A Friend in Need: Activated Protein C Stabilizes YB-1 during Renal Ischemia Reperfusion Injury

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AKI is associated with a rapid decline in renal function and high mortality rates. Furthermore patients that survive an acute illness have a high risk of developing ESRD from concomitant or aggravated CKD. Ischemia and reperfusion injury (IRI) is a leading cause of AKI. In the ischemic kidney decreased delivery of oxygen and nutrients results in tissue hypoxia and microvascular dysfunction while subsequent reperfusion amplifies inflammatory activation and cell death programs. Current treatment of AKI is mainly supportive in nature as there is a lack of effective pharmacologic intervention. Despite advances in supportive care, mortalities from AKI remain very high (ranging between 30% and 70%). Greater understanding of the molecular pathways contributing to AKI will provide the best prospects for developing novel therapeutic strategies for this serious condition.

In the elegant and important study by Dong et al., the functional interaction in renal IRI between the serine protease activated protein C (aPC), Otubain 1 (OTUB1) (a deubiquitinating enzyme), and the cold shock protein Y-box-binding protein 1 (YB-1) is meticulously investigated. A number of previous preclinical studies have indicated a role for aPC and other members of the thrombomodulin/aPC system in the prevention and treatment of both AKI and CKD.4

The findings of this study3 indicate that nephroprotection mediated by aPC is dependent at least in part on stabilization of YB-1 protein in tubule epithelial cells. Interestingly YB-1 has previous been reported to be a key regulator of inflammatory mediators in the kidney. In IRI, microvascular dysfunction in association with inflammation leads to tubular epithelial cell injury. Tubular cell injury is directly related to loss of renal function. Dong et al.3 propose that maintenance of YB-1 protein levels is crucial in protecting tubule cells following IRI and thus is vital in aPC-mediated protection of kidney function.

In the kidney YB-1 is predominantly expressed in tubular cells. YB-1 has pleiotropic actions and functions as a transcription factor, however it can also directly affect DNA repair and RNA splicing (reviewed in Lasham et al.7).

Dong et al.3 investigated the impact of aPC generation on YB-1 protein stability following IRI in rodent models and in proximal tubule cell culture following hypoxia-reoxygenation. Studies using these preclinical models indicated that renal IRI impairs protein C activation and results in reduced tubular YB-1 and OTUB1 expression.

The importance of the loss of YB-1 expression in disease was strengthened by the observation that YB-1 expression was also severely reduced in human renal biopsies following AKI. Furthermore that loss of YB-1 protein expression was seen to be directly related to the severity of renal injury.

Dong et al.3 investigated the relationship between aPC, YB-1, and AKI using transgenic mice with impaired thrombomodulin-dependent protein C activation (i.e., low blood levels of aPC) and those with a hyperactive aPC mutant (i.e., high blood levels of aPC). From these studies they established that following renal IRI low blood levels of aPC are associated with loss of YB-1 protein and increased kidney injury. Conversely, increased blood aPC and associated stabilization of YB-1 protein protected the kidney from IRI.

Stabilization of YB-1 was shown to be an important feature of the nephroprotective function of aPC as genetically modified mice with reduced YB-1 expression were not protected from renal IRI by aPC. Following IRI, increased aPC was found to stabilize YB-1 by reducing K48-ubiquitination, a process that targets protein for degradation.

Dong et al.3 identified the deubiquitinating enzyme OTUB1 as a YB-1 binding protein and reported that overexpression of this enzyme stabilized YB-1 by reducing K48-linked YB-1 ubiquitination. Similar to YB-1, OTUB1 is expressed predominantly in proximal tubule cells and also shows reduced protein expression following IRI. Interaction between OTUB1 and YB-1 was increased by aPC indicating that aPC required OTUB1 to stabilize YB-1.

Dong et al.3 established that OTUB1 was important in aPC-mediated renal protection by demonstrating aPC maintained OTUB1 following IRI. Furthermore they observed aggravated renal IRI with reduced OTUB1 expression. This more severe injury was associated with reduced YB-1 protein and could not be rescued by aPC, further verifying the importance of OTUB1 in maintaining YB-1 and associated renal protection. These data indicated that the reduction of YB-1 ubiquitination by aPC requires OTUB1.
Consistent with previous studies indicating aPC activation of protease activated receptor 1 was protective in AKI, Dong et al. demonstrated that aPC maintains OTUB1 and YB-1 via the tubule epithelial cell receptors protease activated receptor 1 and endothelial protein C receptor.

Exogenous aPC was also found to maintain YB-1 expression and protect against injury, indicating the therapeutic potential of the aPC pathway. Notably, the cytoprotective action of aPC was found to be independent of the anticoagulant action. Separation of these activities seems desirable for renal protection as previous clinical use of aPC was associated with increased incidence of hemorrhage-related adverse events.

This study clearly and comprehensively uncovers a molecular pathway that is important in the protective actions of aPC in IRI, a leading cause of AKI. Furthermore the study establishes an important role for YB-1 stabilization in nephroprotection following IRI. Future studies defining the mechanism by which YB-1 confers renal protection should lead to greater understanding of kidney function and dysfunction. The preclinical findings reported by Dong et al. describing the functional interaction between aPC, OTUB1, and YB-1 may be an important step toward the design of targeted therapies for AKI that minimize injury, assist repair, and reduce progression to CKD.

REFERENCES