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ACUTE KIDNEY INJURY

ACTIVATED PROTEIN C PROTECTIVE IN IRI

The anticoagulant serine protease activated protein C (aPC) provides nephroprotection against ischaemia–reperfusion injury (IRI) by maintaining stability of the cold-shock protein YB-1, according to new research. "Within our study we identify a novel mechanism through which coagulation proteases modulate renal IRI," explain the researchers. "This newly identified nephroprotective mechanism, which depends on the functional interaction of aPC, YB-1, and OTUB1, may lay ground for new translational approaches to renal IRI."

Previous work demonstrating a cytoprotective role of aPC after hepatic IRI led Berend Isermann and colleagues to investigate possible nephroprotective effects of aPC in IRI of the kidney. "As efficient therapies for renal IRI are lacking, and renal IRI and the resulting renal impairment is a major health problem, we felt that determining the role of aPC and coagulation protease-dependent signalling would be of translational relevance," says Isermann.

Using models of renal IRI and hypoxia–reoxygenation of cultured tubular cells, Isermann and colleagues demonstrated nephroprotective effects of aPC that were independent of its anticoagulant properties. Genetically modified mice with low blood levels of aPC had exacerbated indices of kidney injury following IRI whereas mice with high blood levels of aPC were protected. Administration of exogenous aPC also ameliorated kidney injury, even following inhibition of its anticoagulant activity. Further studies revealed that the nephroprotective effect of aPC in IRI was mediated at least in part by YB-1.

To investigate the mechanism by which aPC regulates YB-1 expression, the researchers examined ubiquitination. They found that aPC stabilized expression of YB-1 by preventing K48-linked ubiquitination of YB-1 in response to tubular cell injury. Isermann and coworkers identified interaction between YB-1 and the deubiquitinating enzyme OTUB-1, which was preserved by aPC. aPC was unable to prevent YB-1 ubiquitination in tubular cells that had reduced expression of OTUB-1, demonstrating that OTUB-1 mediates the regulation of YB-1 ubiquitination by aPC.

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Original article Dong, W. *et al.* Activated protein C ameliorates renal ischemia–reperfusion injury by restricting Y-box binding protein-1 ubiquitination. *J. Am. Soc. Nephrol.* doi:10.1681/ASN.2014080846