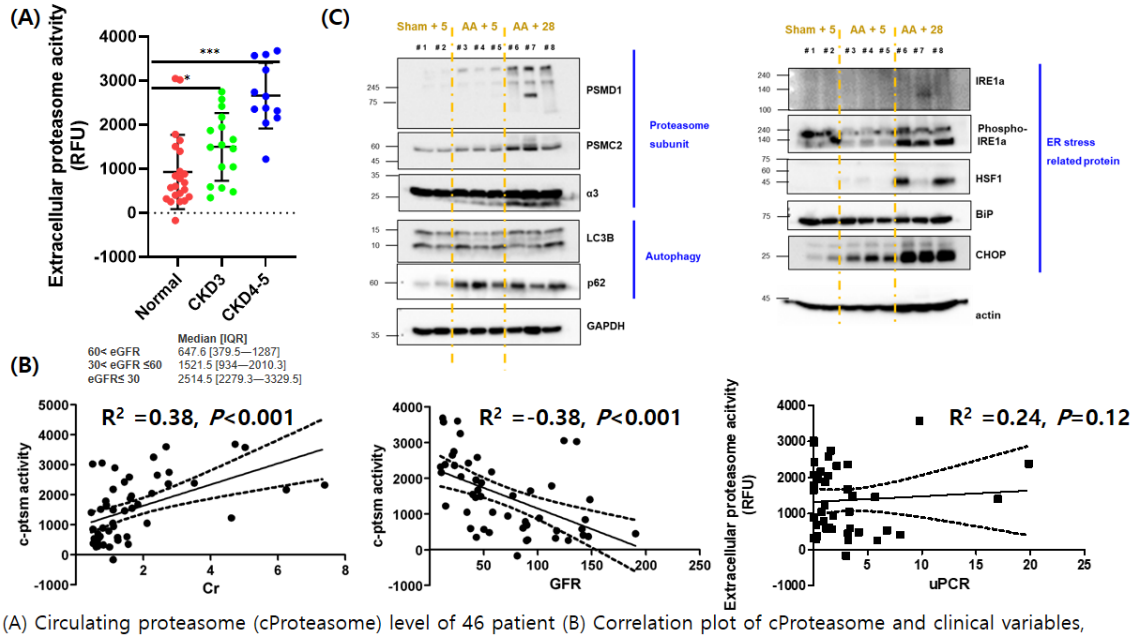
Objectives: The ubiquitin-proteasome system is the vital pathway of cellular protein degradation. While the association between the chronic kidney disease (CKD) and the intracellular 26S proteasome, ~2.5 MDa protease holoenzyme in the eukaryotes, was suggested, the role of circulating proteasomes (cProteasome) in the plasma has not been characterized in the context of kidney fibrosis yet.

Methods: Aristolochic acid (AA)-induced CKD mouse model was used for *in vivo* examination. Mouse plasma and kidney tissue lysates were collected at 5 and 28 days after AA administration. In addition, prospectively collected paired samples of plasma and urine from 70 patients (60 patients distributed evenly from CKD stages 1 to 5 and 10 healthy controls) were prepared. After excluding hemolytic samples (n=16) and outliers (n=5; Dixon's Q-test), 49 patients (6 controls) were finally enrolled for cProteasome activity tests, which employ hydrolysis of fluorogenic proteasome substrate, suc-LLVY-AMC.

Results: The mean cProteasome activity was significantly elevated in AA group (4676.25 [control] vs. 5411.8 [in AA-treated for 5 days] vs. 8197.5 [in AA 28 days] in relative fluorescence units [RFU]). In kidney tissues, proteasome subunit (PSMD1, PSMC2 and α3) and ER stress protein (Phospho-IRE1a, HSF1, BiP and CHOP) were up-regulated at AA 28 days than controls, while global autophagy flux appeared unchanged. There was a significant positive correlation between serum creatinine and cProteasome activity (R^2=0.38, *P*-value = 0.001). Divided into three groups, prominent and largely stage-dependent differences in median cProteasome activity were observed. (Figure1A) cProteasome activity was not correlated with spot urine protein creatinine and was not detected in the urine samples.

Conclusions: The cProteasome level, its activity, and ER stress response appeared to be implicated in kidney fibrosis. While the origin and pathophysiological role remains to be further determined, our data open a novel perspectives on cProteasome not only as biomarker of CKD but also potential therapeutic target for renal-fibrosis.

Figure 1. cProteasome activity in AA-CKD model and humans plasma



(A) Circulating proteasome (cProteasome) level of 46 patient (B) Correlation plot of cProteasome and clinical variables, (C) Western plot result about proteasome subunit, ER stress and autophagy of AA induced CKD model