Biochimica et Biophysica Acta 1833 (2013) 417–424

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Staying cool in difficult times: Mitochondrial dynamics, quality control and the stress response ☆

Timothy E. Shutt [a], Heidi M. McBride [b,*]

[a] University of Ottawa Heart Institute, 40 Ruskin St., Ottawa, ON, Canada K1Y 4W7
[b] Montreal Neurological Institute, McGill University, 3801 rue University, Montreal, Que., Canada H3A 2B4

ARTICLE INFO

Article history:
Received 29 February 2012
Received in revised form 21 May 2012
Accepted 22 May 2012
Available online 7 June 2012

Keywords:
Mitochondrial dynamics
Fusion
Fission
Mitophagy
Vesicle
Quality control

ABSTRACT

One of the critical problems with the combustion of sugar and fat is the generation of cellular oxidation. The ongoing consumption of oxygen results in damage to lipids, protein and mtDNA, which must be repaired through essential pathways in mitochondrial quality control. It has long been established that intrinsic protease pathways within the matrix and intermembrane space actively degrade unfolded and oxidized mitochondrial proteins. However, more recent work into the field of quality control has established distinct roles for both mitochondrial fragmentation and hyperfusion in different aspects of quality control and survival. In addition, mitochondrial derived vesicles have recently been shown to carry cargo directly to the lysosome, adding further insight into the integration of mitochondrial dynamics in cellular homeostasis. This review will focus on the mechanisms and emerging questions concerning the links between mitochondrial dynamics and quality control. This article is part of a Special Issue entitled: Protein Import and Quality Control in Mitochondria and Plastids.

© 2012 Elsevier B.V. All rights reserved.

1. Introduction: Mitochondrial proteases and the first line of defense

The question of mitochondrial quality control was first addressed with the discovery of a series of mitochondrial proteases that were evolutionarily conserved from bacteria. The matrix localized Lon protease has its origins in bacterial quality control pathways [1]. In mammalian cells, the AAA protease Lon has been shown to recognize oxidized cargo like aconitase [2], but it also can regulate mtDNA levels either directly [3], or through the degradation of the mitochondrial nucleoid-associated transcription factor A, TFAM, indirectly regulating mtDNA copy number [4]. As in bacteria, the regulation of protein turnover in the mitochondria is also subject by the "N-end rule", where the stability of the protein is dependent upon the N-terminal exposed residue. Protein stability of imported proteins can be tightly regulated through a second cleavage event mediated by matrix intermediate proteases. This cleavage has been shown to remove unstable N-terminal residues, effectively stabilizing the protein [5,6]. The N-terminal residues of mitochondrial proteins are therefore critical determinants of the half-life of a broad spectrum of proteins.

The importance of mitochondrial proteases in quality control has been demonstrated by the direct links to human diseases where AAA proteases are mutated. These include the inner membrane anchored AAA protease complex, AFG3L2 and Spg7, both of which have been linked to familial forms of human spastic paraplegia and ataxia [7–9]. The function of these proteases is broad, as they often have roles in import and processing of substrates, as well as in mitochondrial dynamics through the regulated cleavage of substrates like the inner membrane fusion GTPase Opa1. Opa1 is highly complex; with 8 splice variants, and at least two different cleavage sites. Some splice variants are cleaved constitutively by the intermembrane space protease Yme1 [10,11], but it was also shown that AFG3L2 participates in the regulation of Opa1 cleavage events, contributing to the balance of long- and short-forms of the GTPase in steady state [12]. Furthermore, upon the loss of mitochondrial electrochemical potential, another inner membrane protease Oma1, cleaves all of the Opa1 variants to the short form, effectively blocking mitochondrial fusion [12,13]. Opa1 has been a particularly complicated substrate, with many different mitochondrial proteases acting upon it, depending on the situation. For example, one of the Opa1 proteases, the rhomboid protein PARL [14], regulates mitochondrial dynamics through a conserved N-terminal matrix domain, which is subject to proteolytic cleavage in a manner dependent upon the phosphorylation state [15,16]. Importantly, PARL has also been identified as a Parkinson's disease gene, further implicating mitochondrial proteases in human disease [17]. The use of complex protease cascades in the regulation of protein turnover and function has become a recurrent theme, placing the mechanisms for protease regulation as a critical focus for future research.

