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일측성 요폐색에 의한 신섬유화 모델에서 soluble RAGE의 효과

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Soluble RAGE Prevents Renal Fibrosis in Rodent Unilateral Ureteral Obstruction Model

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Background: Tubulointerstitial fibrosis is a typical pathologic finding in chronic kidney disease and is associated with disease progression. A recent study reported that high mobility group protein box1 (HMGB1) and the receptor for advanced glycation endproducts (RAGE) as its downstream signaling was implicated in the pathogenesis of epithelial-mesenchymal transition in renal tubular cells. The aim of this study was to investigate the therapeutic role of soluble RAGE (sRAGE) in renal fibrosis in rodent unilateral ureteral obstruction (UUO) model.

Methods: In vivo, SD rats were pretreated at 1 hour before and every 48 hour after UUO operation either with diluent (n=6) or sRAGE (n=6) intraperitoneally. At the time of sacrifice, blood and renal tissues were collected. In vitro, NRK-52E cells were cultured in DMEM media with or without HMGB1 (10 μg/mL) or lipopolysaccharide (LPS, 1 μg/mL). To examine the effect of sRAGE on HMGB1- or LPS-induced tubular epithelial cell injury, NRK-52E cells were also incubated with sRAGE (1 μg/uL).

Results: The protein expression of RAGE was significantly higher in UUO rats compared to the control group. The mRNA and protein expressions of fibrosis-related molecules such as fibronectin, α-SMA, and Collagen I, and JNK and ERK protein expressions were significantly higher in UUO rats compared to the control group. These changes in UUO rats were significantly ameliorated by sRAGE treatment. Tubulointerstitial fibrosis assessed by Masson's Trichrome staining confirmed the protective effect of sRAGE in UUO rats. In vitro, the expressions of fibronectin, α-SMA, and Collagen I were significantly increased in cultured tubular epithelial cells stimulated by HMGB1 or LPS, and these increases were attenuated by sRAGE. NF-κB and MAP kinase pathway were also activated in HMGB1- or LPS-stimulated renal tubular cells, which were significantly abrogated by RAGE inhibition.

Conclusion: These findings suggest that RAGE plays a role in the pathogenesis of renal fibrosis and its inhibition by sRAGE may be a potential therapeutic target for renal fibrosis.

Key Words: 신 섬유화, 일측성 요관 폐색, sRAGE
Renal fibrosis, UUO, sRAGE