Macrophage Dynamics in AKI to CKD Progression

Gilbert R. Kinsey
Division of Nephrology, Center for Immunity, Inflammation, and Regenerative Medicine, University of Virginia Health System, Charlottesville, Virginia

doi: 10.1681/ASN.2013101110

Stemming from the recent and robust clinical data confirming that AKI does indeed increase the likelihood of developing CKD (reviewed by Chawla and Kimmel1), numerous preclinical studies have offered insight into how the transition from AKI to CKD occurs. However, our understanding of this multifactorial process is incomplete. This knowledge is critical if we are to advance therapeutic strategies to combat the detrimental progression of renal injury. The development of CKD is thought to be promoted by an aberrant wound healing response involving tubular epithelial cells (TECs), fibroblasts, pericytes, myofibroblasts, fibrocytes, immune cells, and others, which leads to progressive fibrosis in the kidney and loss of viable nephrons.2 Previous studies have demonstrated that cell cycle arrest of TECs,3 as well as epigenetic modifications in renal fibroblasts,4 are key components in fibrogenesis and the decline in renal function. In an integrated model,5 cell cycle arrest of TECs leads to unchecked production of profibrotic mediators such as TGF-β and connective tissue growth factor, which induce sustained fibroblast activation and proliferation causing excessive extracellular matrix production, establishment of fibrotic lesions, and CKD.

The inflammatory nature of AKI, involving resident cells of the renal mononuclear phagocytic system6,7 and infiltrating immune cells,8 suggests that leukocytes and their products would also influence the fate of the injured kidney. For example, sustained leukocyte accumulation and activation inside the kidney would promote extended periods of ischemia due to vascular congestion and may induce direct tubular and endothelial cell damage by the release of inflammatory mediators. Macrophages are among the innate leukocytes that rapidly accumulate in the kidney and promote inflammation in the acute phase of AKI,9,10 yet macrophages also have a critical role in wound healing as scavengers of proinflammatory cell debris and as promoters of regeneration.7,10–13 It should be mentioned here that the study of renal resident and/or infiltrating monocytes, macrophages, and dendritic cells is complicated by the overlapping phenotypes and surface marker expression by these different cell types in the kidney during health and injury,7 and use of the term macrophage to describe the cell types discussed herein is for simplicity.

The dual role of macrophages in AKI and subsequent repair and regeneration can be explained by the multiple phenotypes that a macrophage can adopt. There are several different major classifications of macrophage phenotype, including M1 (classically activated) and M2 (alternatively activated) macrophages. Most macrophages fall somewhere in the spectrum between M1 and M2 and may change their characteristics depending on their environment.13 M1 macrophages are considered pro-inflammatory and make cytokines such as IL-1, IL-6, and TNF-α, whereas M2 are mainly anti-inflammatory and express arginase, mannose receptor, IL-10, and IL-4 receptor-α.13 Thus, macrophages display considerable diversity and plasticity, such that the same cell can promote and inhibit inflammatory (or other) processes in different contexts.

Early studies suggested that macrophages promote initial ischemia reperfusion injury (IRI) in mice9,14 and promote fibrosis after IRI in rats.15 These observations were made when monocyte/macrophage migration to the kidney, through CCR2- and CX3CR1-dependent mechanisms, was attenuated,14 or when macrophages were depleted using liposomal clodronate before injury or within 3 days after ischemic insult, respectively. Recent mouse studies have added support to the hypothesis that M1-type, clodronate-sensitive macrophages do participate in initial injury,11,16 but have also revealed that macrophages are critical for the normal repair processes that inhibit the progression of fibrosis and CKD.10–12 Using several sophisticated mouse models, Lin et al. demonstrated that macrophages responding to renal injury produce and release the Wnt ligand Wnt7b that acts on injured and regenerating TECs to promote their continuation through the cell cycle and regeneration of the tubule basement membrane, thus re-establishing renal function and reducing fibrosis.12 Importantly, it was demonstrated that the M1 macrophages that traffic to the posts ischemic kidney change their phenotype in situ to the anti-inflammatory M2 phenotype.11 Collectively, these studies have greatly enhanced our understanding of the role of macrophages in the normal and abnormal injury and reparative response of the kidney after AKI. However, the studies investigating the influence of macrophages on recovery/transition to CKD have relied on liposomal clodronate and/or the CD11b-DTR mouse model, and these tools for macrophage depletion have several limitations (discussed elsewhere).7,17
Therefore, new ways to investigate macrophage dynamics in AKI to CKD progression are important for confirming and expanding our knowledge on this topic.

