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Review

Oxidative phosphorylation and aging

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Abstract

This review addresses the data that support the presence and contribution of decreased mitochondrial oxidative phosphorylation during aging to impaired cellular metabolism. Aging impairs substrate oxidation, decreases cellular energy production and increases the production of reactive intermediates that are toxic to the cell. First, the basic principles of mitochondrial oxidative physiology are briefly reviewed. Second, the focus on the relationship of altered mitochondrial respiration to the increased production of reactive oxygen species that are employed by the ''rate of living'' and the ''uncoupling to survive'' theories of aging are discussed. Third, the impairment of function of respiration in aging is reviewed using an organ-based approach in mammalian systems. Fourth, the current state of knowledge regarding aging-induced alterations in the composition and function of key mitochondrial constituents is addressed. Model organisms, including *C. elegans* and *D. melanogaster* are included where pertinent. Fifth, these defects are related to knowledge regarding the production of reactive oxygen species from specific sites of the electron transport chain.

Keywords: Oxidative phosphorylation; Mitochondria; Aging; Reactive oxygen species; Electron transport chain; Complex III; Cytochrome oxidase

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1. Principles of oxidative phosphorylation

Mitochondria are composed of several compartments, each with specific metabolic functions, demarcated by the inner and outer mitochondrial membranes. The outer membrane surrounds the organelle, whereas the inner membrane surrounds the central matrix space (Fig. 1). The intermembrane space is located between the two membranes. The outer membrane is impermeable to molecules larger than 1500 Da. The intermembrane space contains a distinct group of proteins, including the mobile electron carrier, cytochrome *c*. The inner membrane is composed of segments of inner boundary membrane, parallel to the outer membrane, that join the cristae at cristae junctions. The cristae contain the electron transport chain (ETC), phosphorylation apparatus, and membrane transporters. Portions of the inner membrane combine with the outer membrane to form contact sites (Nicolay et al., 1990; Brdiczka and Wallimann, 1994). Contact sites participate in the import of proteins, adenine nucleotides, and fatty acid substrates into mitochondria. Components of these sites include translocase import proteins, TOM (translocase outer membrane) and TIM (translocase inner membrane). Other major components of contact sites are the peripheral benzodiazepine receptor, including the adenine nucleotide translocator and voltage dependent anion channel (Brdiczka et al., 1990; Nicolay et al., 1990), as well as the enzymes of fatty acid activation and transport (Kerner and Hoppel, 2000).

The electron donors, NADH and $FADH_2$, provide reducing equivalents to the ETC. Pyruvate dehydrogenase generates NADH. The enzymes of the tricarboxylic acid cycle located in the matrix space produce $FADH_2$ and NADH. The beta oxidation of fatty acids occurs in the matrix following activation and transport of fatty acids into the matrix via

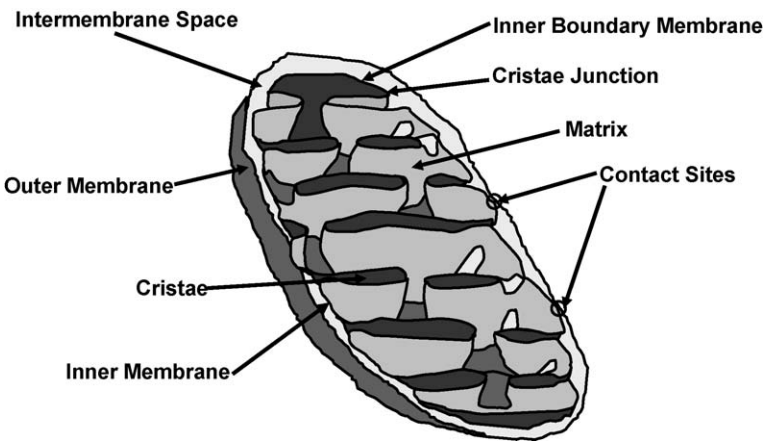

Fig. 1. A cartoon of a mitochondrion with identification major structures is shown. The outer membrane surrounds the organelle. The mitochondrial matrix is surrounded by the inner membrane. The intermembrane space is located between the two membranes. The inner membrane is composed of cristae and the inner boundary membrane that joins the cristae at cristae junctions. Contact sites consist of a fusion of the inner and outer membranes.