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Selective decontamination of digestive tract attenuates kidney ischemia/reperfusion injury and distant organ damage via immune modulatory effect

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Emerging evidence suggests the critical role of gut as an amplifier of systemic inflammation in diverse pathological conditions. Selective decontamination of digestive tract (SDD) is known to inhibit colonization by aerobic gram-negative bacilli while preserving anaerobic microflora and is currently being used to prevent infection, and also to reduce mortality in critically ill patients. SDD could inhibit macrophage maturation in kidney and bone marrow, attenuated kidney ischemic reperfusion injury (IRI)(1). Besides, gut microbioime is responsible for macrophage maturation as well as T cells(2–4). and We aimed this study to examine the effect of SDD on the severity of kidney injury as well as on distant organ damage and the underlying mechanisms.

We used 6-week-old male C57L/B6 mouse (Orient Bio Inc. Seoul, Korea) bilateral ischemia/reperfusion injury (IRI) after SDD, which was the mixture of three antibiotics (neomycin 25mg/kg, ampicillin 60mg/kg, and metronidazole 25mg/kg, vancomycin 0.5g/L) given by orogastric gavage once daily for 12 days. The renal function, colon permeability, immune cells, serum endotoxin level, local and systemic inflammation level were assessed. We measured liver function test to check distant organ injury. Stool microbiome analysis was also performed. The study was approved by the Korea University College of Medicine Laboratory Animal Research Center institutional review board (IRB No. KOREA-2018-0094).

Kidney IRI induces intestinal dysbiosis
Next generation sequencing (NGS) of intestinal microbiom showed that kidney IRI provoked both qualitative and quantitative changes of microbiota on day 1 after IRI. We observed significant reduction in species diversity as well as in the number of OTUs. Hallmarks of kidney IRI induced dysbiosis within the most abundant phyla included the decrease in relative abundance of Bacteroides, Lactobacillus and the increase in relative abundance of E-coli and Proteus. Short chain fatty acids (SCFA) level was significantly lower in stool of IRI mice compared to sham operated mice
Kidney IRI induced dysbiosis is associated with colon inflammation and increased intestinal permeability
Following IRI, the number of $Ly6G^{+}$ neutrophils and $F4/80^{+}$ macrophages increased significantly, suggesting the development of subclinical colitis. Out of macrophage subset, $CX_3CR_1^{int}$ $Ly6c^{+}$ proinflammatory expansion was prominent with increased expression of iNOS, while that of arginase showed a significant decrease in colon of AKI mice, suggesting that these macrophages are likely to be M1 type macrophages. Permeability measured by fluorescein activity of orally administered FITC-dextran significantly increased in the blood along with increased endotoxin level, suggesting that kidney IRI provoked disruption in barrier function. We also examined the protein expression level of tight junction proteins in colon and found that claudin-1 expression significantly decreased after IRI. In addition to altered tight junction proteins, the number of TUNEL positive apoptotic cells increased significantly in colon of IRI mice. Altered regulation of tight junction proteins as well as increased apoptosis of colon epithelial cells are likely contribute to abnormally increased intestinal permeability after IRI.
SDD induced renoprotective effect is partially mediated by Tregs
Administration of oral antibiotic combination before IRI resulted in marked renoprotective effect. It also led to more preserved intestinal permeability with reduced colon inflammation and apoptosis.

SDD was associated with expansion of M2 macrophage in colon and also with expansion of Tregs. Percent Tregs as well as Foxp3 expression in colon, spleen increased significantly and depletion of Tregs by the PC61 anti-CD25 antibody partially offset the renoprotective effect of SDD. Immune cells from mesenteric lymph nodes from SDD mice showed significantly reduced proliferative response to anti-CD3/anti-CD28 stimulation suggesting the tolerance induction by SDD.

In conclusion, we have provided evidence that kidney IRI provoke dysbiosis and profound gut-derived systemic inflammation that further amplify kidney injury. Although our study suggest that targeting this gut derived inflammation might provide novel strategies in prevention or treatment of AKI, more studies identifying the underlying mechanisms of kidney-gut crosstalk are needed.

1. Emal D, Rampanelli E, Stroo I, Butter LM, Teske GJ, Claessen N, et al. Depletion of Gut Microbiota Protects against Renal Ischemia-Reperfusion Injury. J Am Soc Nephrol. 2017 May;28(5):1450–61.
2. Pils MC, Bleich A, Prinz I, Fasnacht N, Bollati-Fogolin M, Schippers A, et al. Commensal gut flora reduces susceptibility to experimentally induced colitis via T-cell-derived interleukin-10. Inflamm Bowel Dis. 2010;17(10):2038–46.
3. Rivollier A, He J, Kole A, Valatas V, Kelsall BL. Inflammation switches the differentiation program of Ly6Chi monocytes from antiinflammatory macrophages to inflammatory dendritic cells in the colon. J Exp Med. 2012 Jan 16;209(1):139–55.
4. Ueda Y, Kayama H, Jeon SG, Kusu T, Isaka Y, Rakugi H, et al. Commensal microbiota induce LPS hyporesponsiveness in colonic macrophages via the production of IL-10. Int Immunol. 2010 Dec;22(12):953–62.