# CD137 Ligand Reverse Signals in Tubular Epithelial Cells Mediate Renal Ischemia-reperfusion Injury Through Recruitment of Neutrophils

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**Backgrounds:** Renal ischemia-reperfusion injury (IRI) after kidney transplantation is a major cause of delayed graft function. Tubular epithelium is a main site for cell injury during renal IRI and damaged tubular epithelial cells (TECs) seem to contribute to the initial recruitment of neutrophils, a key effector cell type for IRI, into kidneys by secreting CXC chemokines. However, the regulation of the initial signals that recruit leukocytes following IRI is not well understood.

**Methods:** We used a mouse model of acute kidney IRI to examine whether the interactions of costimulatory receptor CD137 on NK cells and its ligand (CD137L) on TECs are involved in the early phase of kidney inflammation that is caused by IRI.

**Results:** We report here that the specific expression of CD137 on NK cells and CD 137L on TECs are required for acute kidney IRI. Reverse signaling through CD137L in TECs results in their production of the CXCR2 ligands, CXCL1, and CXCL2 and subsequently induces neutrophil recruitment, actuating a cascade of proinflammatory events during kidney IRI.

**Conclusion:** Our results identify a previously unrecognized innate pathogenic pathway for renal IRI that involves the NK cell-TEC-neutrophil axis where CD137/CD137L interactions have the causal contribution of epithelial dysregulation to renal IRI. Therefore, the CD137L reverse signaling pathway in parenchymal cells such as TECs might be a good target to block the initial stage of inflammatory diseases, including renal IRI.

**Key Words:** Ischemic reperfusion injury, Reverse costimulatory signaling