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Impact of aging on long-term renal outcomes following ischemia-reperfusion injury (IRI)

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Objectives: Acute kidney injury (AKI) in elderly is an important factor contributing to the high incidence of ESRD, but little is known about the mechanism by which aging affects AKI to CKD. Here, we investigated the effects of aging on long-term renal outcomes following IRI in animal models.

Methods:

In old (48wk) and young (7wk) C57BL/6 mice, 25min bilateral IRI was applied, and renal inflammatory cytokines as well as functional and histological changes were examined on day 1,3,7 and 28 after IRI.

Results: Before IRI, renal expression of IL-12 and IFN- γ was higher in old mice than in young mice, indicating upregulation of inflammatory response with aging. On day1 after IRI, there was no significant difference in renal function and tubular injury between old and young mice. However, the expression of TNF- α , IL-12 and IFN- γ was significantly increased on day 1 in old mice than in young mice. The M1 predominant inflammation persisted until 28 days after IRI in old mice. During recovery phase, renal expression of macrophage colony-stimulating factor (M-CSF) and IRF4 significantly increased in young mice, but was much blunted in old mice, suggesting impaired M-CSF/IRF4 signaling for M2 polarization in old mice. In addition, we observed more increased tubular G1 cell cycle arrest during recovery phase in old mice. In vitro study, tubular epithelial cells, pretreated with/without G1 arrest inducer, were co-cultured with M0 or M1 macrophages, and we found that M2 polarization was decreased when co-cultured with G1-arrested tubular cells, suggesting prolonged tubular G1 arrest might be partially responsible for impaired M2 polarization. Finally, the M1 predominant renal inflammation in old mice resulted in more fibrosis progression on day28, but had little effect on GFR loss.

Conclusions: These results suggest that a strategy targeting macrophage polarization may provide new therapeutic opportunities to improve renal outcome in elderly patients with AKI.