SIGNIFICANCE STATEMENT

Gram-negative sepsis carries high morbidity and mortality and frequently results in kidney injury. To date, except for supportive measures, there are no known treatments that alter the outcome of septic patients. In animal models, preconditioning with low dose endotoxin confers unparalleled protection against lethal models of sepsis. Here, we used endotoxin preconditioning as a discovery platform to identify renal and systemic protective mechanisms in sepsis. We found that preconditioning causes macrophage clustering around S1 tubules. Both the clustered macrophages and S1 tubules were essential for successful renal protection. Unbiased omics identified a wide array of S1 and macrophage-derived molecules that could mediate protective preconditioning. Targeting these molecules has great potential for the treatment of human sepsis and sepsis-induced renal injury.