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Soluble RAGE Prevents Sepsis-induced Acute Kidney Injury

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Background: Septic AKI is mainly a tubular injury mediated by inflammation and the receptor for advanced glycation endproducts (RAGE) is involved in the pathogenesis of various inflammatory diseases including sepsis. Soluble RAGE (sRAGE) competitively inhibits the binding of RAGE ligands and is proposed as a potential therapeutic agent. However, little is known about the efficacy of sRAGE in septic AKI.
Purpose: This study was undertaken to investigate the effect of sRAGE on renal function, epithelial-mesenchymal transition (EMT), and inflammatory cells infiltration in septic AKI.
Methods: In vivo, C57/BL6 mice were subjected to cecal ligation and puncture (CLP) or sham operation (control) and were maintained for 24 hours. CLP mice were pretreated either with diluent or sRAGE intraperitoneally (CLP+sRAGE) at 1 hour before operation. At the time of sacrifice, blood was collected for serum BUN and renal tissues for further experiments. In vitro, NRK-52E cells were cultured in DMEM media with or without lipopolysaccharide (LPS, 2 ng/mL). To examine the effect of sRAGE on LPS-induced tubular cell injury, LPS-treated NRK-52E cells were also incubated with sRAGE (1 μg/mL) or RAGE siRNA. Western blot analysis was performed to evaluate E-cadherin, α-smooth muscle actin (α-SMA), and ICAM-1 protein expression. Immunohistochemistry was carried out with renal tissues.
Results: The increase in serum BUN levels in CLP mice were significantly abrogated by the administration of sRAGE (62.4$\pm$24.2 vs. 17.9$\pm$5.67 mg/dL, $p<0.05$). The ratios of α-SMA/E-cadherin protein expression were significantly higher in CLP model compared to control mice ($p<0.05$). The expression of ICAM-1 protein was also significantly increased in CLP model compared to control mice ($p<0.05$). These changes in CLP model were significantly ameliorated by sRAGE pretreatment ($p<0.05$). sRAGE also significantly reduced the number of infiltrated inflammatory cells within kidney in CLP mice. In vitro, RAGE protein expression was significantly increased in LPS-stimulated tubular epithelial cells, and this increase was attenuated by sRAGE and RAGE siRNA ($p<0.05$). The ratios of α-SMA/E-cadherin and ICAM-1 protein expression were significantly increased in LPS-stimulated cells, which were significantly abrogated by RAGE inhibition ($p<0.05$). Conclusions: These findings suggest that RAGE plays a role in the pathogenesis of septic AKI and its inhibition by sRAGE may be a potential therapeutic target for AKI in severe sepsis.

Key Words: Sepsis, AKI, sRAGE