☆ This article is part of a Special Issue entitled: Protein Import and Quality Control in Mitochondria and Plastids.

* Corresponding author at: Montreal Neurological Institute, McGill University, 3801 rue University, Rm 660, Montreal, PQ, Canada H3A 2B4. Tel.: +1 514 398 8501.
E-mail address: heidi.mcbride@mcgill.ca (H.M. McBride).

0167-4889/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamcr.2012.05.024

2. New discoveries explain mitochondrial clearance

A young graduate student named Derek Narendra in the lab of Richard Youle did an experiment that changed the field almost overnight. He simply added a mitochondrial poison, CCCP, which depolarizes the electrochemical potential across the mitochondrial inner membrane [18]. Over the course of an hour, Derek observed an almost complete recruitment of a ubiquitin E3 ligase called Parkin to the uncoupled and fragmented mitochondria. The continued treatment of the cells with CCCP eventually led to the clearance of all of the mitochondria through the autophagic pathway. If ever there was an Archimedes-inspired "Eureka!" moment in mitochondrial quality control, this was it. Neuroscientists had been intensely investigating Parkin, which is mutated in some forms of familial Parkinson's disease, for over a decade. They had established that the loss of Parkin led to mitochondrial dysfunction in *Drosophila Melanogaster* [19–21], yet the mechanistic links to mitochondria remained elusive. Since the publication of this result in 2008, there has been an exponential rise in publications focused on the role of Parkin and other PD related genes in mitochondrial quality control.

Importantly, parkin mediated mitophagy required that the mitochondria be fragmented, since the loss of mitochondrial fission blocked the clearance of the organelles [22]. The recognition of dysfunctional fragments by Parkin is essential in this pathway, as fragmentation alone does not trigger mitophagy [23]. In this way, we learned an important new function for mitochondrial fission — to allow for the removal of damaged organelles. It had been shown a few months before the Narendra study that mitochondrial depolarization occurred during a fission event, and this may function to continually "survey" the reticulum for the ability to recover from transient depolarization [24]. However, the delivery of the depolarized organelle to the autophagosome required a number of hours, so why don't they re-fuse with healthy mitochondria in the interim? As mentioned above, the loss of electrochemical potential leads to the activation of the inner membrane protease Oma1, which cleaves the inner membrane fusion GTPase Opa1 [10–13,25]. Once cleaved to the shorter form, Opa1 was released from the inner membrane, and fusion was blocked. In this way the lone, depolarized organelle becomes excommunicated from the reticulum awaiting the recruitment of parkin and final delivery to the cellular gallows.

We have since learned that additional PD related genes, including the kinase Pink1, are requisite for Parkin recruitment to depolarized mitochondria [22,26–29]. In addition, depolarized organelles recruit the chaperone p97/VCP, which facilitates the extraction and degradation of outer membrane proteins by the proteasome [30,31]. Together, these data provide links between mitophagy and the proteasome, suggesting that the removal of outer membrane proteins is requisite for the recognition of the fragment by the autophagosome. In addition, it was discovered that p97/VCP/Cdc48 are specifically recruited to mitochondria via the adaptor Vms1 in cells experiencing oxidative stress in multiple organisms [32]. The mechanism of retrotranslocation of mitochondrial proteins across the outer membrane to the proteasome is not yet established, but is known to regulate the turnover of many mitochondrial proteins [33–36]. With this, it is clear that ubiquitin-mediated protein degradation occurs in the absence of mitophagy as a mechanism for regulated mitochondrial protein turnover and quality control.

