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AMP-activated protein kinase의 활성화가 ER stress 및 renal fibrosis에 미치는 영향

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Effects of Activation of AMP-activated Protein Kinase on the ER Stress and Renal Fibrosis

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It has been suggested that ER stress facilitates fibrotic remodeling through activation of pro-apoptotic pathways, induction of epithelial-mesenchymal transition (EMT) and promotion of inflammatory responses. Therefore, modulation of ER stress may serve as one of the possible therapeutic approaches to tubulointerstitial fibrosis. We investigated whether and how activation of AMP-activated protein kinase (AMPK) suppressed the ER stress and renal fibrosis. We examined the effects of AMPK on the ER stress induced by either chemical ER stress inducers [tunicamycin (TM), thapsigargin (TG)] or non-chemical inducers such as TGF-β, angiotensin II, aldosterone and high glucose in tubular HK-2 cells. We further examined the effects of AMPK in vivo animal studies. Western blot analysis, immunofluorescence, siRNA experiment and immunohistochemical staining were performed. Metformin (the best known clinical activator of AMPK) suppressed the TM- or TG-induced ER stress, as shown by inhibition of TM- or TG-induced up-regulation of GRP78 and p- eIF2α through induction of heme oxygenase-1 (HO-1). Metformin also suppressed the TM- or TG-induced EMT. AMPK inhibitor (compound C) blocked the effect of metformin. Another AMPK activator (AICAR) exerted the same effects as metformin. Furthermore, transfection with siRNA targeting AMPK blocked the effect of metformin. In tunicamycin-induced acute kidney injury mouse, metformin reduced renal GRP78 expression and increased HO-1 expression. Activation of AMPK also suppressed the ER stress by TGF-β, angiotensin II, aldosterone and high glucose. In animal study using unilateral ureteral obstruction mouse model, metformin reduced GRP78 expression and renal fibrosis. In conclusion, AMPK may serve as a promising therapeutic target to limit renal fibrosis.

Key Words: AMPK, ER stress, Fibrosis