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Mitochondrial Quality Control

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Functions of "healthy" mitochondria

The emergence of the symbiotic relationship between α-purple bacteria and what was to become the eukaryotic cell made possible the origins of multicellular life through the many functions of mitochondria. In animal cells, healthy mitochondria are the major source of NADH and ATP via the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS). Mitochondria also produce intermediates for lipids and pyrimidine nucleotides, and generate Fe-S centers, which in addition to being components of the electron transport chain (ETC) are important elements of many proteins including DNA repair proteins.

Mitochondria are essential for the major pathway of apoptosis, in which mitochondrial outer membrane permeabilization (MOMP) allows the release of proteins of the inter-membrane space, which interact with cytosolic proteins to trigger apoptosis. We have shown this as a function of healthy mitochondria to stress that this function is not a consequence of accumulated mitochondrial damage, per se, but rather a specific consequence of interactions among the BCL-2 family proteins, as reviewed (Green, 2011). While damaged ("sick") mitochondria can function in apoptosis, they need not be damaged, except with respect to MOMP, and apoptosis that is triggered by other forms of mitochondrial damage nevertheless proceeds via BCL-2 protein interactions. Healthy mitochondria also serve as platforms for the response to viral DNA by RIG-I and other sensing proteins, which interact with the outer membrane protein MAVS.

A number of processes sustain healthy mitochondria in the cell:

Low level Ca^{++} "pulses" from the endoplasmic reticulum (ER)

Constitutive pulses of Ca^{++} from the ER IP3-receptor are taken up by mitochondria, and this low level of calcium sustains the activity of the TCA cycle, and the ETC. Without these Ca^{++} pulses, the decline in energy production leads to activation of AMPK and autophagy (Cardenas et al., 2010).

Mitochondrial Dynamics

Mitochondrial fission and fusion sustains healthy mitochondria by effectively mixing mitochondrial components (fusion) and, when combined with biogenesis, "budding" off new mitochondria (fission) (Westermann, 2010) Fission may also allow damaged regions of a mitochondrion to be isolated for removal by mitophagy (see below). Fission in mammals is

to be mediated by the action of DRP1, which is recruited to mitochondria by MFF. When DRP1 is recruited, its GTPase activity promotes fission. Fusion in mammals is mediated by Mitofusin (MTF)-1 and MTF2 on the OMM and OPA-1 on the IMM. Studies in yeast suggest additional players are required for both fission and fussion. Fusion requires $\Delta\Psi m$, while fission does not; if $\Delta\Psi m$ dissipates, fission dominates.

Mitophagy

Mitophagy is a process wherein the autophagy machinery creates double membrane vesicles around damaged mitochondria, and these vesicles fuse with lysosomes to destroy the organelles (Youle and Narendra, 2011). Mitophagy is triggered by the loss of $\Delta\Psi m$. One of several mechanisms for mitophagy involves the kinase PINK1, which is constitutively imported into the mitochondria, where it is degraded. Upon loss of $\Delta\Psi m$, PINK1 accumulates on the OMM, and activates the ubiquitin ligase, PARKIN. The activity of PARKIN recruits the autophagy machinery to remove the damaged mitochondrion.

Mitochondrial Biogenesis and Repair

MtDNA is maintained, transcribed and replicated by enzymes encoded in the nucleus. These proteins are imported by the Tom/Tim/Pam complex and the $\Delta\Psi m$. The mitochondrial genome encodes subunits of complexes I (tan), III (pink), IV (dark blue) and V (light blue). Oxidative mtDNA damage, a byproduct of OXPHOS, is repaired through a process called base excision repair (BER). Loss of several key BER enzymes in the mitochondria, including DNA ligase III, APE1 and ExoG, are incompatible with cell growth (Simsek et al., 2011). Several other key nuclear DNA repair systems, such as nucleotide excision repair, are absent in mitochondria. Unresolved is how mitochondria deal with damage from environmental insults such as UV light. Oxidized proteins are destroyed by the ClpXP and LonP proteases in the matrix.

Effects of “sick” mitochondria

A failure in any of the above processes can promote mitochondrial dysfunction and the accumulation of damaged mitochondria and cellular dysfunction. In addition, environmental contaminants, ischemia/reperfusion injury, and other disease conditions engage two major processes that can overwhelm the reparative mechanisms, as follows.

Reactive oxygen species (ROS)

During OXPHOS molecular oxygen is reduced to water at complex IV. However, superoxide anion radicals ($O_2^{\cdot}$) can be generated primarily at complexes I and III, with a majority produced in the matrix. These ROS can cause cellular damage including nuclear DNA and membrane lipids with pathophysiological consequences. mtDNA is much more susceptible to hydrogen peroxide induced damage, as compared to the nuclear DNA, due to high iron stores in the mitochondria. Protracted bouts of oxidant injury induce persistent DNA damage causing mitochondria dysfunction. Aging, cancer, cardiovascular disease, diabetes, drug toxicity, ischemia-reperfusion injury, liver disease and neurodegeneration have been linked to this damaging process (Van Houten et al., 2006). In addition, low levels of ROS, produced by the ETC, are necessary for some signaling events in the cell, through mechanisms that remain to be elucidated (Hamanaka and Chandel, 2010).

Mitochondrial permeability transition (MPT)

High levels of calcium, such as occur in ischemia/reperfusion injury, as well as high levels of ROS can trigger the so-called MPT, in which cyclophilin D (cypD) is activated. CypD is a cis-trans peptidyl proline isomerase that causes conformational changes in proteins of the IMM. The activity of CypD opens “pores” in the IMM, making it permeable to small (<1.5

kDa) solutes that enter the matrix. As a consequence of MPT, ΔΨm dissipates (losing all ΔΨm -dependent functions), and water swells the matrix. Swelling can burst the IMM and the OMM, releasing mitochondrial components, including mtDNA to the cytosol. Mice lacking CypD show resistance to some forms of ischemia/reperfusion injury, but display no defects in apoptosis (Leung and Halestrap, 2008).

Sick mitochondria lose ΔΨm and as a consequence not only fail to provide energy and biosynthetic products for the cell, also act as an energy drain due to reversal of complex V to hydrolyze ATP. One result is the production of AMP, which activates AMPK kinase that in turn induces autophagy, both as a consequence of inhibiting TORC1, but also by directly activating the autophagic pre-initiation complex. The energy drain and ROS-induced damage can also result in necrotic death of the cell. ROS can promote the formation of the NALP3 inflammasome, a molecular complex that activates caspase-1, which processes inflammatory cytokines and promotes their secretion. Mitochondria that undergo MPT can release mitochondrial DNA, which engages the DNA sensors involved in anti-viral immunity. As a consequence of these events, inflammation ensues, which is further exacerbated by necrotic death (Green, et al., 2011).

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