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Inflammation in Ischemic Acute Kidney Injury (AKI)

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Ischemic acute kidney injury (AKI) is still a devastating disease with high mortality rate and can affect longterm graft dysfunction in kidney transplantation. Recently, much progress has been made in defining pathogenetic mechanisms that contribute to ischemic AKI. A variety of molecular responces occur and result in endothelial and epithelial cell injury, leading to decreased glomerular filtration rate. Inflammation or activation of immune system has been known to be important in extension phase of AKI, causing cell deaths. Although earlier studies demonstrated and addressed the "destructive role of inflammation", recent findings suggest that inflammation or activation of immune system in AKI is much more complex.

Following ischemia/reperfusion (I/R), neutrophils adhere to vascular endothelium through a series of events that involve upregulation of adhesion molecules and are known to produce injurious molecules, such as proteases, reactive oxygen species (ROS) and proinflammatory cytokines. Adherent neutrophils, together with platelets, and red blood cells, also can plug capillaries of vasa recta in outer medulla, aggrevating tissue hypoxia. Although evidence in human is still lacking, neutrophils are thought to contribute to initiation of kidney injury. Macrophages have also been known to infiltrate into kidney following I/R and depletion studies using liposome clodronate (dichloromethylene bisphosphonate) clearly demonstrated the important contribution of macrophages in the initiation phase of kidney injury. Early macrophage activation seems to be mediated as part of innate immune activation through toll like receptors and participate in injury by secreting proinflammatory cytokines, chemokines, ROS and nitric oxide. However, given the heterogeneity of macrophage phenotypes according to their activation status, their critical role in regeneration or repair process can also be suggested. Kidney resident dendritic cells are abundantly distributed in interstititium and their trafficking to draining lymph node in systemic or localized renal parenchymal injury has been reported, suggesting their role linking innate and adaptive immune response, but their role in kidney injury needs to be further investigated.

Despite controversies, evidence that T cells play important role in pathogenesis of AKI has been accumulating. T cell deficient (nu/nu) mice are markedly protected from I/R and adoptive transfer of T cell restore the injury phenotype, suggesting that T cells are key mediator of I/R induced kidney injury. Alternative approaches using CTLA-4Ig to block B7-CD28 costimulatory pathway, or administration of FTY720, a nonspecific S1P analog that inhibits lymphocyte egress from secondary lymph node into circulation, showing protection from I/R injury, support a pathogenetic role of T lymphocyte in ischemic AKI. However, although the mechanism is not clear, a protective function of T cells has also been reported. T cells isolated from ischemic kidney, when transferred to T cell deficient mice, attenuated kidney injury.

Maladaptive inflammatory response and activation of immune system contribute to kidney injury substantially. However, this complex proinflammatory response or immune activation may also be beneficial as a defense mechanism against danger signal that has evolved. Understanding precise mechanisms of inflammation or immune activation can allow better prevention or treatment of AKI and also can lead to better graft survival in organ transplantation.