The role of the EGF receptor in albumin-induced renal fibrosis

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During kidney disease urinary albumin levels increase dramatically. Albuminuria is recognised as an indicator of renal dysfunction is also a major mediator of renal damage and fibrosis. The mechanisms behind albumin induced-renal fibrosis are still unclear, but a number of lines of evidence suggest involvement of the epidermal growth factor (EGF) receptor. Under normal conditions, the EGF receptor plays a key role in the maintenance of normal epithelial cell function, however, inappropriate activation has been shown to have detrimental effects in a number of physiological settings. The primary aim of this study was to examine the role of the EGF receptor in albumin-induced fibrotic effects in proximal tubular cells.

Experiments were performed using the human renal proximal tubular epithelial cell line, HK-2. The effects of increasing albumin concentrations (0.1, 1 and 5mg/ml) were examined over 72 hours. Firstly, the effects of albumin on fibronectin expression were examined. Fibronectin is a major component of extracellular matrix (ECM) and is significantly increased during tubulointerstitial fibrosis. In cell lysate and cell supernatant, fibronectin protein levels were significantly increased by treatment with 1 and 5 mg/ml albumin. Fibronectin protein levels are determined by a number of factors including synthesis and proteolytic degradation by the matrix-metalloproteases (MMPs). To investigate the mechanism of fibronectin accumulation, RT-PCR analysis was performed to assess the levels of fibronectin mRNA. Albumin treatment did not significantly affect fibronectin mRNA levels suggesting that the accumulation was not a transcriptional event. MMP activity is regulated by their physiological inhibitors the tissue inhibitors of metalloproteases (TIMPs). RT-PCR analysis revealed that albumin treatment resulted in an upregulation of TIMP1 mRNA levels leading to the hypothesis that fibronectin accumulation under high albumin conditions may be due to impaired degradation due to MMP inhibition. TIMP production has previously been linked to EGF-receptor activation in the PTECs. In this current study, under high albumin conditions, phospho-EGF-receptor levels were significantly increased. Co-treatment of PTECs with high albumin and an EGF-receptor antagonist, AG1478, resulted in inhibition of albumin-induced TIMP-1 upregulation and fibronectin accumulation. Further experiments revealed that albumin-induced effects were also mediated by the ERK1/2 mitogen activated kinase pathway, downstream of the EGF-receptor.

In conclusion, the results of this study suggest that albumin-induced fibrotic effects are mediated, at least in part by activation of the EGF-receptor. These findings provide novel insights into albumin-induced renal fibrosis and further elucidation of these mechanisms may identify new potential therapeutic strategies.