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Microparticles derived from erythropoietin secreting mesenchymal stem cells attenuate TGF-β1 induced epithelial-to-mesenchymal transition in MDCK cells

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Objectives: Renal tubulointerstitial fibrosis (TIF) is a common end-stage manifestation in kidney diseases and epithelial-mesenchymal transition (EMT) is one of the key mechanisms by which TIF develops upon renal injury. Recombinant human erythropoietin (rhEPO) have shown to decrease fibrosis by inhibiting EMT in various in vivo models. Microparticles (MP) contain numerous bioactive molecules including mRNAs that act to modify target cells. Aim of study was to investigate the role of MP derived from hEPO gene transfected kidney mesenchymal stem cell (hEPO-KMSC) in inhibiting transforming growth factor-β (TGF-β1)-induced EMT.

Methods: MP were isolated from the supernatants of KMSCs cultured in hypoxic condition in serum-free media for 24hours. Madin-Darby Canine Kidney (MDCK) cells were treated with TGF-β1 (5 ng/ml), TGF-β1+rhEPO (100 IU/ml) or TGF-β1+hEPO-KMSC-derived MP. Changes in MDCK cell morphology as well as MP uptake into MDCK cells were assessed. Quantitative real-time PCR for E-cadherin, vimentin and alpha-smooth muscle actin (αSMA) and immunoblotting for E-cadherin, phospho-p38, Smad 2/3 and fibronectin were done.

Results: Treatment with TGF-β1 for 48 hours induced changes in the MDCK cell morphology from cuboidal to an elongated spindle like shape. After treatment with MP, up to 80% of MDCK cells showed incorporation of MP into its cytoplasm. MDCK cells treated with TGF-β1 showed increased mRNA expression for αSMA and vimentin and decreased for E-cadherin. rhEPO or hEPO-KMSC-derived MP treatment decreased αSMA and vimentin and increased E-cadherin mRNA expression. Similarly, MDCK cells treated with TGF-β1 showed increased fibronectin and Smad 2/3 and decreased E-cadherin. rhEPO or hEPO-KMSC-derived MP treatment decreased fibronectin and Smad 2/3 and increased E-cadherin.

Conclusions: Our data demonstrates that hEPO-KMSC derived MP contributes to inhibition of TGF-β1 induced EMT in MDCK cells similar to rhEPO and may be used as an anti-EMT therapy.