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Chemokine Receptor 5 Blockade Modulates Macrophage Trafficking in Renal Ischemic Reperfusion Injury

Kyung Don Yoo[1], Mi-Yeon Yu[3], Ran-hui Cha[2], Jae Wook Lee[5], Sunhwa Lee[3], Hajeong Lee[3], Jung Pyo Lee[4], Dong Ki Kim[3], Yon Su Kim[3], Seung Hee Yang[3]
[1]Department of Internal Medicine-Nephrology, Dongguk University Gyeongju Hospital, Korea, Republic of
[2]Department of Internal Medicine-Nephrology, National Medical Center, Korea, Republic of
[3]Department of Internal Medicine-Nephrology, Seoul National University Hospital, Korea, Republic of
[4]Department of Internal Medicine-Nephrology, SMG-SNU Boramae Medical Center, Korea, Republic of
[5]Department of Internal Medicine-Nephrology, National Cancer Center, Korea, Republic of

Objectives: The CC chemokine receptor 5 (CCR5) is an important regulator of macrophage trafficking in the kidney in response to inflammation and immunity. Thus, we investigated the role of CCR5 in the pathogenesis of experimental ischemic reperfusion injury (IRI).

Methods: Bilateral renal artery pedicle clamping for 30 minutes followed by reperfusion was performed on C57BL/6 mice (B6 WT) and B6.CCR5-deficient (B6.CCR5$^{-/-}$) mice. We performed an adoptive transfer of lipopolysaccharide (LPS)-treated RAW cells following macrophage depletion in mice.

Results: B6.CCR5$^{-/-}$ mice showed less aggravated IRI regarding apoptosis of tubular epithelial cells and creatinine (Cr) compared to that in B6 wild-type mice. CXCR3 expression on CD11b^{+} cells and inducible nitric oxide synthase (iNOS) were more attenuated in B6.CCR5$^{-/-}$ mice than in B6 wild-type mice. Conversely, the B6.CCR5$^{-/-}$ mice showed increased numbers of arginase-1 and CD206-expressing macrophages. Macrophage-depleted wild-type mice showed more severe injury than B6.CCR5$^{-/-}$ mice after the transfer of M1 macrophages. The adoptive transfer of LPS-treated RAW cells, which constitutively express iNOS for M1 tendency, reversed the functional protection against IRI in wild-type mice, but not in B6.CCR5$^{-/-}$ mice. When CCR5 was knocked out in macrophages, bone marrow-derived macrophages showed M2 macrophage activation, and the migration of bone-marrow-derived macrophages from wild-type mice toward the primary tubular epithelial cells with recombinant CCR5 increased. Moreover, the CCR5 blockade inhibited the migration of macrophages. Expression of phospho-CCR5 in the renal tissue of patients with transplant and glomerulonephritis was increased, showing a positive correlation with acute tubular necrosis severity.

Conclusions: These findings show that CCR5 deficiency favors M2 macrophage activation and may be a strategy for treating acute kidney injury by blocking CCR5.