An expanding role of Toll-like receptors in sepsis-induced acute kidney injury

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Among the various causes of acute kidney injury (AKI) in hospitalized patients, sepsis remains the most elusive and challenging for the practicing nephrologist. Decades of intensive basic, translational, and clinical research have failed to significantly alter the grim outcome of sepsis and sepsis-induced AKI (13). Nevertheless, active bench research continues to fuel the hope for successful therapies that will eventually actualize at the bedside.

Over the past few years, Toll-like receptors (TLRs) emerged as key players that mediate the cross talk between host and invading microorganisms. These pattern-recognition molecules, located primarily on cells of the immune system, transduce microbe-host interactions into complex signaling cascades that lead to the early inflammatory state characteristic of sepsis (1). This inflammatory response is needed to halt and eliminate the invading microorganisms. However, when uncontrolled, inflammation spills over and causes massive tissue damage. Furthermore, continued stimulation of TLRs can also lead to immune cell apoptosis, which results in immunosuppression, a late-phase trait of sepsis (4, 10).

Recently, the identification of TLRs on organs and tissues outside the immune system has added an unexpected level of complexity to our understanding of the role of these molecules. This was further confounded by the fact that TLRs can interact with nonmicrobial endogenous substances (14). Thus their role in disease now extends beyond sepsis and well into the realm of many autoimmune and inflammatory conditions (6). For example, TLR2 is known to be involved in renal ischemia-reperfusion injury in addition to its role in interacting with gram-positive bacteria (11). Similarly, the endotoxin receptor TLR4, a key player in gram-negative sepsis, also mediates kidney injury in other conditions like ischemia and cisplatin toxicity (3, 7, 8, 18, 21). Yasuda and colleagues (20) show for the first time that TLR9, previously implicated in the pathogenesis of lupus nephritis, is an important player in sepsis and sepsis-induced AKI (19).

In their study, a modified model of polymicrobial sepsis induced by cecal ligation and puncture (CLP) was utilized in mice. The mortality and severity of renal damage were substantially ameliorated by chloroquine, an inhibitor of endocytic trafficking. DNA byproducts are endogenous ligands of TLR9 (12). Because of this possibility, this model may be optimized to reveal a TLR9-mediated injury. Therefore, in light of these interesting results, consideration of specific TLR9 ligands, perhaps in combination with other factors released by bacterial lysis, might represent a fruitful area of investigation with the potential to delineate pathophysiological mechanisms of sepsis-induced AKI.

Previous studies by this group demonstrated that TLR-4 null mice were as sensitive as wild-type controls to this CLP model of sepsis-AKI (5).

A major source of confusion in sepsis research stems from the various animal models utilized. The commonest model encountered in the literature relies on purified endotoxin injection. This model is easy to perform and very reproducible. The dose of endotoxin can be tailored to achieve a broad spectrum of injury and organ damage. Nevertheless, it generates a very elevated cytokine profile that is rarely attained in clinical sepsis (16). CLP is a model of polymicrobial sepsis. It results in lower systemic cytokine levels and thus seems more clinically relevant. The roles of specific TLRs should be investigated with caution because of the polymicrobial nature of this model. Indeed, mutations in specific TLRs may not significantly alter the pathophysiology of the disease. Conversely, the absence of MyD88, a downstream adaptor molecule common to many TLRs, reduces the inflammatory burst and may even lower mortality (9, 17).

The model utilized in the paper by Yasuda and colleagues (20) is a variant of CLP. It utilizes broad-spectrum antibiotics and vigorous hydration to mimic the clinical setting. This aspect of the model is useful in assessing efficacies of potential therapies in a setting in which a patient would be receiving standard supportive care. It is interesting that the failure of TNF-α blocking therapy in clinical trials, which were predicated using data derived from endotoxin-stimulated AKI, was also not effective in this modified CLP model (20). However, the model introduces potential problems for understanding the underlying pathophysiology. For example, what is the organism responsible for the septic state in this model? Is the nature of organ pathology altered by the anti-inflammatory and anti-apoptotic properties of antibiotics? Finally, antibiotics can cause bacterial lyses and the release of bacterial DNA into the circulation. DNA byproducts are endogenous ligands of TLR9 (12). Because of this possibility, this model may be optimized to reveal a TLR9-mediated injury. Therefore, in light of these interesting results, consideration of specific TLR9 ligands, perhaps in combination with other factors released by bacterial lysis, might represent a fruitful area of investigation with the potential to delineate pathophysiological mechanisms of sepsis-induced AKI.

Because all models have both limitations and advantages, the potential implications of the current study may comprise at least two possibilities that deserve further consideration. One possibility is that this model, by removing bacteria, exaggerates a TLR9 response that would otherwise be minimal in a clinically relevant setting. Conversely, this model may allow the identification of a previously unsuspected pathway present in patients that are unresponsive to current treatment regimens. If this is the case, it also offers a potential therapeutic regimen to treat patients that do not manifest improvement in the face of traditional therapy.

In conclusion, our understanding of human sepsis is driven to a certain degree by the animal models utilized. It is very important to fully understand all the implications of a specific
model and to carefully examine the end points investigated: cytokine generation, organ pathology, or overall mortality. Therapeutic maneuvers might alter cytokine profiles and reduce organ damage without affecting overall mortality. It is very possible therefore that no treatment of sepsis will acquire silver bullet status. Human sepsis is a very complex condition, and it is very likely that its treatment will remain multifaceted.

REFERENCES