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ACUTE KIDNEY INJURY

AIMing to enhance debris clearance and improve outcomes in AKI

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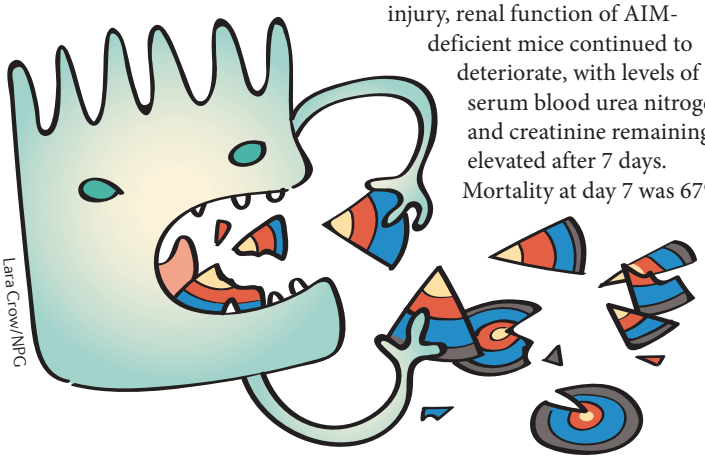
Cell death is an important pathological feature of acute kidney injury (AKI), with debris from dead tubular epithelial cells (TECs) leading to renal tubular obstruction and exacerbating tubular injury. Now, research shows that apoptosis inhibitor of macrophage (AIM; encoded by *Cd5l*) on intraluminal debris interacts with kidney injury molecule (KIM)-1 to promote the efficient clearance of dead-cell debris and facilitate recovery from AKI. "KIM-1 expression is strongly upregulated in injured tubular epithelial cells during AKI, but its exact role has remained obscure, mainly because its counterpart had not been identified," explains researcher Toru Miyazaki. "We now know that KIM-1 is a ligand of AIM and that KIM-1 recognizes and binds to AIM on debris, incorporating AIM together with the debris into the TECs that express KIM-1."

The restoration of tubular structure and renal function after AKI requires the proliferation of surviving epithelial cells and the efficient removal of debris from dead TECs. In the injured kidney, apoptotic and necrotic TECs are phagocytosed by neighbouring injured epithelial cells, which differentiate into a phagocytic phenotype under the control of KIM-1. The importance of this phagocytic process in regeneration and recovery was demonstrated by a study in which mice expressing a mutant form of Kim-1 that lacked the ability to engulf cell debris had more severe kidney injury than mice expressing wild-type Kim-1. "The known role of phagocytosis in AKI and our previous research showing that AIM accumulates at liver cancer cells and induces their elimination led us to hypothesize that AIM might be a sort of signalling molecule that accumulates on undesired biological garbage and induces its clearance," says Miyazaki. "In this respect we thought that AIM might attach to the intratubular dead-cell debris and induce its clearance during AKI."

The researchers first investigated the role of AIM in AKI by studying the response of AIM-deficient mice to ischaemia–reperfusion injury (IRI). In contrast to wild-type mice, which showed evidence of improved renal function 24 h after injury, renal function of AIM-deficient mice continued to deteriorate, with levels of serum blood urea nitrogen and creatinine remaining elevated after 7 days. Mortality at day 7 was 67% in AIM-deficient mice compared to 6.3% in wild-type mice. AIM deficiency did not affect the proliferation of TECs following injury, but resulted in defective clearance of necrotic-cell debris and persistent renal inflammation.



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Miyazaki and colleagues also found that KIM-1 expression remained elevated in TECs of AIM-deficient mice following IRI, whereas wild-type mice showed an initial increase in KIM-1 expression followed by a decrease concomitant with renal recovery. Analysis of the kidneys and urine of wild-type mice after IRI showed that AIM dissociates from the IgM pentamers to which it is normally bound. "This dissociation leads to the excretion of free AIM in urine and accumulation of AIM on intraluminal debris within the proximal tubules," says Miyazaki. "This finding was also observed in tissue from humans with AKI." Further studies demonstrated that AIM binds to KIM-1, and that this interaction enhances the uptake of debris by TECs. Treatment of injured wild-type and AIM-deficient mice, but not KIM-1-deficient mice, with recombinant AIM led to the removal of debris and amelioration of renal pathology.

Miyazaki believes these studies identify AIM as a candidate for future therapeutic strategies to promote renal recovery after AKI by enhancing the removal of harmful dead-cell debris.

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ORIGINAL ARTICLE(S) Arai, S. *et al.* Apoptosis inhibitor of macrophage protein enhances intraluminal debris clearance and ameliorates acute kidney injury in mice. *Nat. Med.* http://dx.doi.org/10.1038/nm.4012