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CCR2, CCR5 면역신호가 신장 허혈-재관류 손상에 미치는 영향

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The Role of CCR5, CCR2 Signals on Renal Ischemia-Reperfusion Injury in Mouse Model

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Background: Various factors including chemokines participate in ischemia-reperfusion injury (IRI). CCR2 is known to be responsible for renal IRI and CCR5 together with its ligand RANTES are also assumed to be associated with renal IRI. We evaluated the role of CCR5 and CCR2 signal on renal IRI via in vitro hypoxia-reoxygenation experiment using human renal tubular epithelial cells (TECs) and in vivo IRI experiment using CCR5 and CCR2 knock out mice.

Methods: Human renal TECs were incubated at a hypoxic condition (1% O_2) for 6 hours and then, cells were placed under a normoxic condition (20% O_2) for 18 hours. Proliferation of TECs was determined using colorimetric MTS assay kits. IRI was induced in C57BL/6 wild, CCR5-/-, CCR2-/-, and CCR5-/-CCR2-/- mice. Kidney tissues were assayed for cytokines using a multiplex cytokine bead array system (Bio-Plex).

Results: In vitro, human renal TECs proliferated well under normoxic condition, but their proliferation was significantly hampered under hypoxic condition. Recombinant CCR5 more inhibited the proliferation of TECs with dose-dependent pattern, on the contrary, neutralizing antibody to CCR5 partially restored. In vivo, the absence of CCR2 and CCR5 lessened the severity of renal IRI, histologically and functionally. IRI induced tubular necrosis and the damage was more extensive in wild type mice than in knock out mice. The intra-renal infiltration of T cells and macrophages was markedly inhibited in knock out mice than in wild type mice. Tubular CCR2 expression was reduced in CCR5-/- mice and CCR5 expression was reduced in CCR2-/- mice, either. Level of serum BUN and creatinine was lower in CCR5-/- and CCR2-/- mice than in wild type, furthermore, CCR5-/-CCR2-/- mice showed the least level of those markers. Results from Bio-Plex revealed that these were mediated by IL-4, IL-10, and IL-13 pathway activation in knock out mice.

Conclusion: These findings demonstrate that absence of CCR5 together with CCR2 exert protective effects on kidneys, suggesting that CCR2 and CCR5 may be a feasible target in protecting kidneys from IRI.

Key Words: CCR2, CCR5 결손, 허혈-재관류 손상
CCR2, CCR5, ischemia-reperfusion injury