High Glucose-induced EMT with Decreased Expression of Anti-fibrotic Cytokines is not Prevented by HGF and/or BMP-7 Treatment in Cultured Human Peritoneal Mesothelial Cells

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Background : Hepatocyte growth factor (HGF) and bone morphogenic protein-7 (BMP-7) are naturally occurring anti-fibrotic cytokines which play an important role in prevent or resolve tissue fibrosis. Recent studies demonstrated the beneficial effect of HGF on high-glucose-induced peritoneal damage. Epithelial-to-mesenchymal transition (EMT) is well known mechanism of various organ damage, which can be inhibited by BMP-7. Despite a significant interest using this anti-fibrotic cytokine as a therapeutic tool to regress tissue fibrosis, there are no studies regarding the role of BMP-7 on EMT of peritoneal mesothelial cells and peritoneal fibrosis. In order to investigate the effect of each component of peritoneal dialysate on EMT of human peritoneal mesothelial cell (HPMC), we have performed a study to examine whether high glucose itself induces EMT with alterations of local expression of HGF and/or BMP-7 of HPMC. We also studied whether HGF and/or BMP-7 treatment prevent high glucose-induced EMT.

Methods : EMT was evaluated by comparing the expression of E-cadherin and α-smooth muscle actin (α-SMA) in HPMCs exposed to high glucose (HG, D-glucose, 60, 120 and 222 mM) with or without recombinant HGF (10 ng/mL) for 24 and 48 hours. Effect of BMP-7 on high-glucose-induced EMT was evaluated in HPMCs transfected with adenoviral vector of human BMP-7. Expressions of HGF and BMP-7 were evaluated by RT-PCR and Western blotting.

Results : HG decreased E-Cadherin expression and increased α-SMA expression in a dose- and time-dependent manner from 24 hours of exposure. Additionally, exposure of HPMC to HG resulted in a decreased expression of anti-fibrotic cytokine, HGF and BMP-7 both at mRNA and protein levels. However, neither rHGF treatment nor BMP-7 transfection prevented HG-induced EMT. Treatment of rHGF in BMP-7 transfected HPMCs did not effectively inhibit HG-induced upregulation of α-SMA. Interestingly, BMP-7 ameliorated HG-induced decrease in HGF expression whereas no effect of HGF on HG-induced alteration in BMP-7.

Conclusion : Although HG induced EMT of HPMC with decreased expression of HGF and BMP-7, HGF and/or BMP treatment may not be sufficient to prevent or reverse EMT in in-vitro condition. This finding suggests the possibility that beneficial effect of anti-fibrotic peptide in peritoneal fibrosis may be not a direct one on HPMC, rather activating other protecting systems inside of peritoneal cavity with cross-talk between HGF and BMP-7. Further studies are necessary to examine the effect of BMP-7 in in-vivo model and other peritoneal residential cells including fibroblast or vascular cells.