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Bone morphogenetic protein-9 (BMP-9) inhibits HMGB1-induced Endothelial-to-Mesenchymal Transition (EndMT) in Human Umbilical Vein Endothelial Cells

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Objectives : In our previous study, high mobility group box 1 (HMGB1) induced EndMT via TGF- β 1 secretion in the venous endothelial cells, suggesting that HMGB1-induced (EndMT) could be a mechanism of neointimal hyperplasia in hemodialysis vascular access. The aim of this study was to investigate the effect of BMP9 on HMGB1-induced EndMT in HUVECs.

Methods : After stimulating the HUVECs with HMGB1 in the presence or absence of BMP9, the key biomarkers for endothelial and mesenchymal cells were evaluated by fluorescent immunocytochemistry and western blot. Role of BMP-9 receptor (BMPRII), EndMT transcription factors (snail1, snail2, and twist1), and TGF- β 1 in the mechanism of HMGB1-induced EndMT was studied by western blot.

Results : When the cells were pretreated with BMP-9, HMGB1-induced EndMT was inhibited morphologically (Immunocytochemistry). In addition, BMP-9 inhibited HMGB1-induced decrease in endothelial markers CD31, VE-cadherin, and von Willebrand factor, and HMGB1-induced increase in mesenchymal cell marker, α -smooth muscle actin for 3 to 5 days. Moreover, BMP-9 inhibited HMGB1-induced p38 phosphorylation, upregulation of transcription factors (snail1 and snail2) and TGF- β 1 secretion up to 72 hrs in a dose-dependent manner. BMP-9 stimulated BMPRII (peak at 24 hr) and p-smad158 expression (peak at 1 hr), and increased HMGB1-induced decrease in BMPRII and p-smad158 expression.

Conclusions : These data suggest that BMP-9 significantly inhibited HMGB1-induced EndMT in HUVECs. BMP-9 might provide a new therapeutic potential to prevent neointimal hyperplasia in hemodialysis vascular access.

Keywords : BMP-9, HMGB1, EndMT