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Differential Effect of High Glucose and Mannitol on Binding of Tonicity-Responsive Enhancer Binding Protein (TonEBP) and ß-catenin to the E-cadherin Promoter and Phenotype Transition of Peritoneal Mesothelial Cells (MCs)

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Objectives: Epithelial-to-mesenchymal transition (EMT) of MCs is considered as an early mechanism of peritoneal fibrosis. TonEBP is a transcriptional factor that enables cellular adaptation to hypertonic osmotic stress. Recent data demonstrated the role of TonEBP in EMT of cancer cells, however the exact mechanisms how TonEBP regulated cell phenotype were not known.

Methods: The expressions of TonEBP and other osmotic stress-related genes including sodium-myoinositol cotransporter (SMIT), betaine/γ-aminobutyric acid transporter (BGT1) and aldose reductase (AR) were evaluated. EMT was evaluated by morphological changes of MCs and the expressions of E-cadherin and α-smooth muscle actin (α-SMA) after stimulation of high glucose (HG, 30-120 mM) and mannitol (30-120 mM). E-cadherin promoter activity was confirmed by luciferase assay. Binding of TonEBP- or β-catenin to E-cadherin promotor was identified by chromatin immunoprecipitation (ChIP) assay. The interaction between TonEBP and β-catenin was analyzed by immunoprecipitation.

Results: Both HG or mannitol enhanced the expression of TonEBP as well as SMIT, BGT1 and AR from the concentration of 30 mM. HG (>30 mM) induced EMT of MCs with a decrease in E-cadherin promotor activity, however mannitol did not induce EMT. HG induced nuclear translocation of TonEBP, which was associated with an enhanced binding to β-catenin. Mannitol also promoted nuclear translocation of TonEBP only at the highest concentration we tested (120 mM), however it was not associated with nuclear binding of TonEBP to β-catenin. In addition, mannitol induced a transient increase in nuclear β-catenin only with the highest concentration (120 mM) whereas HG (>30 mM) showed a persistent increase in nuclear β-catenin.

Conclusions: This is study demonstrated the role of TonEBP in peritoneal EMT for the first time. Not the increased expression of TonEBP per se but binding of TonEBP and β-catenin to the E-cadherin promoter is a key mechanism by which TonEBP induced EMT of MCs.