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Mechanisms of Epithelial-mesenchymal Transition in Human Peritoneal Mesothelial Cells

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We have previously demonstrated that reactive oxygen species (ROS)- extracellular-regulated protein kinases (ERK1/2) axis mediates TGF-beta1-induced epithelial-mesenchymal transition (EMT) of renal tubular epithelial cells. Human peritoneal mesothelial cells (HPMC) also undergo EMT during peritoneal dialysis and contribute to peritoneal fibrosis. We examined the inducers of EMT in HPMC and the signaling pathways.

Growth-arrested and synchronized HPMC were treated with 5.6 mM or 50 mM glucose, 0.1-10 ng/mL of TGF-beta1, or 10-100 μM H_2O_2. In some experiments, cells were pretreated with anti-TGF-beta antibody, TGF-beta 1 receptor inhibitor, mitogen-activated protein kinase (MAPK) inhibitors (PD98059 or p38 MAPK inhibitor), or antioxidants. Alpha-SMA, E-cadherin, fibronectin, collagen, phosphorylated ERK and p38 MAPK were measured by Western blot analysis. We found that high glucose, TGF-beta 1, and H_2O_2 all can induce EMT in HPMC and that high glucose-induced EMT was blocked not only by inhibitors of TGF-beta1 but also by antioxidants or MAPK inhibitors. Since MAPK are downstream target molecules of ROS, our data suggest that ROS and subsequent MAPK activation mediate high glucose-induced EMT in HPMC. Better understanding of signaling pathways to EMT will elucidate new therapeutic targets for peritoneal fibrosis.