



Mitochondria: Beyond Something than Just a Power House of a Cell

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ABSTRACT

Pioneering wet lab experiments have already established the role of mitochondria as a power house inside the cell. Apart from that this organelle has important role in several other cellular processes like calcium signalling, apoptosis, embryonic and tissue development, lipid synthesis, aging etc. Here in the present study the focal theme has set on the role of this organelle towards development and aging process. Research studies have already conferred the role of mitochondrial fusion and fission process in several cellular processes. Here the work is focused to unveil the role of this organelle towards development and aging process in the context of fission and fusion which happens inside this organelle.

Keywords: Aging, Development, Fusion-Fission process, Mitochondria.

INTRODUCTION

Pioneering biochemical studies have put forward the concept that the mitochondria are the 'energy powerhouse of the cell'. These studies, combined with the unique evolutionary origin of the mitochondria, led the way to decades of research focusing on the organelle as an essential, yet independent, functional component of the cell. Mitochondria evolved from a symbiotic relationship between aerobic bacteria and primordial eukaryotic cells. Mitochondria are the primary energy-generating system in most cells by producing ATP through a complex set of chemical reactions. Additionally, they participate in intermediary metabolism, calcium

signaling, programmed cell death and synthesis of lipids. They also house genes for the ribosome, which build proteins as well as the transfer RNA (tRNA) genes and provides a sort of lock-and-key system that helps decipher the genetic code into the amino acid protein code. This way, mitochondria keep each cell humming and building proteins (with a steady supply of tRNA keys). From the structural perspective this a very unusual organelle as it contains only two membranes that separate four distinct compartments, the outer membrane, intermembrane space, inner membrane and the matrix (Figure 1).

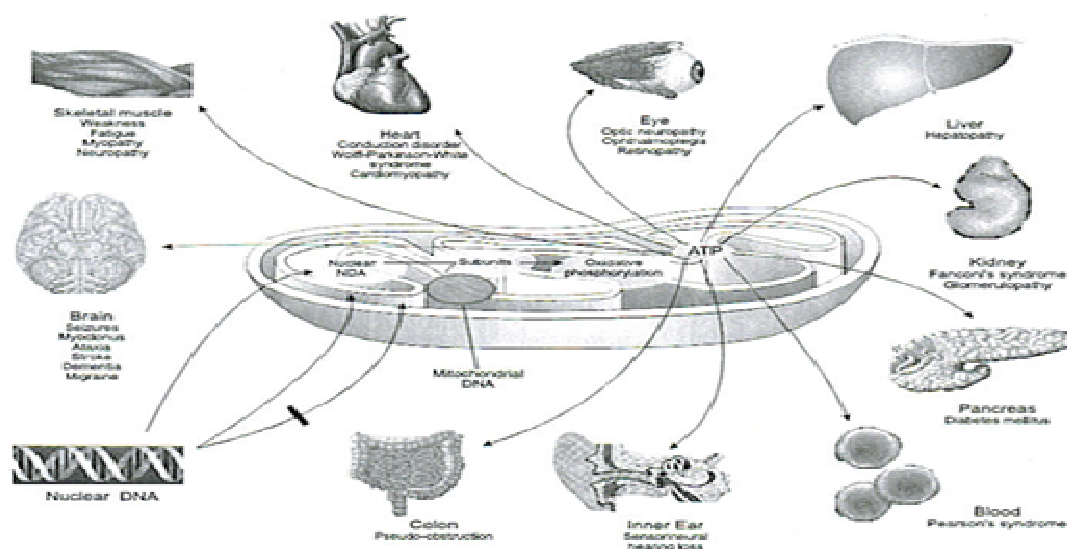


Figure 1: Mitochondria as the source of energy in the cell

Most of the times different wet lab experiments with cell free systems and isolated mitochondria led us to channelize our thoughts that this organelle is working tirelessly in a cell for production of ATP only. In the past

10 years, this concept has changed as newer scientific approaches have allowed the examination of dynamic mitochondrial function and behavior in response to cellular signals within intact cells. In addition, recent

evidence suggests that bi-directional signaling exists between mitochondria and other cellular components. The implication of the enzyme GTPase both regulatory and mechanical, in the governance of mitochondrial dynamics has recently been shown to couple mitochondrial function to cellular demand. This integration allows mitochondrial function, localization and biogenesis to be responsive to changes in cell metabolism, development, death and cell division.

