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THROMBOSIS

Reducing thrombosis in CKD

Chronic kidney disease (CKD) increases the risk of both thrombosis and bleeding in patients, limiting antithrombotic therapeutic options. Now, by further dissecting the molecular mechanisms underlying hyperthrombosis in patients with CKD, Vipul Chitalia and a team of interdisciplinary collaborators identify the regulation of the procoagulant, tissue factor (TF), as a potential target for CKD-specific antithrombotic therapy.

"Uraemic indolic solutes (such as indoxyl sulfate (IS)) accumulate in patients with CKD and mediate the hyperthrombosis in uraemia," explains co-author Jean Francis. Previous studies showed that these toxins bind to the aryl hydrocarbon receptor (AHR) and induce the expression of TF. In the present study, in an IS-specific animal model, elevated AHR signalling increased the level of TF and enhanced thrombosis. The researchers showed that AHR increases TF levels by inhibiting its ubiquitylation by the E3 ubiquitin ligase STUB1. The activity and expression of TF is elevated in *Stub1*$^{-/-}$ mouse embryonic fibroblasts (MEFs) and in *STUB1*-silenced cells. An inverse relationship between STUB1 and TF levels was confirmed in arteriovenous fistulae from patients with CKD using a novel machine-learning algorithm.

The IS–AHR–STUB1–TF axis was perturbed in the flow-loop system that simulates a human blood vessel. Flow loops containing *Stub1*$^{-/-}$ MEFs had more clots than those containing wild-type MEFs after IS infusion, whereas increasing *STUB1* expression using a preclinical compound resulted in fewer clots.

Importantly, in both IS-treated mice and another mouse model of CKD, increasing STUB1 reduced uraemic hyperthrombosis to non-CKD levels, without altering haemostasis. "Although our results in mice require validation in humans, we aim to develop compounds that perturb this axis as a novel class of antithrombotics," conclude Chitalia and Katya Ravid, the other senior co-author.

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ORIGINAL ARTICLE Shahar, M. *et al.* Targeting STUB1–tissue factor axis normalizes hyperthrombotic uremic phenotype without increasing bleeding risk. *Sci. Transl Med.* **9**, eaam8475 (2017)