subsarcolemmal mitochondria and rarefaction of intermyofibrillar mitochondria. Although the maximal activities of respiration of saponin-permeabilized muscle fibers and digitonin-permeabilized fibroblasts were only slightly affected by the *MFN2* mutations, their sensitivity to the cytochrome *c* oxidase (COX) inhibitor azide was increased, which indicates a decrease of *in vivo* activity of COX.

In comparison to controls, the *MFN2* fibroblast samples showed a decrease in the mitochondrial DNA copy number, which explains the observed mitochondrial respiratory chain dysfunction. Additionally, an increased amount of deletions was observed. However, the deletions are unlikely to contribute significantly to the detected respiratory impairment, because of their minor overall amounts in these patients.

Our findings support the viewpoint that impairment of mitochondrial fusion causes mild respiratory chain dysfunction through defective mitochondrial DNA replication.

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8P5

A lung cancer model linking apoptotic resistance and metastatic potential via defects in mitochondrial fission protein Dynamin-related protein 1

Kelly Jean Thomas, Marty R. Jacobson
Colorado Mesa University, Department of Biological Sciences, Grand Junction, CO, USA
Saccomanno Research Institute, St. Mary's Hospital and Regional Medical Center, Grand Junction, CO, USA
E-mail: kjcraig@coloradomesa.edu

Resistance to apoptosis is a hallmark of cancer. Evasion of apoptosis is implicated in almost all aspects of cancer progression, as well as treatment resistance. Apoptosis is regulated in part by mitochondria, which control tissue homeostasis by eliminating damaged cells. In this study, resistance to apoptosis was identified in 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 length correlated with metastatic potential; lung epithelial cells with increased metastatic potential had mitochondria with 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, caspase-3 and PARP cleavage were impaired both basally and with apoptotic stimuli in A549 cells.

Metastatic potential positively correlated with mitochondrial mass, suggesting defects in mitophagy (mitochondrial selective autophagy). A549 cells had decreased LC3-II lipidation and lysosomal inhibition suggesting that defects in autophagy occur upstream of lysosomal degradation. Immunostaining also indicated that 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 that mitochondrial fission defects contribute to apoptotic resistance in lung cancer cells with a high propensity for metastasis.

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8P6

Mitochondrial fusion/fission proteins in NARP and Rho0 human osteosarcoma cells

J. Walczak, J. Duszyński, J. Szczepanowska
Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland
E-mail: jwalczak@nencki.gov.pl

Dysfunctions of mitochondria are usually associated with numerous diseases like metabolic disorders, cancer and neurodegenerative diseases.

Changes caused by the chronic mitochondrial stress include defects in respiratory chain complexes, morphology and organization of the mitochondria, mitochondrial membrane potential ($\Delta\psi$), cytosolic Ca^{2+} concentration, ATP and ROS levels. These parameters are involved in the retrograde signaling from mitochondria to nucleus that triggers mitochondrial stress response (MSR) of the cell and its subsequent adaptation to altered mitochondrial functions [1,2].

Although knowledge about components involved in the mitochondrial retrograde signal transduction is still incomplete, it is likely that mitochondrial morphology and positioning within the cell can play an important role in mitochondrial–nuclear communication. Proteins implicated in dynamics of mitochondria were investigated in cells with chronic mitochondrial stress:

1) Rho0 human osteosarcoma cells, lacking mitochondrial DNA,
2) Cybrid NARP human osteosarcoma cells with point mutation T8993G in subunit 6 of ATP synthase (98% of heteroplasmy).

We have previously shown that many aspects of physiology (calcium homeostasis, ROS metabolism) as well as mitochondrial network and cytoskeleton organization in cells with chronic mitochondrial stress (NARP and Rho0) differs from that in WT cells [3]. Our new results indicate that the profile of proteins responsible for the dynamics of mitochondria (Drp1, Opa1, Mfn1 and Fis1) is different in investigated cell lines. The observations carried out in the confocal microscope show changes in the organization of mitochondria within these cells.

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8P7

The MINOS complex: Keeper of mitochondrial membrane architecture

Ralf M. Zerbes[1,2], Maria Bohnert[1], Karina von der Malsburg[1], Bettina Warscheid[3,4], Ida J. van der Klei[5],