The main focus of this review is to looking insight to the other functions of mitochondria apart from ATP production which are essential for cell survival and also for generation of newer offsprings.

Mitochondria in Tissue Development

The mitochondrial network displays remarkable plasticity during development of certain tissues. Electron microscopy studies have revealed a transition from elliptical and rod shaped mitochondria in embryonic rat myocardiocytes and skeletal muscle cells to an interconnected reticulum in the cardiac muscle and diaphragm of adult animals^{1, 2, 3}. This morphological transitions indicates the possible mechanism through which it is achieved i.e. Mitochondrial fusion. Research studies have already established that expression levels of Mitofusin2 (Mfn2; a GTPase involve in mitochondrial fusion) increase during differentiation of myoblasts⁴ and spermatocytes⁵ (Figure 2).

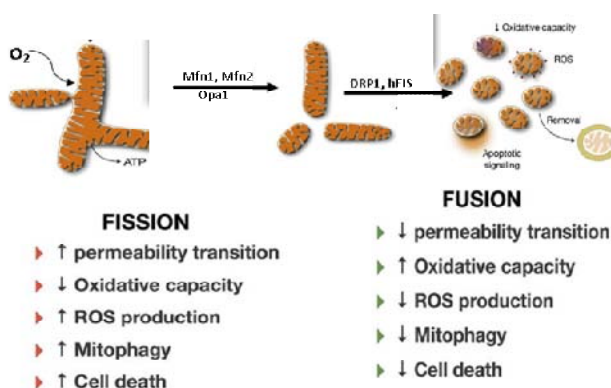


Figure 2: Interaction between mitochondria and fission

Mfn2 null embryos although appear normal but are resorbed at embryonic day 11.5 due to unsuccessful placental implantation whereas Mfn1 null embryos, although developmentally delayed and resorbed by embryonic day 12.5, display normal implantation suggesting the fact that placental malfunction observed in Mfn2 null mice is not directly related to a lack of mitochondrial fusion⁶.

Data so far indicate that Mfn1 functions primarily as an essential component of the fusion machinery and that Mfn1 participates with Opa1 in the fusion process⁷. In addition, the nucleotide-binding properties of Mfn1 and Mfn2 appear to be quite distinct, suggesting unique functional properties⁸. Mfn1 binds to nucleotide with low affinity and shows high rates of hydrolysis for GTP,

consistent with its evolutionary relationship to the dynamin family of GTPases⁸. Mfn2 binds nucleotides with high affinity and exhibits slow intrinsic hydrolysis rates reminiscent of the Rab family of regulatory GTPases⁹. Collectively, these findings strongly indicate that Mfn1 and Mfn2 are functionally distinct GTPases that are both essential for mitochondrial fusion and embryonic development. Cells lacking all mitochondrial fusion due to deletion of both Mfn1 and Mfn2 or loss of OPA1 show severe cellular defects⁶. Such cells grow very slowly and have reduced activity for all respiratory complexes. The respiratory deficiency is associated with extensive interorganellar heterogeneity.

RNA interference against Drp1 in *Caenorhabditis elegans* leads to early embryonic lethality, before embryos reach 100 cells¹⁰. Disruption of Drp1 causes loss of proper mitochondrial localization and probably improper segregation of mitochondria in dividing cells suggesting its role in development as *Caenorhabditis elegans* contains 60 cells only.

Mitochondria in Aging

Research studies reported till date have not established the role of mitochondrial fusion or fission process in aging but in this section an attempt will be made to speculate studies linking mitochondrial dysfunction to aging and metabolic disorders. Mitochondrial respiratory chain transfers electron to NADH or FADH to series of electron acceptors and final transfer to oxygen leads to water production.

