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The role of mitochondria in metabolism and cell death

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ABSTRACT

Mitochondria are complex organelles that play a central role in energy metabolism, control of stress responses and are a hub for biosynthetic processes. Beyond its well-established role in cellular energetics, mitochondria are critical mediators of signals to propagate various cellular outcomes. In addition mitochondria are the primary source of intracellular reactive oxygen species (ROS) generation and are involved in cellular Ca^{2+} homeostasis, they contain a self-destructive arsenal of apoptogenic factors that can be unleashed to promote cell death, thus displaying a shared platform for metabolism and apoptosis. In the present review, we will give a brief account on the integration of mitochondrial metabolism and apoptotic cell death.

Contents

1. Introduction

Mitochondria are cytosolic organelles that started to receive attention in the late 19th century during which they were still referred to as bioblasts. It was however, not until 30–40 years later attempts to isolate mitochondria were undertaken that shed light on its biochemical function. Over time it was discovered that, unlike other organelles in mammalian cells, mitochondria were maternally inherited, had double membrane structure and possessed their own genome [1]. They originated from symbiotic bacteria but have co-evolved with their host, as most mitochondrial proteins are nuclear encoded. However, mitochondria are semi-autonomous since they retain a small genome that encodes proteins essential for respiration. Today, it is well established that mitochondria are crucial for energy production in the form of adenosine triphosphate (ATP) through the process of oxidative phosphorylation and hold a central role in cellular bioenergetics

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[1]. Equally, they play an essential role in the biosynthesis of macromolecules, such as nucleotides, lipids, heme, and iron-sulfur clusters. Mitochondria have become an important subject of research within numerous disciplines owing to its involvement in a plethora of cellular processes. Beyond metabolism (anabolism and catabolism), also in regulating signals for propagation of diverse biological outcomes, including cell death, Ca^{2+}-homeostasis, gene expression, differentiation as well as specific aspects of the aging process, such as cellular senescence, chronic inflammation and the age-dependent stem cell activity [2]. Moreover, the mitochondrial architecture is highly dynamic, and its structure as well as its proteome has been recently shown to display significant cell-type differences, allowing mitochondria to operate in a highly adaptive fashion to meet the cell-specific requirements [3]. Consistent with its multifunctional role, altered mitochondrial function involve pathological conditions including metabolic disorders, cardiomyopathies, neurodegeneration and cancer, disorders tightly associated with dysregulated cell death [4–6]. Furthermore, considering that programmed cell death is accompanied with the disruption of metabolic functions, the impairment of mitochondrial signaling is tightly connected to developmental processes and tissue homeostasis. However, the wide range of mitochondrial functions in cells is centered on a relatively small number of proteins in the mitochondria [3], of which some that exerts both metabolic and pro-death functions that will be discussed in the following sections.

2. Mitochondrial metabolism

2.1. Oxidative phosphorylation

Mitochondria are often referred to as the powerhouse of the cell. This is due to that the mitochondria are the main source of cellular ATP production via oxidative phosphorylation (OXPHOS). OXPHOS is the metabolic pathway in which enzymes coordinated by a cascade of redox reactions organized in protein complexes embedded in the inner mitochondrial membrane, known as the electron transport chain (ETC), transfers electrons to oxygen and generates energy which is used to reform ATP. Briefly, in the mitochondrial matrix, the tricarboxylic acid (TCA) cycle enzymes produce electron carriers including nicotineamide-adenine-dinucleotide (NADH) and Flavin adenine dinucleotide ($FADH_2$) [7]. These in turn, donate electrons to the ETC, which comprises of protein complexes (I-IV), and two soluble factors, cytochrome *c* and coenzyme Q. Complex I is the first and largest of the complexes consisting of 45 core subunits. Complex I and II mediate a two-electron transfer from the electron carriers ($NADH/FADH_2$), respectively, to the mobile electron carrier coenzyme Q. The latter can also receive electrons from breakdown of a number of nutrients, such as oxidation of fatty acids, amino acids and choline. Complex III, is an adaptor that receives two electrons from reduced coenzyme Q and shuttles single electrons to cytochrome *c*. Complex IV ends the respiratory chain by accepting electrons from cytochrome *c*, to fully reduce oxygen to water [8,9]. The sequential reduction/oxidation (redox) reactions in the ETC cause conformational changes in the respiratory complexes that allow them to pump protons out from the matrix to the intermembrane space, generating an electrochemical gradient known as the mitochondrial transmembrane potential ($\Delta\psi_m$). The proton gradient produced by Complex I, III and IV create a proton drive force used by (Adenosine triphosphate) ATP synthase (Complex V) that phosphorylates (Adenosine diphosphate) ADP to produce ATP [8]. Beyond ATP generation, additional processes including mitochondrial protein import across the inner mitochondrial membrane are dependent on the transmembrane potential [10].

