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The Role of macrophages in acute kidney injury

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Infiltrating cells play an important role in both the development of and recovery from acute kidney injury (AKI). Macrophages and renal dendritic cells are of particular interest because they can exhibit distinctly different functional phenotypes, broadly characterized as proinflammatory (M1) and tissue reparative (M2) phenotypes. We investigated the role of resident renal macrophages and dendritic cells in recovery from acute kidney injury in response to ischemia/reperfusion or a novel model of selective proximal tubule injury. For the latter model, we generated a transgenic mouse expressing the human diphtheria toxin receptor selectively in proximal tubule. Diphtheria toxin (DT) induced-acute kidney injury in transgenic mice was characterized by marked renal proximal tubular cell apoptosis. In both models, macrophage/dendritic depletion during the recovery phase led to greater functional and histologic injury and delayed regeneration. Following ischemia/reperfusion-induced acute kidney injury, there were early increases in renal macrophages derived from circulating monocytes that expressed "M1" (inflammatory) markers, followed by accumulation of renal macrophages/dendritic cells with an "M2" (wound healing) phenotype. In contrast, in renal injury induced by DT, only reparative macrophages/dendritic cells increased. Therefore, these studies demonstrate that CSF-1-mediated expansion and polarization of resident renal macrophages/dendritic cellsis a novel and important mechanism mediating renal tubule epithelial regeneration following acute kidney injury.

Colony Stimulating Factor-1 (CSF-1) is an important factor mediating the recovery from AKI, and CSF-1 can stimulate macrophage and dendritic cell proliferation and polarization during the recovery phase of AKI. The kidney, and specifically the proximal tubule, is a major source of intrarenal CSF-1 production in response to AKI. We induced selective deletion of proximal tubule CSF-1 to determine its role in expansion and proliferation of renal macrophages and dendritic cells and in recovery from AKI. We found that in models of AKI, there was decreased M2 polarization, delayed functional and structural recovery and increased tubulointerstitial fibrosis. These studies provide definitive evidence for an important role of intrarenal CSF-1 production in mediation of macrophage/dendritic cell polarization and recovery from AKI.

Cytokines IL-4 and IL-13 also play important roles in polarization of macrophages/dendritic cells to an M2 phenotype, which is important for recovery from acute kidney injury (AKI). Both IL-4 and IL-13 activate JAK3/STAT6 signaling. In mice with selective diphtheria toxin receptor expression in proximal tubule ("DTR mice"), a relatively selectiveJAK3 inhibitor, tofacitinibled to more severe kidney injury, delayed recovery from AKI, increased M1 markers and decreased M2 markers of macrophages/dendritic cells and development of more severe renal fibrosis following DT administration. Similarly, there was delayed recovery and increased tubulointerstitial fibrosis in DT-treated DTR mice with tamoxifen-inducible deletion of both IL-4 and IL-13, with increased levels of M1 markers (iNOS and CCL3) and decreased levels of M2 markers (arginase-1, IL-4Rα, and CD206) in macrophages/dendritic cells. Furthermore, deletion of IL-4 and IL-13 led to decreased M2a markers but had no effect on M2c markers. Deletion of IL-4 and IL-13 also inhibited recovery from ischemia/reperfusion injury in association with increased M1 markers and decreased M2 markers and promoted subsequent tubulointerstitial fibrosis. These studies demonstrate that IL-4 and IL-13 are required to effectively polarize macrophages/dendritic cells to an M2a phenotype and to promote recovery from acute kidney injury.