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TLR2 Signaling in Tubular Epithelial Cells Initiates Sterile Tissue Inflammation by Recruiting NK Cells in Kidney Ischemic Reperfusion Injury

Jong Soo Lee[1], Hye Jung Kim[4], Hyun Chul Chung[1], Jongha Park[1]
Kyung Sun Park[1], Hee Jung Cha[3], Hong Rae Cho[2], Byung Suk Kwon[4]

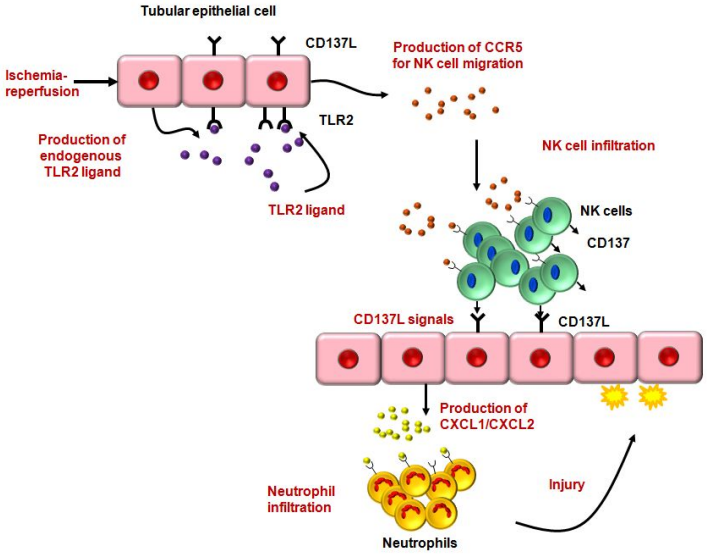
Division of Nephrology, Department of Internal Medicine[1],
Ulsan University Hospital, University of Ulsan College of Medicine
Department of Surgery[2], Ulsan University Hospital,
Department of Pathology[3], Ulsan University Hospital
School of Biological Sciences[4], University of Ulsan, Ulsan, Korea
Biomedical Research Center Ulsan University Hospital

Background: We have previously identified an inflammatory loop between tubular epithelial cells (TECs) and inflammatory cells during kidney ischemic reperfusion injury (IRI) (PNAS 2012). NK cells infiltrate the kidney early after ischemic reperfusion and approach the tubular epithelium. Infiltrating NK cells in turn stimulate TECs to produce CXCR2 chemokine by stimulating CD137L signaling and inducing neutrophil migration. Currently, the regulation of signals that recruit NK cells following ischemic reperfusion is not well understood. The aim of this study was to determine the mechanism of NK cell recruitment to the kidney after ischemic reperfusion.

Methods: We adopted mouse kidney ischemic reperfusion injury model. CD137-/-, CD137L-/- , CCR5-/- , and TLR2-/- C57BL/6 mice were used between 7 and 8 weeks of age. To identify interactions between inflammatory cells and TECs, we applied our own method which implants TECs under kidney capsule.

Results: We report here that endogenous TLR2 ligands released from ischemic TECs induce CCR5 chemokine expression, which is critical to promoting NK cell recruitment. By implanting CD137L-/- TECs into the kidney capsule of TLR2-/- mice, we further showed that TLR2-mediated NK cell recruitment is an uncoupled event that can occur independently of CD137L signaling in TECs, which is responsible for recruiting neutrophils. We found that TECs produced CCR5 chemokine, which are required for NK cell chemotaxis, early after ischemic reperfusion in a TLR2- dependent manner. Moreover, NK cell and neutrophil recruitment by TECs was a sequential and independent event. These results indicate that epithelial cells actively regulate sterile tissue inflammation more than was previously recognized.

Conclusions: Our findings identify TECs as both a target for kidney damage and also as a master regulator that actively modulates stepwise signaling, leading to the initiation and amplification of acute sterile inflammation which inflicts kidney IRI. Being clinically important, the signaling pathway of innate receptors in epithelial cells may therefore be a good target to block acute sterile inflammation resulting from tissue damage, including kidney IRI.



Key Words: 신세뇨관 상피세포, 자연살해세포, 톨양수용체2
Tubular epithelial cell, NK cell, TLR2