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Endothelin-1 (ET-1) modulates epithelial-mesenchymal transition (EMT), which contributes to kidney tubulo-interstitial fibrosis in angiotensin II-dependent hypertension

Anna Sandra Belloni[1], Teresa Maria Seccia[2], Diego Guidolin[1], Brasilina Caroccia[2], V. Sartor[1], Lucia Petrelli[1], GianPaolo Rossi[2]

[1] Department of Human Anatomy and Physiology,
[2] Department of Clinical and Experimental Medicine, University of Padova, Italy

The origin of myofibroblasts remains uncertain, but studies suggest that the epithelial cells may acquire a fibroblast-like phenotype via epithelial-mesenchymal transition (EMT). Objective of the study was to investigate whether EMT may contribute to the development of kidney fibrosis in a model of angiotensin II-dependent hypertension and to identify the role of ET-1 via ETA/ETB receptors. Transgenic rats TGRen2 (n=35) received for 4 weeks one of the following treatments a) irbesartan, b) bosentan, non selective ETA /ETB receptor antagonist, c) BMS-182874, selective ETA,antagonist, d) BMS+irbesartan, e) placebo. EMT was assessed by investigating coexpression of a marker of epithelial cell (E-cadherin) and one of myofibroblast (S100A4 or alfa-SMA) with double immunofluorescence. Specific immunoreactivity was measured using QWinStandard Leica ImageTMsoftware. A reduction in blood pressure was found only with irbesartan, whereas both bosentan and irbesartan significantly lowered tubulo-interstitial fibrosis. Coexpression of E-cadherin and S100A4, or E-cadherin and alfa-SMA, markedly decreased in the tubular cells of TGRen2 treated with irbesartan or bosentan. Alfa-SMA expression decreased after irbesartan, bosentan and BMS+irbesartan, but not after BMS. S100A4 expression was reduced after irbesartan, bosentan and BMS+irbesartan. E-cadherin increased only after irbesartan. Coexpression of the markers of myofibroblasts and kidney epithelial cells, by demonstrating the development of EMT during the onset of kidney hypertension-induced damage, suggests a crucial role of EMT in the pathogenesis of Ang II-mediated fibrosis. The reduction of myofibroblast markers not only after irbesartan, but also after blockade of ETA/ETB receptors, suggests an involvement of ET-1 in the development of Ang II-mediated EMT.