Editorial: A missing link? Monocyte activation by uremic toxins in cardiorenal syndrome

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KD, defined as progressive renal damage leading to a reduced glomerular filtration rate, is a major cause of cardiovascular morbidity and mortality. Until recently, the pathophysiologic mechanisms linking CKD and cardiovascular disease were uncertain. Current research on this “missing link” has focused on a group of protein-bound uremic toxins that are elevated significantly in the blood of patients with CKD and not amenable to clearance by hemodialysis. Such toxins may promote oxidative stress and endothelial dysfunction and ultimately lead to the accelerated atherosclerosis commonly observed in patients with CKD [1].

The best studied of the uremic toxins is indoxyl sulfate, which is derived from the essential amino acid tryptophan (Fig. 1). Local gut flora in the distal intestine convert tryptophan to indole, which is then transported across enterocytes into the hepatic circulation. Hepatocytes then convert indole to indoxyl sulfate, which circulates in the blood, primarily bound to albumin. In patients with normal renal function, indole is excreted in renal tubules and is barely detectable in the blood. In CKD, inadequate renal clearance leads to significantly elevated serum levels of indoxyl sulfate. This can trigger a host of proinflammatory oxidative pathways, resulting in renal and cardiac fibrosis, including direct induction of cardiac fibroblast collagen production and fibrosis of renal proximal tubular cells [2, 5]. AST-120 (Kreemzin) is an oral charcoal that reduces serum levels of indoxyl sulfate by adsorbing indole in the intestines, thereby promoting fecal excretion of this metabolite. The role of indoxyl sulfate–activated monocytes on tissue pathology is uncertain, but AST-120 reduced renal monocyte/macrophage infiltration significantly in a nephrectomized model of CKD in rats [4]. Treatment with AST-120 may thereby reduce renal fibrosis and limit further kidney injury in patients with CKD by various mechanisms.

REFERENCES

KEY WORDS: T-box transcription factors · virus · KLRG1 · PD-1

Abbreviations: CKD=chronic kidney disease, Mac-1=macrophage antigen-1

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One major mechanism of renal fibrosis involves elaboration of TGF-β1 via monocytes/macrophages that are attracted by local production of chemokines (e.g., MCP-1) and recruitment from the microcirculation by up-regulation of ICAM-1, osteopontin, and endothelin-1. Secreted TGF-β1, in turn, stimulates production of TIMP-1 and collagen. Over time, injured tubular cells are transformed into myofibroblasts that facilitate interstitial fibrosis. Whereas monocytes play an important role in the pathophysiology of renal fibrosis, direct evidence for the mechanisms linking CKD with monocyte activation and renal fibrosis has been lacking. In this issue of *JLB*, Ito et al. [5] examined the process by which indoxyl sulfate activates monocyte superoxide production, membrane up-regulation of CD11b/CD18 (Mac-1), and recruitment of monocytes to inflamed endothelium.

To study the link between CKD and monocyte activation, Ito et al. [5] used a nephrectomized mouse model and demonstrated that oral administration of indoxyl sulfate activated a number of proinflammatory functions in monocytes, including up-regulation of Mac-1 expression and ROS production. Treatment of mice with AST-120 reduced Mac-1 up-regulation and ROS production, measured ex vivo in blood monocytes, but interestingly, not in neutrophils. Thus, vascular recruitment and subsequent ROS elaboration as a result of indoxyl sulfate may be monocyte-specific and contribute to renal dysfunction. To pursue this hypothesis, Ito et al. [5] performed in vitro studies on the monocytic cell line THP-1 to assess the mechanistic basis of activation. They demonstrated that THP-1 cells were captured in a Mac-1-dependent manner to a monolayer of umbilical vein endothelial cells that were activated with indoxyl sulfate. Further, integrin activation occurred specifically via a p38MAPK pathway, as its phosphorylation was induced by indoxyl sulfate and adhesion inhibited by blocking p38MAPK. Superoxide production via membrane translocation of the NADPH oxidase subunit p47phox was induced upon THP-1 exposure to indoxyl sulfate, and the inhibitor apocynin reduced THP-1 cell adhesion to endothelium. Although THP-1 cells are not as responsive nor as heterogeneous as blood monocytes, these results do reveal a pathway that links ROS, integrin activation, and intracellular signaling with endothelial recruitment under shear flow.

Have Ito et al. [5] identified a missing link between CKD and cardiovascular disease? Indoxyl sulfate has been implicated previously in oxidative stress of many cell types, including renal tubular cells, mesangial cells, vascular smooth muscle cells, endothelial cells, and osteoblasts. This study, however, is the first to demonstrate direct mechanisms of indoxyl sulfate on monocyte activation. Given the critical link between monocyte activation, endothelial dysfunction, and atherosclerosis, indoxyl sulfate may therefore be an important mediator of CKD-driven atherogenesis.

AST-120 is already used clinically in Japan to enhance renal function of uremic patients by preventing monocyte-driven kidney fibrosis and limit atherosclerotic progression through reduction of oxidative stress [6]. However, recent studies have questioned the clinical use of AST-120. Preliminary results of two combined Phase III clinical trials [Evaluating Prevention of Progression in CKD (EPPIC)] in Europe and the Americas did not show a clinical benefit of AST-120 over placebo when combined with standard-of-care therapy in CKD patients [7]. Interestingly, there was a trend for effectiveness of AST-120 in a subpopulation of patients with rapidly progressive CKD. These patients may approximate more closely animal models, where renal failure is acute and quickly progressive. Evidence of the benefit of AST-120 on limiting cardiac fibrosis is also often based on early intervention in these models [8]. It is therefore possible that intervention with AST-120 early in the course of CKD will provide clinical benefit but that patients with established CKD may not benefit as much from AST-120. Additionally, other uremic toxins and their effects on monocyte activation should be considered. For example, p-cresylsulfate is another uremic toxin whose levels correlate with levels of indoxyl sulfate and also with progression of CKD [9, 10].

Whether AST-120 exerts its ameliorative effect by removal of indoxyl sulfate and systemically suppressing inflammatory monocyte activation and recruitment to inflamed endothelium remains unknown. As these studies have only correlated disparate inhibitory effects of AST-120 on blood monocytes in the mouse CKD model and indoxyl sulfate activation of human monocytes, it remains to be shown that these two
are related in the underlying disease etiology. Investigations, such as this, represent important progress in improved understanding of a serious disease entity. However, studies on monocyte activation ex vivo from blood samples of CKD patients and those with comorbidities, such as atherosclerosis, should provide more direct evidence to unravel the pathogenesis of indoxyl sulfate-related diseases.

REFERENCES


KEY WORDS: chronic kidney disease · Kremezin · renal pathology · monocytes
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