The established paradigm has been developed primarily using cultured cells. The best example of mitophagy within physiology is the example of the red cell. In this cell type, an outer membrane protein Nix (Nip3 like protein X) plays a critical role in the clearance of all mitochondria during development [37,38]. In this developmental system, the clearance of mitochondria is not precipitated by their dysfunction or loss of potential. Nix functions directly as an adaptor to couple the mitochondria to the autophagic proteins LC3 and GABARAP, leading to the engulfment of mitochondria by the autophagosome in a developmentally regulated manner [39,40]. Studies in this model system have also shown roles for Parkin [41], the outer membrane kinase Ulk1, and the cytosolic chaperones Hsp90 and Cdc37 [42]. In another tissue-specific model of autophagy within the heart, the Nix-related protein Bnip3 (Bcl2/E1B 19 kDa-interacting protein 3-like protein) was shown to be requisite for mitophagy in a mechanism that also requires mitochondrial fission and parkin recruitment [43]. From all these studies, it appears that two distinct steps must occur to facilitate mitophagy; the activation of the autophagic machineries, and the selection of the dysfunctional mitochondria, [41,44,45]. There is a growing complexity in the signals, adaptors and regulation of mitophagy that are currently under investigation [46].

In skeletal muscle, the regulated cellular program of muscle atrophy also requires active mitophagy [47]. In that study, mitochondrial fission was required in order to activate transcription of at least two genes encoding ubiquitin ligases required for atrophy-induced protein degradation, Atrogen-1 and MURF-1 [47]. This demonstrates that the process of mitophagy may also play a signaling role in determining cell fate in addition to the clearance of dysfunctional organelles.

The loss of electrochemical potential is a primary trigger for mitophagy, yet it is not clear whether mitochondria significantly depolarize on a regular basis in vivo. In primary neurons, CCCP does not necessarily lead to global uncoupling of mitochondria. A recent study showed a differential effect depending on the carbon source provided to the cells [48]. When cells were grown on glucose, CCCP depolarized and parkin was recruited, however when grown on galactose which drives mitochondrial respiration, the drug did not lead to parkin recruitment. This is because mitochondria have evolved mechanisms to ensure they remain polarized in cells that require their services. For example, the addition of oligomycin to these galactose treated cells reverted the phenotype, and parkin was again recruited [48]. Oligomycin blocks the ATP synthase (complex V), which had been running in reverse to hydrolyze ATP, pumping protons back out of the matrix to regenerate the electrochemical potential. More recent work has confirmed the relative resistance of neuronal mitochondria to depolarization, but demonstrated a direct functional role for parkin recruitment in the neuronal survival [49]. Rather than the rapid parkin recruitment in transformed cells, it took 12–24 h before Parkin recruitment was observed in only 5–30% of neurons. This work demonstrates the universality of the paradigm. Future work will continue to focus on establishing the molecular details of parkin recruitment to depolarized mitochondria.

3. Mitochondrial fusion as cellular stress response

Equally exciting has been the realization that the mitochondria band together in times of stress (Fig. 1). In a term coined by Daniel Tondera in the lab of Jean-Claude Martinou, stress induced mitochondrial hyperfusion (SIHM) was observed in the hours following a number of cellular stresses [50]. Prolonged stress ultimately leads to mitochondrial fragmentation, due to accumulated damage and depolarization. Whether or not the fragmented mitochondria trigger apoptosis would depend on the extent and duration of the stress trigger. Once fragmented, dysfunctional organelles may be cleared through mitophagy, potentially restoring the reticulum to the normal state (see model, Fig. 1).

In the initial study, a prohibitin related protein Slp-2 was identified as requisite for the hyperfusion response, and its presence ensured the stability of Opa1 against stress-induced cleavage and degradation [50]. Although the precise mechanisms of Opa1 protection by Slp2 remain unclear, the data support the idea that the architecture of the inner membrane is likely very dynamic, responding to stress cues in various ways. The cristae themselves are tightly controlled through a conserved protein complex, recently named the MINOS (*m*itochondrial *in*ner membrane *o*rganizing *s*ystem), mitOS (*mit*ochondrial *o*rganizing *s*tructure) or MICOS (*mi*tochondrial *co*ntact *s*ite) complex present in yeast, *Caenorhabditis elegans* and mammalian cells [51–58]. This

Download English Version:

https://daneshyari.com/en/article/10802718

Download Persian Version:

https://daneshyari.com/article/10802718

Daneshyari.com