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Uremic toxins are conditional danger- or homeostasis- associated molecular patterns, which are highly selective increase rather than purely passive accumulation, in chronic kidney disease and coronary arteria disease

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Cardiovascular morbidity and mortality in patients with advanced CKD are 10- to 30- folds greater than that in the general population. In the U.S. and worldwide, the incidence of CKD is increasing, and atherosclerosis- related CVD is a major cause of mortality in these patients. We performed novel metabolomics/gene database mining, where we identified protein-bound uremic toxin (UT) receptors as well as the enzymes for UT generation, and analyzed their gene expression changes in chronic kidney disease (CKD), vascular and metabolic diseases. We made the following findings: *1)* In CKD, UTs represent a very small fraction of the total human serum small-molecule metabolome, roughly $1/80^{th}$; *2)* The serum concentrations of some UTs are increased not only in CKD but in other diseases; *3)* Protein-bound UTs either induce or suppress the expression of pro-inflammatory molecules; *4)* The expression of UT genes is significantly modulated in the tubules of CKD patients, and adipose tissue of coronary artery disease (CAD) patients, compared with those of metabolic syndrome and type 2 diabetes patients; *5)* The expression of UT genes is upregulated by caspase-1 and TNF-α pathways, more than toll-like receptors (TLRs), IL-1β and IFN-g pathways; and *6)* The expression of UT genes is inhibited by regulatory T cells. Our results have demonstrated that UTs are highly selectively accumulated, and serve as danger signal-associated molecular patterns (DAMPs) and homeostasis-associated molecular patterns (HAMPs) that modulate inflammation. In addition, our results show that some UT genes are upregulated in CKD and CAD, presumably via caspase-1/inflammatory cytokine pathways, rather than by purely passive accumulation.

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