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진행성 만성 콩팥병에서 RBP peptide를 이용한 항섬유화 치료의 효과

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RBP-peptide Based Anti-fibrotic Therapy in Chronic Progression of Renal Disease

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Interstitial fibrosis, associated with extensive accumulation of extracellular matrix in the renal cortical interstitium, is correlated to the progression of chronic kidney disease. In previous study, Oh et al introduced a novel recombinant fusion protein of albumin-retinol binding protein (albumin domain I/III coupled to RBP, R-III), which induced phenotypic reversal of pancreatic stellate cells from the myofibroblast to the fat storing cells. Considering the importance of pathlogic changes into myofibroblasts in renal fibrosis and the increased uptake of R-III in the kidney, we investigated the potential of R-III to reduce fibrogenic and inflammatory responses in an established interstitial fibrosis model-unilateral ureteric obstruction (UUO). C57/BL6J mice were divided into three groups: sham-operated group, vehicle-treated UUO group, and R-III treated UUO group. After inducing UUO, R-III was injected every day for 7 days through the tail vein. Compared to UUO group, R-III treated group showed decreased urinary protein excretion ($p<0.05$) and lower level of urinary 8-isoprostane ($p<0.05$). R-III treatment also suppressed the increase of renal levels of MCP-1,TGF-β1, CTGF, collagen(I) ($p<0.05$) and phosphorylation of Smad3. Sirius red staining also showed decraesed in renal fibrosis by fusion protein treatment. Myofibroblast cells were increased in the tubulointersterstitial tissues in UUO kidney confirmed by aSMA staining, and RBP-peptide was co-localized in the aSMA positive myofibroblast cells. Interestingly, most fusion protein was localized In the tubule and myofibroblast cells in the obstructed kidney by IHC. Additionally, macrophage infiltration measured by F4/80 staining was markedly decreased in fusion protein treatment. In cultured cell lines, the uptake of fusion protein was increased in the podocyte and relatively little uptake was also seen in HK2 proximal tubule cells, mouse mesangial cells(MMC). The expression of STRA6, RBP specific receptor, was increased in the podocytes, MMC. Our results suggest that the recombinant fusion protein (albumin-RBP) has an anti-fibrotic effect in an experimental UUO murine model, probably via RBP receptor mediated uptake to the kidney.

Key Words: 신섬유화, 일측요관폐색, 재조합단백질(R-III)
Renal fibrosis, UUO, Albumin-RBP fusion protein