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Endoplasmic Reticulum Stress to prevent Peritoneal Fibrosis in Peritoneal Dialysis

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Peritoneal dialysis (PD) is one of the modalities for the treatment of end-stage renal disease (ESRD), which is based on the use of the peritoneum as a living dialysis membrane. Continuous exposure to nonphysiologic PD solutions and episodes of peritonitis cause damage to the peritoneum, which results in functional and structural deterioration of the peritoneal membrane. Previous studies suggested that peritoneal mesothelial cells underwent phenotype transition, epithelial-to-mesenchymal transition (EMT), during the process of PD. In addition to EMT, apoptosis of the peritoneal mesothelial cells is also believed to be one of the early mechanisms of peritoneal damage. The endoplasmic reticulum (ER) plays a key role in the maintenance of protein homeostasis through its control of the content, structure, folding and trafficking of proteins. The accumulation of misfolded proteins and the induction of ER stress have been implicated in the development of phenotypic transition and apoptosis of epithelial cells in the kidney and lung, however there are no studies on the association of ER stress and peritoneal fibrosis.
We investigated the potential role of ER stress in the development of EMT or apoptosis of human peritoneal mesothelial cells (HPMCs) isolated from omentum or dialysate effluent. ER stress inducers, tunicamycin (TM) and thapsigargin (TG), induced EMT with Smad2/3 phosphorylation, an increased nuclear translocation of β-catenin and Snail expression. Low concentrations of TM and TG did not induce apoptosis within 48 hours; however, high concentrations of TM (>1 ng/ml) and TG (>1 nM) induced apoptosis at 12 hours with a persistent increase in C/EBP homologous protein (CHOP). TGF-β1 induced EMT and apoptosis in HPMCs, which was ameliorated by taurine-conjugated ursodeoxycholic acid, an ER stress blocker. Interestingly, pre-treatment with TM or TG for 4 hours also protected the cells from TGF-β1-induced EMT and apoptosis, demonstrating the role of ER stress as an adaptive response to protect HPMCs from EMT and apoptosis. Peritoneal mesothelial cells isolated from dialysate effluent of PD patients also displayed an increase in GRP78/94, which was correlated with the degree of EMT. In animal model of peritoneal fibrosis, in which intraperitoneal injection of adenovirus carrying TGF-β1 (5X108 pfu), an enhanced ER stress in mesothelium was found as early as 4 days of virus injection evidenced by an increased expression of GRP78/94, followed by EMT and apoptosis at 1 week. These findings suggest that the modulation of ER stress could serve as a novel approach to ameliorate

or prevent peritoneal damage in PD patients. Also, clinical study to investigate the effect of ursodeoxycholic acid on peritoneal function is now on-going (NCT02338635).