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Defects in mitochondrial fission protein dynamin-related protein 1 are linked to apoptotic resistance and autophagy in a lung cancer model

Kelly Jean Thomas Craig
Colorado Mesa University, USA

Evasion of apoptosis is implicated in almost all aspects of cancer progression, as well as treatment resistance. In this study, resistance to apoptosis was identified in tumorigenic lung epithelial (A549) cells as a consequence of defects in mitochondrial and autophagic function.Mitochondrial function is determined in part by mitochondrial morphology, a process regulated by mitochondrial dynamics whereby the joining of two mitochondria, fusion, inhibits apoptosis while fission, the division of a mitochondrion, initiates apoptosis. Mitochondrial morphology of A549 cells displayed an elongated phenotype—mimicking cells deficient in mitochondrial fission protein, Dynamin-related protein 1 (Drp1). A549 cells had impaired Drp1 mitochondrial recruitment and decreased Drp1-dependent fission. Cytochrome c release and caspase-3 and PARP cleavage were impaired both basally and with apoptotic stimuli in A549 cells. Increased mitochondrial mass was observed in A549 cells, suggesting defects in mitophagy (mitochondrial selective autophagy). A549 cells had decreased LC3-II lipidation and lysosomal inhibition suggesting defects in autophagy occur upstream of lysosomal degradation. Immunostaining indicated mitochondrial localized LC3 punctae in A549 cells increased after mitochondrial uncoupling or with a combination of mitochondrial depolarization and ectopic Drp1 expression. Increased inhibition of apoptosis in A549 cells is correlated with impeded mitochondrial fission and mitophagy. We suggest mitochondrial fission defects contribute to apoptotic resistance in A549 cells.

Biography

Kelly Jean Thomas Craig is an assistant professor of biological sciences at Colorado Mesa University. She studies mitochondrial dysfunction in disease etiology, focusing on the role of mitochondrial dynamics in cancer. She was a research scientist at Saccomanno Research Institute at St. Mary's Hospital and Regional Medical Center and a fellow and *ad-hoc* member of the scientific advisory board of the Keystone Symposia on Molecular and Cellular Biology. She received her training at the National Institute on Aging at the NIH and earned her doctorate in biochemistry and molecular biology from Georgetown University for her work on mitochondrial dysfunction in neurodegenerative disease.

kjcraig@coloradomesa.edu