Inhibiting the Progression from AKI to CKD by Modulating the CCL20/CCR6 Pathway

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Background/Aims: Chronic kidney injury promotes renal inflammation and oxidative stress, highlighting precondition for organ fibrosis. Here, we investigated how chemokine receptor CCR6 and its ligand can alter acute kidney injury (AKI) to chronic kidney disease (CKD).

Methods: Unilateral ischemia-reperfusion injury (uIRI) was induced for 30 minutes in 7- to 8-wk-old male C57BL/6 mice, and the animals were observed for 4 weeks. Meanwhile, rats with 5/6 nephrectomy were performed to evaluate transcriptome changes via RNA sequencing at 8 weeks. In vitro experiments, primary-cultured human tubular epithelial cells (hTECs) were cultured on hypoxia (5% O2, CO2, and 90% N2, 4days) with/without CCL20 blocking antibody. In addition, CCR6/CCL20 expressions in kidney tissues of patients with CKD were assessed.

Results: In both animal models, the expression of CCL20 increased as inflammation and fibrosis increased. Therefore, a positive correlation was observed for CCL20 in fibrosis. Furthermore, CCL20 blockade in human tubular epithelial cells ameliorated apoptotic damage in a dose-dependent manner on hypoxia and ROS injury. Interestingly, the CCL20 blockade led to a more significant reduction of intracellular ROS, 8-OHDG, and ICAM-1 level. We also analyzed CCR6/CCL20 expression from patients with CKD stages 1-2/3/4-5, respectively. Morphometry of CCR6/CCL20 co-expression revealed that CKD stage 3 patients were more likely to possess CCR6 expressions than CKD stage 1-2 patients (p=0.001). At final, we confirmed that inflammatory maker such as TNFR1 and 2 were significantly increased in the CKD stage 3 group. compared to the CKD stage 1/2 group.

Conclusions: CCL20/CCR6 activation is associated with uIRI progression, and CCL20 may be an essential contributor. CCR6/CCL20 inhibition could be a potential therapeutic target for managing AKD progression to CKD.