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Review

Organellar vs cellular control of mitochondrial dynamics

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ABSTRACT

Mitochondrial dynamics, the fusion and fission of individual mitochondrial units, is critical to the exchange of the metabolic, genetic and proteomic contents of individual mitochondria. In this regard, fusion and fission events have been shown to modulate mitochondrial bioenergetics, as well as several cellular processes including fuel sensing, ATP production, autophagy, apoptosis, and the cell cycle. Regulation of the dynamic events of fusion and fission occur at two redundant and interactive levels. Locally, the microenvironment of the individual mitochondrion can alter its ability to fuse, divide or move through the cell. Globally, nuclear-encoded processes and cellular ionic and second messenger systems can alter or activate mitochondrial proteins, regulate mitochondrial dynamics and concomitantly change the condition of the mitochondrial population. In this review we investigate the different global and local signals that control mitochondrial biology. This discussion is carried out to clarify the different signals that impact the status of the mitochondrial population.

Contents

1. Introduction

Mitochondria exist as a dynamic network within living cells, undergoing fusion and fission events that facilitate inner and outer membrane fusion and the exchange of organelle contents such as solutes, metabolites, proteins, and mitochondrial DNA (mtDNA) [1–6]. Processes of fusion and fission are necessary for many cellular functions including mitosis, fuel sensing, ATP production, autophagy, and apoptosis [6–11]. Mitochondria are evolutionarily derived from the endosymbiotic relationship of prokaryotic bacteria within eukaryotic cells. Although the coexistence of these two organisms have become genetically integrated through natural selection, the individual mitochondrion is still in many ways its own organism [12–14]. In this review we explore the dynamic relationship between "global" cellular and "local" organelle specific control of individual mitochondria, and the implications of these controls on the mitochondrial population.

Mitochondrial proteins are encoded both by nuclear and mtDNA, however all mitochondrial proteins can be post-translationally modified, degraded, oxidized, or otherwise altered by conditions specific to the individual organelle. This process can be described as "local" control which refers to the effect of micro-environmental changes at the level of the individual mitochondrion that affect fission and fusion events. Local control can affect the

Abbreviations: $\Delta\psi_m$, mitochondrial membrane potential; BCL-2, B-cell lymphoma-2; BID, BH3 interacting domain; DRP1, dynamin related protein 1; ERRα, estrogen related receptor alpha; Ga12, GPCR a 12; mtDNA, mitochondrial DNA; mtPA-GFP, mitochondrial photoactivatable green fluorescent protein; MFN1/2, mitofusin 1 and 2; NRF1/2, nuclear respiratory factor 1/2; OF, optical flow method; OPA1, optic atrophy protein 1; PARL, presenilin-associated rhomboid-like; PGC1α, PPAR gamma coactivator 1 alpha; PPARα, peroxisome proliferation activated receptor alpha; TMRE, tetramethylrhodamine ethyl ester; Yme1L, Yme1-like protein.

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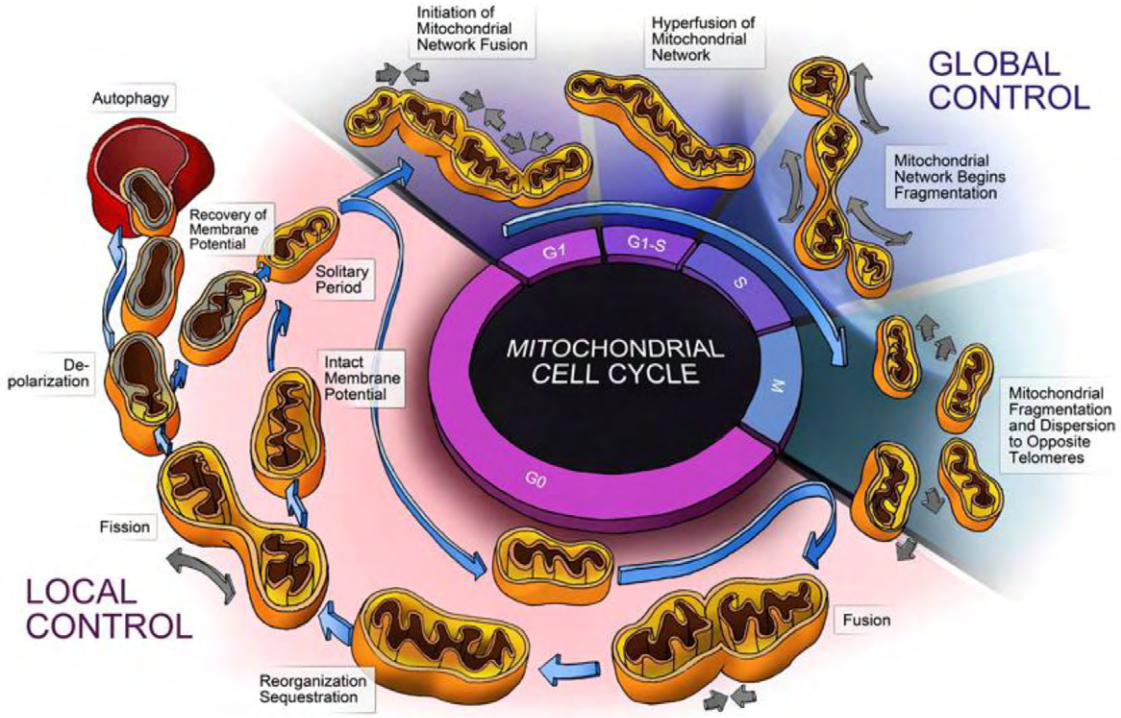