In this issue of JASN, Lech et al. have taken advantage of the monocyte/macrophage-specific expression of IL-1 receptor-associated kinase M (IRAK-M) to examine the role of macrophages in the progression of AKI in a novel way. IRAK-M is an inactive kinase that antagonizes Toll-like receptor– and IL-1β–mediated proinflammatory signaling in macrophages. IRAK-M expression is normally induced after activation of macrophages, and IRAK-M is recruited to the Toll-like receptor–MyD88-IRAK signaling complex, where it inhibits the downstream activation of NF-κB due to its lack of kinase activity. IRAK-M is critical for the phenomenon of LPS tolerance, whereby macrophages that were previously activated by LPS show a reduced response to subsequent exposures to LPS. In the kidney, IRAK-M mRNA is upregulated within 1 day of ischemic injury and remains elevated for up to 10 weeks. After confirming that the lack of IRAK-M did not influence the initial renal injury induced by IRI, the authors compared the progression of AKI to CKD in wild-type (WT) and IRAK-M–deficient (IRAK-M KO) mice. Whereas WT postischemic kidneys demonstrated normal reparative and regenerative responses to injury and no measurable increase in markers of renal fibrosis compared with contralateral nonischemic kidneys, IRAK-M KO kidneys did not recover from ischemic injury and displayed marked renal fibrosis and atrophy at 5 weeks after injury. The IRAK-M KO kidneys contain a large number of F4/80+ macrophages at 5 weeks after injury and these macrophages produced increased amounts of TNF-α compared with the WT controls. IRAK-M KO macrophages isolated from the postischemic kidney also expressed significantly more IL-12, IFN-γ, and inducible nitric oxide synthase mRNA (all M1 macrophage markers) compared with WT macrophages, whereas M2 macrophage markers were unchanged. When stimulated ex vivo, IRAK-M KO macrophages generated higher amounts of TNF-α and less IL-10 compared with WT macrophages. To test the functional significance of TNF-α in the AKI to CKD transition in IRAK-M KO mice, the authors treated these mice with the TNF-α inhibitor etanercept beginning at day 5 after ischemia. Compared with untreated ischemic IRAK-M KO mice, etanercept partially but significantly reduced the atrophy, F4/80+ macrophage accumulation, and fibrosis observed during the recovery from IRI-induced AKI. This suggests that TNF-α is one of the critical mediators of the impaired renal recovery in this model. In conjunction with the studies discussed above, this study demonstrates that, in addition to acquiring a proregeneration phenotype (i.e., M2-like, Wnt7b producing), an active process of dampening the proinflammatory M1 response in macrophages (through IRAK-M) is also required for the effective recovery and regeneration of the kidney after acute injury. Furthermore, this study adds independent confirmation of the role of macrophages in AKI to CKD progression, without the caveats of macrophage depletion strategies in the previously mentioned studies.

Understanding which renal cells are affected by macrophages after AKI is a key question. Coculture experiments suggest that macrophages in the recovering kidney interact with TECs to either promote their proliferation or induce TEC death, as shown in the current report by Lech et al., depending on the phenotype of macrophage. In vivo studies support the relevance of these in vitro findings. There are numerous other targets inside the regenerating kidney that are likely influenced by macrophage phenotype, including fibroblasts, myofibroblasts, endothelial cells, other leukocytes, and pericytes.

Continued exploration of the role of macrophages in the transition from AKI to CKD is likely to reveal novel ways to use pharmacologic agents to influence their phenotype or administer engineered macrophages with just the right phenotype to promote effective repair and regeneration of the kidney after AKI.

ACKNOWLEDGMENTS

The author thanks Dr. Mark D. Okusa, University of Virginia, for careful reading of the manuscript.

G.R.K. is supported by grants from the National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases (Grants K01-DK088967 and R03-DK099489).

DISCLOSURES

None.

REFERENCES


