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Review

Mitochondrial energy metabolism and ageing

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ABSTRACT

Ageing can be defined as "a progressive, generalized impairment of function, resulting in an increased vulnerability to environmental challenge and a growing risk of disease and death". Ageing is likely a multifactorial process caused by accumulated damage to a variety of cellular components. During the last 20 years, gerontological studies have revealed different molecular pathways involved in the ageing process and pointed out mitochondria as one of the key regulators of longevity. Increasing age in mammals correlates with increased levels of mitochondrial DNA (mtDNA) mutations and a deteriorating respiratory chain function. Experimental evidence in the mouse has linked increased levels of somatic mtDNA mutations to a variety of ageing phenotypes, such as osteoporosis, hair loss, graying of the hair, weight reduction and decreased fertility. A mosaic respiratory chain deficiency in a subset of cells in various tissues, such as heart, skeletal muscle, colonic crypts and neurons, is typically found in aged humans. It has been known for a long time that respiratory chain-deficient cells are more prone to undergo apoptosis and an increased cell loss is therefore likely of importance in the age-associated mitochondrial dysfunction. In this review, we would like to point out the link between the mitochondrial energy balance and ageing, as well as a possible connection between the mitochondrial metabolism and molecular pathways important for the lifespan extension.

1. Introduction: Mitochondrial energy metabolism

Mitochondria have a central role in the energy metabolism. Part of the free energy derived from the oxidation of food is inside mitochondria transformed to ATP, energy currency of the cell. This process depends on oxygen. When oxygen is limited, glycolytic products are metabolized directly in the cytosol by the less efficient anaerobic respiration that is independent of mitochondria.

The mitochondrial ATP production relies on the electron transport chain (ETC), composed of respiratory chain complexes I–IV, which transfer electrons in a stepwise fashion until they finally reduce oxygen to form water. The NADH and FADH2 formed in glycolysis, fatty-acid oxidation and the citric acid cycle are energy-rich molecules that donate electrons to the ETC. Electrons move toward compounds with more positive oxidative potentials and the incremental release of energy during the electron transfer is used to pump protons (H+) into the intramembrane space. Complexes I, III and IV function as H+ pumps that are driven by the free energy of coupled oxidation reactions. During the electron transfer, protons are always pumped from the mitochondrial matrix to the intermembrane space, resulting in a potential of ~150–180 mV. Proton gradient generates a chemiosmotic potential, also known as the proton motive force, which drives the ADP phosphorylation via the ATP synthase (F_oF_1 ATPase — complex V). F_o domain of ATPase couples a proton translocation across the inner mitochondrial membrane with the phosphorylation of ADP to ATP [1]. The rate of mitochondrial respiration depends on the phosphorylation potential expressed as a [ATP]/[ADP] [Pi] ratio across the inner mitochondrial membrane that is regulated by the adenine nucleotide translocase (ANT). In the case of increased cellular energy demand when the phosphorylation potential is decreased and more ADP is available, a respiration rate is increased leading to an increased ATP synthesis. There is usually a tight coupling between the electron transport and the ATP synthesis and an inhibition of ATP synthase will therefore also inhibit the electron transport and cellular respiration. Under certain conditions, protons can re-enter into mitochondrial matrix without contributing to the ATP synthesis and the energy of proton electrochemical gradient will be released as heat [2]. This process, known as proton leak or mitochondrial uncoupling, could be mediated by protonophores (such as FCCP) and uncoupling proteins (UCPs) [3,4]. As a consequence, uncoupling leads to a low ATP production concomitant with high levels of electron transfer and high cellular respiration [2].

2. Mitochondrial theory of ageing

Even though the process of oxidative phosphorylation is efficient, a small percentage of electrons may "leak" from the ETC, particularly from complexes I and III, during normal respiration and prematurely reduce oxygen, forming reactive oxygen species (ROS) [5]. It has

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been shown that other mitochondrial proteins such as the α-glycerophosphate dehydrogenase, the α-ketoglutarate and the pyruvate dehydrogenase have a role in ROS production [6]. Outside mitochondria, ROS can be produced by plasma membrane NADPH oxidases, lipid peroxidation and by some cytosolic enzymes [6]. Nevertheless, ROS produced within mitochondria presents almost 90% of the total ROS produced in the cell. The fact that the mitochondrial electron transport chain is the major ROS production site lead to the suggestion that mitochondria are a prime target for oxidative damage and hence the mitochondrial theory of ageing, a correlate to the free radical theory [7]. This idea is intellectually very appealing, as mitochondria are also the only organelle in animal cells that posses their own DNA, mtDNA, which is localized in the physical proximity to the mitochondrial respiratory chain (MRC). Over the years, substantial evidence has emerged from morphological, bioenergetic, biochemical and genetic studies to lend support to this theory. It was shown that mitochondria become larger and less numerous with age, accumulating vacuoles, cristae abnormalities and intramitochondrial paracrystalline inclusions [8]. Mitochondrial respiratory chain enzyme activities decrease, as well as mitochondrial membrane potential, on which the production of ATP is dependent, while the amount of oxidative damage to proteins and mtDNA increases, with an associated accumulation in the quantity of mtDNA mutations [9]. In addition, age-associated decrease in the MRC capacity was reported in various tissues, such as skeletal muscle [10] and liver [11]. Point mutations and deletions of mtDNA accumulate in a variety of tissues during ageing in humans, monkeys and rodents [12]. These mutations are unevenly distributed and can accumulate clonally in certain cells, causing a mosaic pattern of the respiratory chain deficiency in tissues such as heart, skeletal muscle and brain [13]. In terms of the ageing process, their possible causative effects have been intensely debated because of their low abundance and purely correlative connection with ageing [12].