Fig. 1. Mitochondrial life in the cell cycle—this diagram depicts the normal life cycle of an individual mitochondria during the G0 phase of the cell cycle. The mitochondrion undergoes fusion, fission, depolarization, and degradation by autophagy. This process is depicted as one of local control where by mitochondrial events are largely dictated by the local energetic status and associated local signals. During the cell cycle global signals cause concerted changes in the mitochondrial population, as noted by hyperfusion in G1-S and fragmentation during M phase. These global population effects are governed by the cells demand for energy required by cell division and the need for homogenization and sequestration of cellular components during met-phase. The cell cycle serves as an elegant example of the parities of local and global control.

capacity of the individual mitochondrion to function in energy production, sequester apoptotic stimuli, or propagate mtDNA. For example, loss of mitochondrial membrane potential ($\Delta\psi_m$) can lead to the isolation of the mitochondrial unit from the mitochondrial network, and increased probability of autophagic degradation [6,15].

In contrast to "Local" controls, "Global" controls are mechanisms that can either override or monopolize mechanisms of local control to alter the dynamic status of mitochondria in the entire cell. The cell cycle is a prime example of global control. A key phase of the cell cycle is G1-S mitochondrial biogenesis which is controlled by nuclear transcription factors PGC1α, PPARα, NRF1/2, and ERRα [16,17]. Activation of these transcription factors leads to increased mitochondrial mass, respiratory capacity and energy production required during the etropic S phase of cell division [17]. Observational findings during the cell cycle have demonstrated that individual mitochondria act in a concerted manner at different stages of the cell cycle [17–20]. Specifically, network hyperfusion was found to occur at G1-S phase and be required for progression to S phase [16]. Additionally, hyper fragmentation of the mitochondrial network begins in S Phase [20]. Lastly, fragmented mitochondria localize to opposite telomeres of daughter mitochondria in M phase suggesting concerted movement and dispersion between daughter cells. A depiction of this process as well as the roles of global and local control can be found in Fig. 1.

2. Regulation and monitoring of dynamic events

Recent findings have begun to elucidate the life cycle of a mitochondrion. It has been shown that mitochondria exist in networked and solitary phases within the cell, undergoing cycles of fusion and fission in response to a variety of stimuli [6,10,16,21–24]. Additionally, mitochondria can be subjugated from the dynamic life cycle and targeted for degradation by the autophagosome [6,25,26]. Biophysical and morphologic parameters can be monitored for extended periods of time using mitochondrially targeted photoactivatable GFP (mtPA-GFP) [27–29]. Real time tracking of fluorescently labeled individual mitochondria enables quantification of size, motility, shape, $\Delta\psi_m$ as well as temporal properties of fusing organelles. Gerencser and Nicholls have developed the optical flow (OF) method by which mitochondrial movement, redox status, and $\Delta\psi_m$ can be correlated using imaging techniques [30]. These experiments confirm that mitochondria exist in two states, networked and solitary, and that fusion and fission events are correlated to the bioenergetic state change of individual mitochondria.

In several cell types prolonged tracking (up to 2 h) of individual mitochondria demonstrated the organelle's ability to maintain a stable $\Delta\psi_m$ during the solitary period [6,15,27]. During most of that time (95% of the recording period) the $\Delta\psi_m$ of the individual mitochondrion was within ±2.7 mV of its average baseline. This observation indicates that continuous deterioration in $\Delta\psi_m$ is an unlikely (or infrequent) route for the generation of depolarized mitochondria under normal conditions. The majority of fission events yield heterogeneous daughter mitochondria with opposite $\Delta\psi_m$ deflections, usually greater than 5 mV. Probability analysis has found that the depolarized daughter mitochondria are 6 times less likely to rejoin the mitochondrial network through fusion [6]. Non-fusing mitochondria can be identified using a procedure in which a small group of mitochondria are tagged by laser photoconversion of matrix-targeted mitochondrial photoactivatable green fluorescent protein (mtPA-GFP) and observed over time. These mitochondria fail to dilute their activated mtPA-GFP through fusion events. Co-staining with the membrane potential dependent dye TMRE revealed that non-fusing mitochondria are depolarized by ~7 mV compared to average $\Delta\psi_m$, while co-staining with an OPA1