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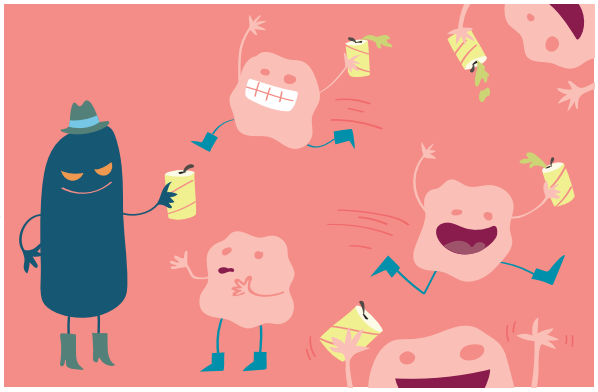

CHRONIC KIDNEY DISEASE

Uraemic toxin-induced platelet hyperactivity

Thrombosis is a common complication of chronic kidney disease (CKD); however, the underlying mechanisms are not well understood. New findings show that the uraemic toxin, indoxyl sulfate, induces platelet hyperactivity, contributing to thrombus formation. Moreover, the researchers show that KLOTHO counteracts indoxyl sulfate-induced platelet hyperactivity. "Our results provide new insights into the mechanisms of CKD-associated thrombosis," says Jinghong Zhao.

> "Indoxyl sulfate… stimulated platelet activity"

To assess the relationship between indoxyl sulfate and thrombosis in CKD, Zhao and colleagues studied platelets in mice with CKD-induced increases in serum indoxyl sulfate levels. Platelets from CKD mice exhibited hyperactivity in response to collagen and thrombin, with significantly increased levels of platelet-derived microparticles and increased formation of platelet–monocyte aggregates. Administration of indoxyl sulfate further stimulated platelet activity and shortened the time for carotid artery occlusion to occur, whereas administration of a charcoal adsorbent of indoxyl sulfate, AST-120, attenuated platelet hyperactivity.

AST-120 also inhibited reactive oxygen species (ROS) production and p38MAPK activation, and inhibition of ROS or p38MAPK attenuated indoxyl sulfate-induced platelet hyperactivity, suggesting a key role for ROS–p38MAPK signalling in indoxyl sulfate-induced platelet activation. Similarly, the antioxidant protein, KLOTHO, dose-dependently inhibited indoxyl sulfate-induced platelet activation and thrombus formation.

To investigate the effects of low KLOTHO levels — as found in CKD — on platelet activation, Zhao and colleagues used heterozygous *klotho*$^{+/-}$ mice. These mice had higher levels of serum indoxyl sulfate and platelet-induced monocyte activation, with enhanced ROS–p38MAPK signalling compared to that of wild-type mice.

The researchers now plan to further assess how indoxyl sulfate activates platelets and to investigate the effects of other uraemic toxins on platelet activation. "We hope that our future work will provide deep insights into the pathogenesis and treatment of CKD-associated cardiovascular disease," says Zhao.

Susan J. Allison

ORIGINAL ARTICLE Yang, K. *et al.* Uremic solute indoxyl sulfate-induced platelet hyperactivity contributes to CKD-associated thrombosis in mice. *Blood* https://doi.org/10.1182/blood-2016-10-744060 (2017)