

## 신세뇨관 세포에서 ER stress에 의한 epithelial-mesenchymal transition 발현 증가에 autophagy가 미치는 영향

울산대학교 서울아산병원 신장내과

문수영, 김효상, 노경우, 장영주, 김준석, 백충희, 김미연, 이상구

### Endoplasmic Reticulum (ER) Stress Induces Epithelial-mesenchymal Transition (EMT) Through Induction of Autophagy in Tubular Epithelial Cells

Soo Young Moon, Hyo Sang Kim, Kyeong Woo Nho, Young Joo Jang  
Joon Seok Kim, Chung Hee Baek, Mi Yeon Kim, Sang Koo Lee

University of Ulsan Asan Medical Center Division of Nephrology

Endoplasmic reticulum (ER) stress has been implicated in promoting epithelial-mesenchymal transition (EMT). ER stress is also known to induce autophagy. However, relationship between ER stress-induced autophagy and ER stress-induced EMT has not been explored so far. We hypothesized that ER stress might induce EMT through induction of autophagy in tubular epithelial cells.

All experiments were performed using HK-2 cells. Protein expression was measured by Western blot analysis. Small interfering RNA (siRNA) experiment were also performed.

Chemical ER stress inducer such as thapsigargin (TG, 0.2  $\mu$ M) and tunicamycin (TM, 0.2  $\mu$ M) induced autophagy, as shown by up-regulation of LC3-II and beclin. ER stress inhibitors such as 4-PBA and salubrinal suppressed the TG- and TM-induced autophagy.

TG and TM also induced EMT, as evidenced by conversion to fibroblast-like morphology, down-regulation of E-cadherin and up-regulation of  $\alpha$ -smooth muscle actin, which were abolished by pretreatment with ER stress inhibitors. Transfection with siRNA targeting ER stress protein (IRE-1) also blocked the TG- and TM-induced autophagy and EMT. Suppression of TG- and TM- induced autophagy by autophagy inhibitors such as 3-methyladenine and bafilomycin inhibited the TG- and TM-induced EMT. siRNA targeting autophagy protein (beclin) also blocked the TG- and TM-induced EMT. As expected, an autophagy inducer, rapamycin, induced EMT as well.

Both TG and TM activated the c-Src kinase and inhibitor of c-Src kinase (PP2) blocked the TG- or TM-induced autophagy and EMT.

In conclusion, ER stress induced EMT through induction of autophagy in tubular epithelial cells, via c-Src kinase dependent pathway.

**Key Words:** Autophagy, EMT, ER stress