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Review

Mitochondrial remodeling: Rearranging, recycling, and reprogramming

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ABSTRACT

Mitochondria are highly dynamic and responsive organelles that respond to environmental cues with fission and fusion. They undergo mitophagy and biogenesis, and are subject to extensive post-translational modifications. Calcium plays an important role in regulating mitochondrial functions. Mitochondria play a central role in metabolism of glucose, fatty acids, and amino acids, and generate ATP with effects on redox poise, oxidative stress, pH, and other metabolites including acetyl-CoA and NAD^+ which in turn have effects on chromatin remodeling. The complex interplay of mitochondria, cytosolic factors, and the nucleus ensure a well-coordinated response to environmental stresses.

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Asthma's a problem of inhaling too much
Hyperinflation, air trapping, and such.
But physicians find themselves just as aghast
When a patient finally exhales his last.
So which deserves the frowning pout:
Breathing in or breathing out?
So it is with the mitochondrion,
Which is better, fission or fusion?
Both out and in make good respiration
Ditto for mitochondrial undulation.

Roberta A. Gottlieb

1. Introduction

Mitochondria can present many different faces depending on environmental conditions and cellular requirements. They change their structure, their proteome, their metabolism, and even their genome, in response to cellular and environmental cues. As they remodel, they in turn alter cellular programs and capabilities. Mitochondrial remodeling is a component of the pathophysiology of diverse diseases, including neurological, cardiovascular, metabolic and oncologic. In this setting, mitochondrial alterations may be either secondary processes or primary mechanisms due to mutations in genes that regulate mitochondrial remodeling. However, the role of mitochondrial remodeling in normal physiological processes is gaining increased recognition. In this review we will cover structural remodeling, comprising fusion and fission; mitochondrial turnover accomplished by mitophagy and biogenesis; proteomic alterations and posttranslational modifications; metabolic alterations; reactive oxygen species; and retrograde signaling whereby mitochondria modify the nuclear program.

2. Mitochondrial structural remodeling: rearranging and recycling

The dynamic nature of mitochondrial morphology was apparent even to the 19th century scientists who first proposed the name: mitos (thread-like) and chondrion (granule-like) [1,2]. Mitochondrial dynamics are those processes that regulate mitochondrial morphology, including: (a) *Mitochondrial fission:* the process that creates more numerous, smaller and more circular mitochondria; (b) *Mitochondrial fusion:* the process that creates fewer, larger and more elongated mitochondria; (c) *Mitophagy:* the process of removing damaged mitochondria; and (d) *Mitochondrial biogenesis:* the process that increases mitochondrial number and/or volume through increased expression of both mitochondrial and nuclear transcripts. This is illustrated in Fig. 1.

2.1. Mitochondrial fission

Mitochondrial fission is mediated by dynamin-1-like protein (Drp1), a member of the dynamin superfamily, consisting of a GTPase and GTPase effector domain separated by a helical segment. Fission occurs when Drp1 is translocated from the cytosol to the outer mitochondrial membrane (OMM) leading to a complex, and as yet still not fully understood, interaction with three integral OMM proteins, Fis1, Mff, and MIEF1.

1. *Fis-1*. Fis1 is the most evolutionarily conserved pathway, and is a major regulator of fission in yeast. In yeast cells, two adapter proteins (Mdiv1 and Caf4) link Drp1 and Fis1, although similar adapters have not been found in mammalian cells. The role of Fis1 in fission in mammalian cells is still controversial, with some studies supportive (overexpression of Fis1 induces fragmentation; knockdown of Fis1 results in elongation [3–5]), yet others arguing against a role (the absence of bridging proteins; Fis1 is uniformly distributed on the OMM, whereas when Drp1 is translocated, it localizes to punctate structures; altering the level of Fis1 does not affect the distribution of Drp1 on the OMM [5,6]; ablation of Fis1 does not alter mitochondrial morphology or block fission [7]). It is possible, therefore, that Fis1 may play a role in recruitment of Drp1 in certain cell types and under certain stressors, but not others [8,9]. Some of the strongest evidence confirming the role of Fis1 in mammalian cells comes from studies showing that a peptide designed to specifically inhibit the Drp1-Fis1 interaction can block fission in both cardiomyocytes and neuronal cells, attenuating ischemic injury or neurodegeneration, respectively [10–12].
2. *Mff* is an OMM protein not found in yeast. Knockdown of Mff leads to increased mitochondrial fusion whereas overexpression leads to fragmentation. However, Mff and Fis1 are located in different complexes on the OMM [13] and Mff-mediated fission is independent of Fis1 [7,14], suggesting that these two proteins play different roles or activate fission in response to different stressors.
3. *MIEF1* (mitochondrial elongation factor 1). Also known as MiD51 and MiD49 (mitochondrial dynamic proteins), MIEF1 is co-localized with Drp1 in punctate structures on the OMM. Overexpression of MIEF1 recruits Drp1 but, intriguingly, induces mitochondrial elongation rather than fragmentation; similarly, knockdown of MIEF1 leads to fragmentation. As well, the recruitment of Drp1 by MIEF1 is independent of Drp1 phosphorylation or its GTPase activity [15]. The current paradigm is that although MIEF1 recruits Drp1, it sequesters it from interaction with Fis1, thus inhibiting its activity. MIEF1 also associates with Fis1 in a Drp1-independent manner [15], competing for MIEF1 binding

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