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SIRT1 (silent mating type information regulation 2 homolog 1)의 활성화가 ER stress 및 renal fibrosis에 미치는 영향

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Effects of Activation of SIRT1 (Silent Mating Type Information Regulation 2 Homolog 1) on the ER Stress and Renal Fibrosis

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It has been suggested that SIRT1 (silent mating type information regulation 2 homolog 1), a class III histone deacetylase exert reno-protective effects. However, the underlying mechanisms are not revealed completely. Endoplasmic reticulum (ER) stress and unfolded protein response (UPR) pathways are emerging as important factors in the development of organ fibrosis through activation of pro-apoptotic pathways, induction of epithelial-mesenchymal transition, and promotion of inflammatory responses.

Therefore, we postulated that reno-protective effect of SIRT1 might be mediated in part through inhibition of ER stress via induction of heme oxygenase-1 (HO-1) and thioredoxin. We examined whether SIRT1 could suppress the ER stress induced by both chemical ER stress inducers [tunicamycin (TM), thapsigargin (TG)] and non-chemical inducers through HO-1 and thioredoxin in tubular HK-2 cells. We further examined the in vivo effects of SIRT1 on the ER stress and renal fibrosis.

SIRT1 activator (SRT1720) induced SIRT1 expression in a time and dose dependent manner in our HK-2 cells. SRT1720 suppressed the TM- or TG-induced ER stress, as shown by inhibition of TM- or TG-induced up-regulation of GRP78, p-eIF2α and CHOP through HO-1 and thioredoxin, which were abolished by pretreatment with SIRT1 inhibitor (sirtinol). Consistent with the results of cell culture study, SRT1720 reduced the tubular expression of GRP78 and increased the expression of HO-1 and thioredoxin in a mouse model of TM-induced ER stress. SRT1720 also suppressed the ER stress induced by non-chemical ER stress inducers such as angiotensin II, aldosterone, high glucose and albumin. Furthermore, SRT1720 reduced the tubular GRP78 expression and renal fibrosis in unilateral ureteral obstruction mouse model. In conclusion, SIRT1 may serve as a promising therapeutic target by reducing ER stress and renal fibrosis.

Key Words: SIRT1, ER stress, Renal fibrosis