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Fate of Neutrophils in I/R Induced AKI

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Background: Neutrophils rapidly infiltrate kidney and detrimental in IRI. Although effective clearance of inflammatory cells seem to be prerequisite for kidneys to repair or restore normal function, precise mechanisms underlying resolution of inflammation or regeneration have not well been characterized. Here we show an in-vivo evidence that apoptosis, reverse transendothelial migration (rTEM), transepithelial migration into urinary space are important mechanisms in elimination of neutrophils and thus resolution of neutrophilic inflammation and repair following IRI.

Methods & Results: 1) apoptosis ; to determine the role of neutrophil apoptosis in resolution of inflammation, chimeric mice in which only bone marrow derived cells are resistant to apoptosis was created by transplanting bone marrows from apoptosis resistant Bax KO mice to sublethally irradiated WT mice (Bax KO^{BM}→WT). While initial Scr and neutrophil influx were comparable between Bax KO^{BM}→WT vs WT^{BM}→WT, persistence of neutrophils in Bax KO^{BM}→WT mice was associated with delayed functional, histologic recovery, higher level of tissue proinflammatory cytokines, and impaired regeneration throughout the recovery phase. 2) rTEM ; In contrast to naïve circulating neutrophils, neutrophils that have remigrated from the tissue back into circulation is known to have higher level of surface ICAM-1 expression and lower $CXCR_1$ expression. Number of ICAM-$^{1+}$ $CXCR_1^{low}$ neutrophils with rTEM phenotype began to appear from day 2 and predominate throughout the recovery phase (day 2-5). Blockade of JAM-C in vivo resulted in not only increase in circulating ICAM-$^{1+}$ $CXCR_1^{high}$ neutrophils, but also faster resolution of neutrophilic inflammation and functional, histologic recovery. Presence of Tomm-Horsfall protein in neutrophils obtained during the recovery phase (day 3) could suggest that these neutrophils are derived from injured kidneys. 3) Urinary expulsion ; Gr-$^{1+}$ neutrophils were also identified by flow cytometric analysis of sterile urine obtained in recovery phase.

Conclusion: We suggest that apoptosis, rTEM and transepithelial migration into urinary space are critically involved in natural resolution mechanisms of neutrophilic inflammation and also in repair process. Better identification of precise molecular pathoways involved in resolution of inflammation might hasten the development of new strategies to facilitate recovery in AKI.

Key Words: 급성신부전, 호중구
Acute kidney injury, Neutrophil