

Soluble RAGE as a potential therapeutic agent in inflammation associated renal injury

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Objectives : Receptor for advanced glycation end products (RAGE) has been implicated in the pathogenesis of inflammatory renal injury. A recent study also suggests that RAGE and its ligands, including high-mobility group protein box1 (HMGB1), play an important role in extracellular matrix (ECM) accumulation in tubulointerstitial fibrosis in the kidney. Meanwhile, soluble RAGE (sRAGE) competitively inhibits the binding of RAGE ligands to RAGE, and thus attenuates the development of RAGE-induced inflammatory cascades. The aim of this study was investigated the effects of sRAGE on septic AKI and unilateral ureter obstruction (UUO)-induced renal fibrosis models.

Methods : C57/BL6 mice with cecal ligation and puncture (CLP) were injected with sRAGE (CLP+sRAGE) 1 hr before operation. SD rats were also pretreated with sRAGE 1hr before UUO operation and then treated with sRAGE for every 48hours until 10days. In addition, NRK-52E cells were treated with lipopolysaccharide (LPS, 1 µg/ml), HMGB1 (10 µg/ml) and sRAGE (1 µg/ml). RAGE-associated signaling molecule, apoptosis-related protein, and ECM accumulation related protein expression levels were analyzed.

Results : BUN and Cr levels were significantly higher in CLP mice compared to control, and these increases were significantly abrogated in CLP+sRAGE mice. Renal inflammatory cascades and apoptosis were activated in CLP mice and their increases were attenuated by sRAGE pretreatment. IN UUO models, RAGE and HMGB1 expression and ECM accumulation were significantly increased. All these changes were significantly ameliorated by sRAGE treatment. In vitro, RAGE-associated activation of mitogen-activated protein kinase and increases in apoptosis-related protein expression in LPS-stimulated cells were significantly ameliorated by sRAGE. In addition, the ECM related protein expressions were significantly increased in HMGB1-stimulated NRK-52E cells, and these increases were attenuated by sRAGE.

Conclusions : These findings suggest that sRAGE may be a potential therapeutic approach to kidney diseases associated with septic AKI and renal fibrosis transited from AKI.

Keywords : septic AKI, renal fibrosis, HMGB1, soluble RAGE