Endotoxin and AKI: Macrophages Protect after Preconditioning

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Sepsis remains a major cause of morbidity and mortality in hospitalized patients, with AKI serving as an ominous prognostic factor. According to the current literature, the pathogenesis of AKI-induced sepsis, albeit being poorly understood, is thought to be multifactorial. Consequently, therapeutic interventions to curtail deterioration in kidney function in the setting of sepsis have been mostly supportive and, at best, modestly successful. In this issue of JASN, Hato et al. present data that demonstrate a renoprotective effect of macrophages in a model of endotoxin preconditioning and sepsis-induced AKI. The concept of disease tolerance as a possible host defense strategy against infection was recently highlighted in animal immunity. New data suggest that tissue protection by being “tolerant” to an insult may play an important role in sepsis.

Endotoxin preconditioning, or “tolerance,” is achieved by pretreatment with a low dose of endotoxin and has been shown in various models to alleviate the adverse effects of a large dose of endotoxin, as would be present in Gram-negative sepsis. Endotoxin preconditioning not only protects the host from damage caused by secondary exposure to endotoxin, but also mediates protection from other insults (cross-tolerance) such as ischemia-reperfusion injury and other Toll-like receptor (TLR) agonists. Endotoxin preconditioning has shown promise in improving outcomes of sepsis in various organs, including the kidney. A more profound understanding of the underlying mechanisms of protection by endotoxin preconditioning is key to developing therapeutic interventions in sepsis.

In previous work, the authors demonstrated that S1 proximal tubular epithelial cells acquire systemically administered endotoxin via a TLR4-dependent mechanism, subsequently initiating oxidative stress in S2 and S3 segments downstream. These findings established that endotoxin damage to renal tubular epithelial cells is a local renal event. Furthermore, the application of 2-photon (2P) intravital microscopy allowed the authors not only to interrogate the temporal and spatial location of endotoxin uptake in the kidney but also to assess the outcome of endotoxin uptake. Oxidative stress, directly visualized in vivo by fluorescent markers, was shown to occur in the S2 and S3 tubules.

In this issue of JASN, Hato et al. continue this work by investigating whether endotoxin preconditioning protects the kidney in vivo against future sepsis-induced AKI and elucidate the mechanism of endotoxin preconditioning in the mouse kidney. They first show in bone marrow chimeric mice that are reconstituted with TLR4−/− bone marrow that endotoxin-mediated renal injury is independent of hematopoietic cells and their produced cytokines. Furthermore, they demonstrate that exposure to low-dose endotoxin is protective not only against high-dose endotoxin but also in cecal ligation and puncture and live Escherichia coli injection models of sepsis. This was evident by decreased kidney injury markers (kidney injury molecule-1, neutrophil gelatinase-associated lipocalin), preserved kidney function, and decreased oxidative stress detected by intravital imaging of renal proximal tubules. Notably, protection occurred despite the increased uptake of endotoxin by S1 tubular cells in preconditioned mice. On the basis of the evidence established by the authors, it was thus likely that endotoxin preconditioning was also a local renal event independent of hematopoietic cells. However, experiments using bone marrow chimeric mice revealed that TLR4-expressing hematopoietic cells are required for the renoprotective effects of endotoxin preconditioning. Likewise, bone marrow chimeric mice demonstrated that the LPS coreceptor CD14 on hematopoietic cells is necessary. CD14 is expressed on monocytes, macrophages, and dendritic cells (DCs). The following data support the importance of macrophages: Histology demonstrated that M2 polarized macrophages in the preconditioned kidneys of CX3CR1-eGFP reporter mice but not other mononuclear phagocytes such as DCs. On the basis of the intermediate GFP expression, it is likely that this subset represents the Ly-6C− macrophages.

Using poly(I:C) as a “labeling” agent, macrophages were tracked in vivo and clustered around S1 proximal tubule segments. The subsequent events and mediators of this interaction (e.g., cytokines) remain to be investigated. A finding...
that might shed light on the biochemical pathways activated by macrophages in endotoxin preconditioning is the upregulation of heme oxygenase-1 and Sirtuin 1 (SIRT1), proteins involved in iron metabolism, in both macrophages and renal tubular cells. The sequelae of this observation remain to be tested; however, it is critical to highlight that an increase in heme oxygenase-1 and SIRT1 solely in renal tubules of TLR4KO/WT chimeric mice failed to mediate protection.

This work provides researchers with a pivotal macrophage-controlled pathway involved in protection from sepsis-induced AKI. Because patients with sepsis usually cannot be identified beforehand, new treatment strategies during the early disease stage are needed. Németh et al. have shown that giving bone marrow stromal cells ameliorates sepsis-induced organ dysfunction via reprogramming of host macrophages. In this study, kidney function was significantly improved after bone marrow stromal cell administration. Targeting macrophages or the involved signaling pathways could prove to be a more specific therapeutic approach.

In conclusion, Hato et al. have demonstrated in vivo that low-dose endotoxin administration is protective against sepsis-induced AKI in mice and that macrophages are the principal mediators of this effect. Better understanding of the mechanism by which macrophages mediate their protective effect, the involved signaling pathways, and the role of redox and iron-handling proteins may lead to novel treatment options not only for sepsis-induced AKI but also potentially for other insults that can be alleviated by cross-tolerance after preconditioning.

DISCLOSURES

None.

REFERENCES