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CCL20 blockade mitigates acute kidney disease progression via oxidative stress regulation

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Objectives: Chemokine receptor 6 (CCR6) and its ligand, CCL20, axis exhibits pleotropic effects for T and B cell interaction. We investigated pathogenic role of CCR6/CCL20 axis in acute kidney disease (AKD) using ischemic reperfusion injury (IRI) model.

Methods: This model was established by clamping unilateral renal artery pedicle for 25 minutes in C57BL/6 mice for IRI. We evaluated expression of CCR6/CCL20 at 4 week after IRI. In vitro study, conducted on hypoxia and H2O2-induced oxidative stress. CCR6/CCL20 expressions in kidney tissues of patients with AKD and chronic kidney disease (CKD) were assessed. Transcriptome changes was evaluated by RNA sequencing in rats with 5/6 nephrectomy.

Results: Tubular epithelial cell (TEC) apoptosis showed more severe IRI in B6 mice than in CCL20 antibody-treated mice. CCR6, NGAL mRNA expression, IL-8 level was higher on hypoxia than on normoxia and was attenuated by CCL20 antibody in primary cultured human TECs. Furthermore, CCL20 blockade ameliorates apoptotic damage in a dose-dependent manner on hypoxia and ROS injury. Interestingly, CCL20 blockade leads to more significant reduction of intracellular ROS, 8-OHDG and ICAM-1 levels. IRI provoked CCR6 expression that showed a similar severity in patients with AKD phenotype. We analyzed CCR6/CCL20 expression from 22/18/16 patients with CKD stages 1-2/3/4-5, respectively. Morphometry of CCR6/CCL20 expression revealed that CKD stage 3 patients were more likely to possess CCR6 cells than CKD stage 1-2 patients (10.94% vs. 5.79%, p=0.001). Kidney tissues of CKD patients frequently contained CCL20 cells and positively correlated with interstitial inflammation (p=0.001), and $CCL20^{+}CCR6^{+}$cells in CKD stage 3 patients. CCL20/CCR6 levels were overexpressed on 5/6 nephrectomy at 4 and 8weeks, in fibrotic kidney. Based on RAN-seq results, CCR 6 (fold-change >4) and CCL20 (fold-change >2) levels were increased after 8weeks, compared to sham operation.

Conclusions: CCR6/CCL20 pathway modulation could be a potential therapeutic target for managing AKD progression to CKD.