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Title: Thrombin induces epithelial-mesenchymal transition via PAR1, PKC and ERK1/2 pathways in A549 cells

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Body: Introduction: Thrombin activates the protease-activated receptor (PAR)-1 and induces a myofibroblast phenotype in normal lung fibroblasts. The origin of myofibroblasts are from the resident fibroblasts, fibrocytes and epithelial-mesenchymal transition (EMT). We investigated the effects of thrombin, which is an important mediator of the interstitial lung fibrosis, on EMT in A549 human alveolar epithelial cells. Methods: A549 cells were stimulated with thrombin (2 units/ml) and PAR1 agonist, TFLLRN (300 μ M). The development of EMT was confirmed by real-time RT-PCR, western blot and immunofluorescence staining. A549 cells were transfected with small interfering RNA (siRNA) directed against PAR1 mRNA and thrombin inhibitor, argatrovan were added before thrombin for the inhibition experiment. To determine the possible PKC and ERK1/2 signaling pathways in the development of thrombin-induced EMT, 10 nM of Gö6976 (PKC- α inhibitor), 4 μ M of rottlerin (PKC- δ inhibitor), 10 μ M of PKC- ϵ antagonist peptide and PD98059 (ERK1/2 inhibitor) were used. The amount of collagen 1 and TGF- β in the cell culture supernatants were also measured by ELISA. Results: Thrombin induced the α -SMA expression and decreased the E-cadherin expression from the A549 pulmonary epithelial cells. This EMT phenomenon was accompanied by increased PAR1 expression. Transfection of PAR1 siRNA or argatrovan inhibited the EMT and PAR1 expression simultaneously. Thrombin and TFLLRN also increased the production of TGF- β and collagen 1 from the A549 cells. In addition, we confirmed that this thrombin-induced EMT was mediated through the PAR1 activation and PKC-ERK1/2 phosphorylation.