EDITORS' CHOICE | KIDNEY DISEASE

Angiotensin Blockade—A Double-Edged Sword in Renal Failure

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"One size fits all" may be true in a number of situations, but not in the molecular machinery involved in chronic kidney disease (CKD). CKD affects 500 million people worldwide, including 20 million Americans. Renal fibrosis is typically progressive even with appropriate therapy and causes deterioration of renal function. Renin-angiotensin signaling (RAS), activated by renal damage, exacerbates fibrosis, providing a rationale for angiotensin blockers as a standard of care for the treatment of CKD patients. Challenging this long-held dogma, Zhang *et al.* present the "dark side" of angiotensin blockade in CKD.

In a well-established animal model of CKD caused by ureteric obstruction, the authors demonstrated robust infiltration of bone marrow–derived macrophages in the obstructed kidneys compared with that of controls. They used a macrophage-specific angiotensin receptor (*AT1*) gene knockout (Macro KO) to determine the biological function of the angiotensin system in infiltrating macrophages. The obstructed Macro KO kidneys showed striking renal fibrosis and collagen deposition. The number of infiltrating macrophages remained the same in wild-type (WT) and Macro KO obstructed kidneys, but the type of macrophages (M1 versus M2) differed between the two groups, as evidenced by their cytokine fingerprint and inflammatory potential. Macro KO obstructed kidneys contained predominantly M1 macrophages secreting proinflammatory and profibrotic cytokines such as interleukin-1 (IL-1), whereas WT obstructed kidneys harbored anti-inflammatory macrophages of the M2 subtype.

Coculture and cross-transplantation experiments further showed that in Macro KO obstructed kidneys, IL-1 secreted by M1 macrophages up-regulated mediators of renal fibrosis through the IL-1 receptor on renal tubular epithelial cells. Experiments with losartan, a global angiotensin blocker, were particularly informative. Losartan's antifibrotic effect was blunted in WT obstructed compared with Macro KO kidneys because in WT kidneys, losartan also blocked the beneficial antifibrotic signaling in infiltrating macrophages.

Overall, it appears that RAS, which promotes renal fibrosis, also activates AT1 receptors on macrophages, polarizing them toward the M2 subtype and thus retarding fibrosis. The balance of these opposing processes may ultimately determine the progression of renal fibrosis. Thus, this study uncovers a potential shortcoming of global angiotensin blockade—worsening of renal fibrosis by blocking the protective antifibrotic pathway in macrophages. This study may partially explain the progression of renal fibrosis observed in some CKD patients on angiotensin inhibitors. The present study supports the development of cell-type–specific angiotensin blockers and the characterization of factors influencing the M2-to-M1 transition in macrophages, a potential target for renal fibrosis. While the complexity of RAS continues to unfold, a word of caution for global angiotensin blockade and a refinement of the paradigm to "multiple sizes fit one" are both warranted.

J. Zhang *et al.*, Type 1 angiotensin receptors on macrophages ameliorate IL-1 receptor–mediated kidney fibrosis. *J. Clin. Invest.* **124**, 2198–2203 (2014). [PubMed]

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