Mitochondrial Quality Control

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Mitochondria are semi-autonomous organelles involved in a variety of vital cellular processes.

- Respiration (ATP generation)
- Cofactors & key metabolites synthesis
- Ion homeostasis
- Lipid homeostasis
- ROS production/signaling
- Regulation of apoptosis

Sustaining normal mitochondrial function is critical as mitochondria are not produced de novo.
• The inner membrane is extremely protein-rich and is one of the major sites of essential mitochondrial functions

• Composed of 1,000 -1,500 proteins, majority of which are synthesized in the cytosol and imported into the organelle

• A small fraction of proteins (8-13) originates from the organelle’s own genome

What can go wrong in a mitochondrion?

- Extensive ROS production by mitochondrial respiratory chain (MRC) can damage proteins and mtDNA which are in the close proximity to the MRC

- Improperly assembled redox cofactors can act as pro-oxidants (inherent ability to generate ROS via Fenton reactions)

- Mismatches in subunits stoichiometry may lead to accumulation of unassembled/misfolded proteins

Mitochondrial dysfunction - the road to ruin

- Impaired mitochondrial dynamics
- Ca\(^{2+}\) overload
- Impaired cellular energetics
- Cellular damage/death

Cancers:
- Gliomas
- Lymphomas

Neurological:
- Leigh syndrome
- Leukodystrophy
- Optic nerve atrophy
- Ataxias

Neurodegenerative:
- Parkinsonism
- ALS

Cardiovascular:
- Cardiomyopathies
- Peripheral artery disease

...and Aging

Levytskyy et al., J. Neuroimmune Pharm. (2016)

Vafai and Mootha, Nature (2012)
We’re doomed!!

…or are we?
• Multiple mechanisms are involved in sustaining of normal mitochondrial function

Adapted from Figge et al., Bioessays (2013)
Mitochondrial quality control (MQC)

- **Two levels of MQC:**
  1). Organellar
  2). Molecular (aka intramitochondrial)

- Molecular and organellar MQC are interdependent and functionally intertwined

Rugarli & Langer, EMBO J. (2012)
Mitochondrial content mixing via fusion helps to “dilute” the damage.

Youle & van der Bliek, Science (2012)
Heiko Bugger (unpublished)
OM and IM fusion are coordinated but **physically separate** events.

**Charcot-Marie-Tooth Syndrome**

**Dominant Optic Atrophy**

SIMH = Stress-induced mitochondrial hyperfusion

- SIMH relies on thiol oxidation of the conserved cysteine residues in Mfn1/2

Anand et al., BBA (2013); Wai & Langer, Trends Endocrin. Metab. (2016)
Neurodegeneration
Myocardial Infarction

Organellar MQC – fission

Otera & Mihara, J. Biochem. (2011); Hoppins & Nunnari, Science (2013);
• Damaged mitochondria can be segregated through fission and eliminated by mitophagy

Organellar MQC – mitochondria-derived vesicles

- Mitochondria-derived vesicles – recently identified non-mitophagy clearance mechanism

Anand et al., BBA (2013);
Soubannier et al., PLoS One (2013);
Bohovych et al., Antioxid. Redox Signal. (2015)
Organellar/Molecular MQC – UPS “delivers”

- Several other factors appear to work in parallel or concomitantly with PINK1/Parkin system (MITOL, MULAN, Mdm30, Vms1, DJ-1, etc.)

- MITOL, MULAN and Mdm30 are ubiquitin ligases involved in mitochondria-associated degradation (MAD)

Paget’s disease ALS

Anand et al., BBA (2013)
• Vms1 is an auxiliary factor that “tags” damaged mitochondria and helps to recruit UPS machinery

When neither hyperfusion, nor mitophagy can help – cells undergo apoptosis...
Molecular MQC - Proteases

- Removal of misfolded, damaged or non-assembled polypeptides

- Central roles in:
  - mitochondrial biogenesis
  - mitochondrial dynamics
  - mitochondrial signaling
  - lipid homeostasis
  - apoptosis

Bohovych et al., Antioxid. Redox Signal. (2015)
Two major classes of IMQC proteases:
1). ATP-dependent (AAA+ proteases)
2). ATP-independent
Syndrome
Hereditary Spastic Paraplegia Spinocerebellar Ataxia type 28 Spastic Ataxia-Neuropathy Syndrome
HFD-induced obesity Amyotrophic Lateral Sclerosis
Molecular MQC - Proteases
Genetic interactions indicate tight functional coupling between MQC proteases

Bohovych et al., J. Biol. Chem (2014)
Molecular MQC in the matrix

- Matrix MQC involves both soluble and mitochondrial inner membrane anchored proteases

Removal of processed mitochondrial targeting signal peptides is yet another critical aspect of the matrix MQC

Levytskyy et al., J. Neuroimmune Pharm. (2016)
Molecular MQC in the IM and IMS

Proteolytic processing

Regulatory proteolysis

Proteolytic removal of damaged proteins

Adapted from Anand et al., BBA (2013)
Where molecular and organellar MQC intersect

- Stress-triggered cleavage of L-OPA1 by activated OMA1 protease stimulates fission and leads to metabolic “re-tuning”

Where molecular and organellar MQC intersect

- PINK1 accumulation is a consequence of its attenuated turnover by PARL protease

Anand et al., BBA (2013)
Mitochondrion to nucleus stress communication

Retrograde responses

- Various signals are produced by mitochondria to communicate their functional states.

- LON, m-AAA and likely Oma1 proteases participate in modulation of mitochondrial ROS and Ca\(^{2+}\) levels.
Mitochondrion to nucleus stress communication

**Mitochondrial unfolded protein response (UPRmt)**

- AFTS-1 = Activating transcription factor associated with stress (bZip transcription factor)

- Under normal conditions AFTS-1 is sent to mitochondria and degraded by LON protease

- Upon stress, AFTS-1 localizes to the nucleus and initiates UPRmt-like response

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Nargund et al., Science (2012); Ed Germany (unpublished)
Mitochondrion to nucleus stress communication

- Destabilization of the respiratory supercomplexes in Oma1-deficient that impinges on TORC1-Rim15-Msn2/4 signaling axis

Take home messages

• Sustaining normal mitochondrial function is critical for cellular welfare

• Several aspects of mitochondrial function may turn into “disaster routes” and need to be tightly controlled by mitochondrial quality control mechanisms

• Mitochondrial quality control is a multi-faceted and hierarchal set of interdependent mechanisms at both molecular and organellar levels

• Mitochondrial proteases play key roles in the majority of MQC mechanisms

• Mitochondria effectively communicate with nucleus and other organelles via several mechanisms which involve MQC proteases

• Under certain conditions, transient mitochondria-derived ROS can be amplified and act as hormetic-like signals interfering with key cellular signaling pathways