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mTOR complex 2 as a novel regulator of cell metabolism and survival in pulmonary arterial hypertension

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Increased proliferation and survival of pulmonary arterial vascular smooth muscle cells (PAVSMC) coupled with metabolic shift to glycolysis are key pathophysiological components of vascular remodeling in PAH, molecular mechanisms of which are not fully understood. Mammalian target of rapamycin (mTOR), a central controller of cell growth, proliferation and survival, acts through two distinct complexes, rapamycin-sensitive mTORC1 that modulates cell growth and rapamycin-resistant mTORC2 that activates Akt. The importance of mTORC1 for VSMC proliferation and pulmonary vascular remodeling is demonstrated by the use of rapamycin. The role of mTORC2 in PAVSMC metabolism, proliferation and survival in PAH is not known. We demonstrate that mTORC2-Akt signaling is up-regulated in PAVSMC from subjects with idiopathic PAH (iPAH) and from rats with chronic hypoxia-induced pulmonary hypertension (PH) in vivo and in vitro. We also found that human iPAH and rat PH PAVSMC have elevated cellular energy levels, proliferation and survival that fully depend on glycolytic metabolism. Importantly, inhibition of mTORC2 signaling by siRNA rictor or specific Akt1/2 inhibitor decreases cellular energy levels and inhibits human iPAH and rat PH PAVSMC proliferation via activation of energy sensor AMPK. mTORC2 disruption with siRNA rictor increases levels of pro-apoptotic protein Bim, decreases anti-apoptotic Bcl2 and induces apoptosis in human iPAH, but not control PAVSMC. Collectively, our data demonstrate that mTORC2-Akt signaling is up-regulated in pulmonary hypertensive conditions that is required for glycolytic energy metabolism, increased proliferation and survival of human iPAH and rat PH PAVSMC and suggest that mTORC2-Akt represents novel potential therapeutic target for human PAH.

Biography

Goncharova has completed her PhD from Cardiology Research Center, Russian Academy of Sciences, and postdoctoral studies from University of Pennsylvania Perelman School of Medicine. She is a research assistant professor in the University of Pennsylvania Perelman School of Medicine. Her research interests are in the cellular and molecular mechanisms of smooth muscle cell remodeling as it relates to PAH, pulmonary lymphangioleiomyomatosis, asthma and COPD. Dr. Goncharova has published 25 manuscripts in reputed journals and serves as a reviewer for the American Journal of Respiratory Cell and Molecular Biology and the American Journal of Physiology: Lung Cellular and Molecular Physiology.

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