Suppression of transient receptor potential melastatin 4 expression promotes conversion of endothelial cells into fibroblasts via transforming growth factor/activin receptor-like kinase 5 pathway

Echeverría, Cesar

Montorfano, Ignacio

Cabello-Verrugio, Claudio

Armisén, Ricardo

Varela, Diego

Simon, Felipe

Objective: To study whether transient receptor potential melastatin 4 (TRPM4) participates in endothelial fibrosis and to investigate the underlying mechanism. Methods: Primary human endothelial cells were used and pharmacological and short interfering RNA-based approaches were used to test the transforming growth factor beta (TGF-?)/activin receptor-like kinase 5 (ALK5) pathway participation and contribution of TRPM7 ion channel. Results: Suppression of TRPM4 expression leads to decreased endothelial protein expression and increased expression of fibrotic and extracellular matrix markers. Furthermore, TRPM4 downregulation increases intracellular Ca²⁺ levels as a potential condition for fibrosis. The underlying mechanism of endothelial fibrosis shows that inhibition of TRPM4 expression induces TGF-?1 and TGF-?2 expression, which act through their receptor, ALK5, and the nuclear translocation of the profibrotic tran