

허혈성 급성신손상에서의 Chemokine Receptor 5의 역할

서울대학교병원¹, 서울대학교병원 신장연구소²

유경돈¹, 양승희², 이하정¹, 권영주¹, 양승민¹, 김연수¹

Chemokine Receptor 5 Blockade Modulates Inflammation and Immunity in Renal Ischemic Reperfusion Injury

Kyung Don Yoo¹, Seung Hee Yang², Hajeong Lee¹, Young Ju Kwon¹, Seung Min Yang¹, Yon Su Kim¹

Department of Internal Medicine¹, Seoul National University College of Medicine, Seoul, Korea
Kidney Research Institute², Seoul National University Hospital

Macrophages, which exhibit great pliability, are important components of renal ischemic reperfusion injury (IRI) and are closely correlated with loss of renal function. Chemokine Receptor (CCR) 5 signaling is involved in mechanisms of inflammation, and expression of chemokine (C-X-C motif) receptor by macrophages has been reported. We aim to determine the effect of macrophage phenotype on the expression of CCR5, the influence of the macrophage phenotype in blockade of CCR5 signaling and the relevance of this pathway in IRI.

Bilateral renal artery pedicles clamping for 30 min followed by reperfusion was performed to B6 wild type and CCR5 KO mice in order to investigate the functional role of macrophage/CCR5 in IRI.

CCR5 KO mice showed less aggravated IRI in terms of the apoptosis of tubular epithelial cells and creatinine compare to B6 wild type. CCR5 deficiency decreased mRNA expressions of TNF α , IFN γ and MCP-1 mRNA but increased mRNA expressions of IL-13. These changes were associated with a significant increase of M2 macrophage cells in CCR5 KO mice. Moreover, the absence of T cells in B6 wild type mice activated greater number of M2 macrophage cells and this led to attenuation of the severe renal injury. However, we could not find any difference of the renal injury in the CCR5 KO mice, irrespective of T cell depletion. Intra-renal mRNA expressions of IL-10, arginase1 and Mac2 were up-regulated in CCR5 KO mice rendered IRI, but the levels of those mRNA were not increased following the deletion of T cells. There was no difference in a number of M2 macrophage cells. In addition, CXCR3 positivity in CD11b+ cells and iNOS were decreased in CCR5 KO mice compared to that in B6 wild type mice. Bone marrow-derived macrophages from CCR5 KO mice were polarized towards CD206+M2 phenotype. The expressions of IL-10 effectively increased during the differentiation processes of macrophage cells. TAK 779, combined CXCR3 and CCR5 blockade, is effective in preventing apoptosis of renal tubular cells after transient hypoxia. Renal tissue of patients with delayed graft function frequently contained CCR5 cells, and the number of these cells tended to positively correlate with acute tubular necrosis severity. These findings show that CCR5 deficiency favors M2 macrophages activation, and that T cells are less involved in polarization of macrophages in CCR5 deficiency. Blocking CCR5 may provide a potential strategy for treating acute kidney injury.

Key Words: 케모카인, 급성신손상, 대식세포

Chemokine, Ischemic reperfusion injury, Macrophage