A Novel Role for MIRO2 in Autophagy. DP Boulton (Ph.D., GS), M Furnish, and MC Caino, Department of Pharmacology, University of Colorado | Anschutz Medical Campus.

Mitochondrial dynamics support their multifunctional roles in maintaining cell function. Improper regulation of mitochondrial dynamics are implicated in a variety of diseases—including neurodegenerative diseases and cancer—supporting a need for a comprehensive understanding of how these dynamics are controlled. Here we identify a novel signaling pathway revolving around Mitochondrial Rho GTPase 2 (MIRO2). MIRO1/2 are outer-mitochondrial membrane proteins known for their roles in mitochondrial trafficking, however recent evidence suggests that MIRO2 may have alternate functions in regulating mitochondrial dynamics in cells where MIRO2 is dispensable for mitochondrial trafficking. Using cell models of immortalized prostate epithelium, we find that MIRO2 knockdown (KD) dramatically reduces proliferation rates and increases cellular reactive oxidative species (ROS). To further characterize the role of MIRO2 in these cells, we performed proteomics to identify novel effectors of MIRO2. One of the top hits was mammalian target of rapamycin (mTOR), a serine/threonine kinase that functions as a master regulator of growth and metabolism. Amongst canonical mTOR substrates, MIRO2 KD only affected the phosphorylation of S757 Unc-51-like kinase 1 (ULK1) following insulin stimulation. Phosphorylation of S757-ULK1 by mTOR inhibits the initiation of autophagy, a lysosome mediated degradation process. To this extent, we show that autophagosome formation upon nutrient starvation is increased in MIRO2 KD cells and reduction of these autophagosomes by insulin is dampened in cells without MIRO2. Taken together we show that MIRO2 regulates cell growth and cellular ROS. Furthermore, we show that MIRO2 acts as a scaffold for mTOR to mitochondria, which leads to an inhibition of global autophagy in response to insulin.