However in this biological process if leakage of electron occurs, it will leads to production of Reactive Oxygen Species (ROS) inside the cell. A low level of ROS production is an unavoidable by product of respiratory chain function, and therefore mitochondria are a major source of ROS in a eukaryotic cell. Because mitochondrial DNA is closely associated to the source of ROS production, it is thought to be particularly vulnerable to ROS-mediated mutations. Levels of oxidized guanosine are much higher in mitochondrial DNA than in nuclear DNA. In addition to impairment in respiration process in mitochondria there is a chance of another event i.e. mitochondrial DNA mutation which leads to ROS production and mitochondrial DNA lesions and ultimately this leading the so called viscous cycle. This scenario is the basis for the hypothesis that mitochondrial dysfunction plays a critical role in the aging process^{11, 12, 13}. In this view, aging is caused by the ROS-accelerated accumulation of mitochondrial DNA damage, leading to a progressive decline in respiratory function over time. In support of this hypothesis; many tissues from aged individuals have lower respiratory function compared to those from younger individuals¹⁴ (Figure 3).

Both mitochondrial DNA point mutations and deletions are indeed more prevalent in aged tissues and cells. Numerous studies have documented the presence of large mitochondrial DNA deletions from muscle and brain

from old individuals, at levels ranging from 1%–10%. Muscles from old individuals also have a higher incidence of fibers defective for cytochrome *c* oxidase, a mitochondrial enzyme with subunits encoded by mitochondrial DNA. Thus it appears that occasional cells from old individuals can have high levels of mitochondrial DNA containing deletions, leading to heterogeneity in respiratory function between individual cells.

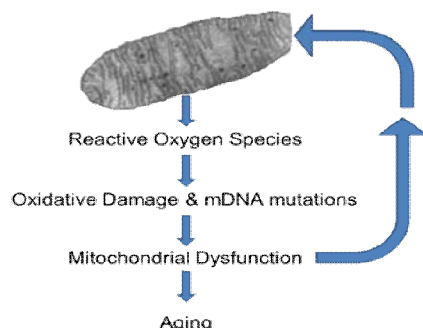


Figure 3: Relation between mitochondria and aging

Aging process is associated with clonal mitochondrial DNA mutations and respiratory incompetence in single neurons in substantia nigra. Research studies have observed that predomination of such defects accumulate in normal aging process which later responsible for loss of neurons in substantia nigra cells in Parkinsons Disease¹⁵. Furthermore, there is evidence that markers of ROS-mediated nucleotide damage, such as 8-hydroxy-2-deoxyguanosine, are more prevalent in aged tissues. Point mutations in mitochondrial DNA also appear at a higher frequency in tissues of old individuals whereas some point mutations are found at very low levels, others accumulate to very high abundance, from 20%–50% of the total mitochondrial DNA¹⁶.

However finally it can be concluded that mitochondrial DNA mutations and ROS generation are the main cause for onset of aging process as conferred from several research studies. However research studies that amalgamates mitochondrial role towards aging process will unveil newer scientific findings in the future.

CONCLUSION

In this study the main focal theme was to establish the other role that mitochondria plays apart from oxidative phosphorylation, electron transport. Mitochondria have several roles in different cellular process but in this study only two are discussed. Several prominent clinical features of mitochondrial DNA encephalomyopathies remain untouched till date, suggesting that much remains to be unveiled about how mitochondrial DNA mutations lead to disease. These processes will influence the study of mitochondrial DNA mutations and therefore disease progression. For example, does mitochondrial fusion play a protective role in dampening fluctuations in the amounts of mutant mitochondrial DNA in mitochondrial disease and aging? If so, agents that affect mitochondrial dynamics may have promise in ameliorating disease progression. With recent animal models for mitochondrial

DNA mutations and mitochondrial fusion, these issues can be addressed directly.

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