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AMP-activated protein kinase 활성화가 TGF-β, angiotensin II, aldosterone, high glucose 및 albumin에 의한 epithelial-mesenchymal transition에 미치는 영향 및 그 기전

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AMP-activated Protein Kinase Inhibits TGF-β-, Angiotensin II-, Aldosterone-, High Glucose- and Albumin-induced Epithelial-mesenchymal Transition

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Epithelial- mesenchymal transition (EMT) is a novel mechanism that promotes renal fibrosis. TGF-β, angiotensin II, aldosterone, high glucose and urinary albumin are well known cause of EMT and renal fibrosis. We examined whether and how activation of AMP-activated protein kinase (AMPK) suppressed TGF-β-, angiotensin II-, aldosterone-, high glucose-, and albumin-induced EMT in tubular epithelial cells. All experiments were performed using HK-2 cells. Protein expression was measured by Western blot analysis. Intracellular reactive oxygen species (ROS) were analyzed by flow cytometry. Activation of NF-κB was assessed by electrophoretic mobility shift assay. Exposure of tubular cells to TGF-β (10 ng/ml), angiotensin II (1 μM), aldosterone (100 nM), high glucose (30 mM) and albumin (5 mg/ml) for 5 days induced EMT, as shown by up-regulation of α-smooth muscle actin and down-regulation of E-cadherin. ROS were also induced and anti-oxidants such as tiron and N-acetylcysteine inhibited TGF-β-, angiotensin II-, aldosterone-, high glucose-, and albumin-induced EMT. Nox4 expression was increased as well. Metformin (the best known clinical activator of AMPK) suppressed TGF-β-, angiotensin II-, aldosterone-, high glucose-, and albumin-induced EMT through inhibition of ROS and Nox4 via induction of heme oxygenase-1 and endogenous anti-oxidant thioredoxin. AMPK inhibitor (compound C) blocked the effect of metformin and another AMPK activator (AICAR) exerted the same effects as metformin.Furthermore, AMPK suppressed TGF-β-, angiotensin II-, aldosterone-, high glucose-, and albumin-induced NF-κB expression. In conclusion, AMPK activation might be beneficial in attenuating the tubulointerstitial fibrosis induced by TGF-β, angiotensin II, aldosterone, high glucose and urinary albumin.

Key Words: AMPK, EMT, ROS