The respiratory complexes are generally described as freely moving, via a random-collision model [11], however accumulating evidences support a solid-state model [12]. Tight association between the proteins in the respiratory complexes might optimize substrate channeling while minimizing electron slippage and consequently reactive oxygen species (ROS) formation. However, the electron transport can leak and react with oxygen to generate superoxide, the precursor for ROS. Complex I and complex III are the main sources for its production, although Complex II can also contribute to ROS production [13–15].

2.2. The TCA cycle

The tricarboxylic acid cycle (TCA cycle) is a series of enzyme-catalyzed chemical reactions that form a key part of aerobic respiration in cells. Catabolism of nutrients such as lipids, carbohydrates and proteins leads to the production of smaller units and metabolites, that merge on the level of the tricarboxylic acid (TCA) cycle as the final joined metabolic pathway for the oxidized carbon molecules to generate energy (Fig. 1). While there are different ways for metabolites to enter the TCA cycle most nutrients often converge on the production of Acetyl-CoA, a crucial fuel for the TCA cycle, via distinct pathways. During glycolysis, glucose is oxidized to pyruvate in the cytosol. Pyruvate is then transported into the mitochondrial matrix where it is oxidized and reacts with Coenzyme A, to form Acetyl −CoA. Additionally, pyruvate can also be carboxylated to directly form oxaloacetate, a constituent of the TCA cycle. In fatty acid beta oxidation, however, long-chain fatty acids are catabolized in cycles where two carbons per cycle are cleaved off in the mitochondrial matrix, to ultimately form Acetyl-CoA. Furthermore, glutamine, which is catabolized via glutaminolysis, during which glutamine forms glutamate, that in turn can be converted in the mitochondria to alpha-ketoglutarate, a constituent of the TCA cycle [16].

Mitochondria, besides being a major metabolic hub for catabolism, are also an important source of intracellular metabolites used for biosynthetic building blocks. In particular, the TCA cycle functions in biosynthetic pathways where TCA intermediates exit the cycle and are utilized as precursors in the biosynthesis of many macromolecules, including lipids, carbohydrates, proteins, amino acids and nucleotides. For instance, the mitochondrial citrate synthase combines two carbon units from Acetyl-CoA with four carbon units from oxaloacetate to form citrate, that can be exported from the mitochondria and contribute to biosynthesis of macromolecules. The TCA cycle intermediates are continuously replenished by anaplerosis, ensuring that the TCA cycle can continue its function after loss of these intermediates [16]. Thus, mitochondria can regulate the intracellular levels of amino acids and co-factors for multiple enzymes, including DNA modifying enzymes such as histone deacetylases. Other critical metabolic functions of mitochondria include metal ion metabolism by synthesizing heme and Fe-S clusters and control steps of ketogenesis as well as reactions involved in lipogenesis, steroidogenesis, gluconeogenesis and ammonium detoxification (urea cycle) [5,17].

3. Mitochondrial functions beyond metabolism

In addition to its primary function as a bioenergetic and biosynthetic organelle, mitochondria are central to diverse cellular processes including proliferation, differentiation and adaptation to stress. In this regard, mitochondria function as signaling organelle to communicate their capacity to meet the biosynthetic/bioenergetics demands of the cell in response to environmental changes and propagate rather than dictate decision-making signals to initiate cellular outcomes. To that end, mitochondria employ various mechanisms to constantly communicate with its