We recently developed a mouse model that provided the first experimental evidence for a causative link between mtDNA mutations and ageing phenotypes in mammals [14]. We created homozygous knock-in mice that expressed a proofreading deficient form of the nuclear-encoded mitochondrial DNA polymerase (Polg) [14]. The introduced mutation was designed to create a defect in the proofreading function of Polg, leading to the progressive, random accumulation of mtDNA mutations during the course of mitochondrial biogenesis. As the proofreading is efficiently prevented, these mice develop an mtDNA mutator phenotype (mtDNA mutator mice) with a three to fivefold increase in the level of point mutations, as well as increased amounts of linear mtDNA molecules with deletions. The mtDNA mutator mice display a completely normal phenotype at birth and early adolescence but subsequently acquire many features of premature ageing. The increase in somatic mtDNA mutations is associated with reduced lifespan and premature onset of ageing-related phenotypes such as weight loss, reduced subcutaneous fat, alopecia, kyphosis, osteoporosis, anemia, reduced fertility and heart enlargement [14].

The mitochondrial theory of ageing predicts that levels of mtDNA mutations should increase exponentially as a consequence of a vicious cycle by accelerating the oxidative stress. However, an approximately linear increase of mtDNA mutation levels from midgestation to late adult life was detected in mtDNA mutator mice, implying that there is no vicious cycle [15]. Furthermore, it has been shown that there is no direct connection between increased levels of mtDNA mutations and elevated ROS production and this argues against direct role of oxidative stress in the ageing process [15]. We have detected a moderate increase of mitochondrial mass and a progressive reduction of both respiratory chain enzyme activities and mitochondrial ATP production rates in mtDNA mutator mice, consistent with previous reports in aged wild type animals [14,16]. In addition, we found a general reduction in all inducible respiratory states in both mtDNA mutator heart and liver mitochondria, while the basal respiration rate, limited by the mitochondrial membrane proton leak and not by the respiratory chain, was not altered [17]. Our latest results strongly argue that the observed phenotypes in mtDNA mutator mice are a direct consequence of the accumulation of mtDNA point mutations in protein-coding genes, leading to a decreased assembly of MRC complexes, respiratory chain dysfunction and thus to premature ageing [17].

3. “Uncoupling to survive”

The relationship between energy metabolism and longevity has been suggested by two seemingly opposing theories. According to the “rate of living hypothesis” proposed by Pearl in 1928, there was a direct link of the metabolic output of an organism to its longevity [18]. This is only the modern interpretation of probably the oldest explanation of ageing. Already Aristotle believed that we possess a finite amount of some “vital substance.” When that substance is consumed, we die. In essence, people recognized that things wear out when we use them and if we use them a lot they will not last as long. Some philosophers even argued that each person had only a finite, predetermined number of breaths or heartbeats and that once they were used, death ensued. Until recently many people believed this to be true, especially after it was supported by celebrities like Neil Armstrong, an American astronaut and the first man on the moon, who said: “I believe every human has a finite number of heartbeats. I don't intend to waste any of mine by running around doing exercises”. In the 20th century, scientists proposed a new twist on this old theory: energy consumption limits longevity. In other words, an organism's metabolic rate determines its lifespan [18]. Later, after the discovery of oxidative stress and formulation of the free radical theory of ageing the interpretation was simplified to factors that decrease an organism's metabolic rate would increase the longevity and vice versa. Today the rate of living theory is rejected as being a valid overall explanation for why we and most other species age. Scientists now believe that although the metabolic rate can affect ageing, that doesn't mean that it always does so. Caloric restriction, the only intervention known to extend life in many different species, does so without reducing the animal's metabolic rate. In addition, experimentally boosting an animal's metabolic rate does not always reduce longevity. And even though there is a rough correlation among species between body size, metabolic rate, and longevity, there are many exceptions to this rule. For example, birds typically have a metabolic rate 1.5–2.0 times as high as similar-sized mammals, yet they live on average about three times as long. Besides, a number of recent studies have demonstrated that even within a species, metabolic rate and longevity are not inversely related — a pattern inconsistent with the rate of living theory [19,20].

On the other hand, the “uncoupling to survive” theory proposes that energy metabolism is in a positive relation with longevity [21]. While following MF1 female mice throughout their lifespan, Speakman et al. observed that mice with higher metabolic intensities had higher proton conductance across skeletal muscle inner mitochondrial membrane and lived longer, providing evidence in favor of the “uncoupling to survive theory” [22].

This theory is also based on the notion that inefficiency in the mitochondrial ATP generation may be necessary to reduce ROS generation in the cell [21]. High proton motive force that drives an efficient ATP synthesis comes with an additional cost, the production of ROS. Because ROS production is highly dependent on the proton motive force, proton leak might help to limit the oxidative damage. There are a number of articles suggesting that UCPs could play an important role in this process [23]. UCPs are mitochondrial transporters present in the inner mitochondrial membrane and are found in all mammals. The term “uncoupling protein” was originally used for UCP1, a brown fat specific proton carrier that is activated by fatty acids