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Title: ESSENTIAL ROLE OF MIRO1 IN MAINTAINING ENDOTHELIAL CELL INTEGRITY

Abstract:
MIRO-1, a mitochondrial Rho GTPase1, is an important regulator of trafficking and subcellular distribution of mitochondria to meet the local demands of energy, Ca2+, and redox balance to drive a number of cellular responses, particularly in cancer cells. However, the role of MIRO-1 in endothelial cells (EC), particularly in their quiescent state, is not known. To address this question, we used siRNA-mediated knockdown approach to impair the function of MIRO-1 in human pulmonary artery EC. The MIRO1-depeleted EC exhibited elongated cell shape, increased mitochondrial ROS generation, and reduced barrier function. These cells were also impaired in their ability to proliferate, migrate, and form capillary-like network on Matrigels. Consistent with the reduced barrier function and proliferative/migratory capacity, VE-cadherin and VEGFR2 levels were markedly decreased in MIRO1-depleted cells. In contrast, EC overexpressing wild-type MIRO-1 (MIRO1-WT) showed increased VE-cadherin and VEGFR2 levels. However, unlike MIRO1-WT, overexpression of a MIRO-1 mutant (MIRO-1 E208K/E328K) which is defective in its Ca2+-binding ability failed to increase VE-cadherin and VEGFR2 levels. These data establish the essential role played by MIRO-1 in maintaining EC integrity and the requirement of Ca2+ in driving MIRO-1's action in the endothelium.