A16

Signaling Pathways Involved in Tubular Cell VCAM-1 Expressionin Response to Myoglobin

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Background : It is well known that reabsorbed albumin by proximal tubular cells is capable of exerting direct pro-inflammatory and pro-fibrotic effects. Myoglobin, one of the common endogenous nephrotoxins, is also taken up by proximal tubular cells through endocytosis. However, the cellular effect of myoglobin has not been known well. We investigated the signaling pathway linking myoglobin to the c-Src kinase, MAP kinase, activation of AP-1 and NF-κB, and vascular cell adhesion molecule-1 (VCAM-1) expression in human proximal tubular cells.

Methods : Activation of AP-1 and NF-κB were assessed by electrophoretic mobility shift assay. Phosphorylation of protein kinases including c-Src, p38, ERK1/2, JNK and amount of c-Jun was examined by western blot analysis. VCAM-1 mRNA and protein expression was measured by Northern blot analysis and cell ELISA.

Results : It was found that myoglobin induced activation of AP-1 and NF-κB. Myoglobin-induced AP-1 activation was mediated through activation of c-Src kinase, followed by MAP kinase (P38, ERK 1/2, JNK) pathway. And also myoglobin- inducedNF-κB activation was mediated through activation of c-Src kinase, followed by degradation of IκB-α. The c-Src kinase inhibitor, PP2 suppressed the myoglobin- induced c-Src kinase, ERK1/2 kinase, c-Jun, AP-1 and NF-κB. Myoglobin induced VCAM-1 mRNA and protein expression as well via AP-1 and NF-κB. PP2 and specific MAP kinase inhibitors inhibited the myoglobin- induced AP-1 and VCAM-1 expression. Protein kinase C inhibitors (staurosporine, calphostin), tyrosine kinase inhibitors (genistein, herbimycin A), anti-oxidants (NAC, tiron), intracellular calcium chelator (BAPTA-AM) and simvastatin suppressed the myoglobin- induced activation of c-Src kinase.

Conclusion : c-Src kinase played a central role in the signaling pathway that linked myoglobin to the activation of AP-1 and NF-κB and increased expression of VCAM-1. In addition, protein kinase C, tyrosine kinase, reactive oxygen species and intracellular calcium were involved in the myoglobin- induced activation of c-Src kinase.