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Growth Arrest and DNA Damage 45γ의 일측폐색성요관에서의 증가와 배양 신세뇨관세포에서의 기능에 관한 연구

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Upregulation of Growth Arrest and DNA Damage 45γ in Unilateral Ureteral Obstruction and in vitro Evidence of its Function in Kidney Tubular Cells

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Background : Growth Arrest and DNA Damage 45γ (GADD45γ) is a stress responsive molecule that interacts with cell cycle regulating proteins. GADD45γ is associated with the cell cycle checkpoint, apoptosis and activation of mitogen activated protein kinases (MAPK) in some cell lines. With regard to kidney diseases, data implicating GADD45γ are virtually non-existent.

Methods : We performed differential display analysis using rat kidneys with unilateral ureteral obstruction (UUO) to search for novel genes that are associated with tubulointerstitial injury. The results were substantiated with competitive polymerase chain reactions (PCR) and in situ hybridization. To determine whether GADD45γ is a relevant molecule in human kidney disease, we examined GADD45γ expression in kidney biopsy tissue by immunohistochemisty. To identify its function, GADD45γ was overexpressed in human renal tubular cells using adenoviruses harboring the open reading frame, and Western blotting and microarray analysis were done. Microarray results were verified using PCR and ELISA.

Results : We found that GADD45γ is a molecule that is significantly upregulated in UUO. The upregulation of GADD45γ started as early as 6 h post-UUO, and remained elevated up to 3 d post-UUO. GADD45γ mRNA was strongly expressed in the kidney tubules with UUO even before they were dilated. GADD45γ was expressed in biopsy specimens with chronic glomerulonephritis, but not in those with normal findings. In cultured renal tubular cells, GADD45γ strongly activated p38 MAPK, but not ERK or JNK. Microarray analysis showed that the expression levels of 164 genes were differed by more that two fold difference. We selected 24 genes that have been considered implicated in kidney diseases and performed PCR. We found that GADD45γ significantly upregulated the mRMA expression of proinflammatory chemokines including chemokine (C-C motif) ligand 20 (CCL20), chemokine (C-X3-C motif) ligand 1 (CX3CL1), interleukin 8 (IL8), and of fibrosis related factors including matrix metalloproteinase-1, -9, -10, bone morphogenetic protein 2, decorin and transforming growth factor-β1. GADD45γ markedly increased the proteins levels of CCL20, CX3CL1 and IL8 in cell cultured media.

Conclusion : This study demonstrates for the first time that GADD45γ is upregulated in UUO. We also show evidence that GADD45γ is linked to the production of various molecules that may be implicated in kidney disease pathogenesis.