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Brain aging and neurodegeneration: from a mitochondrial point of view

1 Aging is defined as a progressive time-related accumulation of changes responsible for or at least involved in the increased susceptibility to disease and death. The brain seems to be particularly sensitive to the aging process since the appearance of neurodegenerative diseases, including Alzheimer's disease, is exponential with the increasing age. The aging process was defined by Harman as a 'progressive accumulation of changes with time that are associated with or responsible for the ever-increasing susceptibility to disease and death which accompanies advancing age'. Indeed, age is the main risk factor for prevalent diseases, including neurodegenerative disorders.

2 The brain is a high energy consuming organ that requires about 20% of body basal oxygen to fulfill its function. Thus, it is not surprising that disturbances in brain energy metabolisms lead to disease, ranging from subtle alterations in neuronal function to cell death and neurodegeneration. Cellular energy is mainly produced via oxidative phosphorylation (OXPHOS) taking place within mitochondria. These organelles are often compared to powerhouses, providing cellular energy under the form of ATP molecules. Mitochondria produce the energy required for almost all cellular processes, from cell survival and death, to the regulation of intracellular calcium homeostasis, synaptic plasticity and neurotransmitter synthesis. However, when mitochondria fulfill their physiological functions, they can also be compared to a double-edged sword that, on one hand, produces the energy necessary for cell survival, and on the other hand, induces the formation of reactive oxygen species (ROS) that can be harmful for cells when produced in excess with mitochondria as the first target of toxicity.

Mitochondria and the free radicals theory of aging

3 The 'free-radicals theory of aging' was stated for the first time by Harman in 1956, and postulates that aging, as well as age-associated degenerative diseases, is a consequence of free radicals attacks on cells and tissues. But how these 'harmful' molecules are they generated?

ROS derive mainly from the OXPHOS taking place within mitochondria. Indeed, the production of ATP by mitochondria requires about 85% of oxygen (O_2) consumed by cells. Mitochondrial complex IV reduces O_2 into H_2O using electrons derived from NADH or $FADH_2$ driven in the respiratory chain. An inevitable byproduct of electron transport chain (ETC) activity is the formation of superoxide anion radicals ($O_2^{\cdot -}$), mostly by complexes I and III.

4 In physiological conditions, ROS are involved in processes such as immune response, inflammation, as well as synaptic plasticity, learning and memory. However, when produced in excess, those molecules can induce oxidative stress, damaging proteins and DNA, and inducing lipid peroxidation, with the corresponding mitochondrial structures as the first targets of toxicity. Furthermore, since mitochondrial DNA (mtDNA) is localized close to free radical production sites, it is directly in contact with those molecules and can exhibit oxidative damages. Oxidative stress can trigger cell death and has been implicated in the pathogenesis of many neurodegenerative diseases, such as Alzheimer's disease.

Redox homeostasis and mitochondrial bioenergetics in brain aging

5 A growing body of evidence highlights bioenergetic impairments as well as disturbances in the reduction-oxidation (redox) homeostasis in the brain with increasing age.

Neuronal mitochondria: what makes our brain so special?

6 The brain is a remarkable organ composed by highly differentiated cells that populate different anatomical regions. Neurons are polarized cells with different morphology, according to their role and their localization. These post-mitotic and excitable cells have really high energy requirements: (i) to maintain their membrane potential allowing the propagation of electric signals, (ii) to re-establish the ion balance after the firing of action potential (e.g. via the Na^+/K^+ ATPase activity), (iii) to trigger the release of neurotransmitters by fusion of vesicles to the plasma membrane, (iv) to allow the recapture of neurotransmitters from the synaptic cleft. Glucose oxidation is the most relevant source of energy in the brain, since other fuel sources, such as fatty acid oxidation, have an ATP generation rate too slow to sustain neuronal energy demands, and produce too much ROS that may cause oxidative stress. In consequence, neurons rely almost exclusively on the mitochondrial OXPHOS system to fulfill their energy needs supplied under the form of ATP.

7 Some studies aimed to compare mitochondrial properties in different organs, including the brain. For instance, mitochondria isolated from rat liver, kidney, brain and skeletal muscle showed significant and similar proton leak, but the phosphorylating systems appeared to be more active in the brain and the muscle. Differences in the rat mitochondrial proteome were also observed when comparing the kidney, liver, heart, skeletal muscle, and brain. Moreover, each organ possesses different protein composition, especially in the expression of proteins involved in the OXPHOS system.

8 It is important to note that neurons are post-mitotic cells with a life span similar to that of the whole organism. Unlike in other organs, such as the skin or the liver, damaged neurons are not (or rarely) replaced during life, stressing the importance of protecting systems, including antioxidant defenses, to maintain neuronal integrity and survival. Post-mitotic cells, such as neurons, seem to be more sensitive to the accumulation of oxidative damages compared to dividing cells, and are more prone to accumulating defective mitochondria during aging.

9 In addition, to bring a higher degree of complexity, neurons are exceedingly compartmentalized, comprising structures like: cell body, axon, dendrites, and even more specific compartments that are the synapses. Consequently, a proper mitochondrial distribution is paramount to sustaining the energy requirement at specific locations within the different neuronal compartments. Thus, it is not so surprising that synaptic mitochondria, which need to sustain the energy required for synaptic activity, present functional differences when compared to non-synaptic mitochondria. Indeed, peroxide production was found higher in synaptic mitochondria of rats, compared to non-synaptic ones. Interestingly, aging seems to accentuate the differences between these two populations of mitochondria. In 14-month-old rats, respiration was significantly decreased only in synaptic mitochondria, when compared with 3-month-old rats. Besides, a higher susceptibility to calcium insult was observed only in synaptic mitochondria of old animals. In non-synaptic mitochondria, oxygen consumption was not significantly affected by aging, and both populations of mitochondria generated higher levels of peroxide in 14-month-old animals compared to young animals.

Age-related mitochondrial defects and the importance of mitochondrial dynamics in aging

Mitochondrial fusion/fission and mitophagy

10 Mitochondria possess a residual genome (approximately 16 kilobase) coding for 13 proteins essential for mitochondrial respiratory chain function, which make them unique organelles carrying autonomous DNA. It appears that the quality control of mtDNA replication is not as efficient as nuclear DNA (nDNA), resulting in an increased risk of mtDNA mutations. Fortunately, to avoid the accumulation of such mutations, mitochondria are remarkably dynamic organelles that divide and fuse in order to maintain a homogenous mitochondrial population by content mixing (mtDNA, metabolites, and proteins), quality control and distribution of mitochondria within the cell.

11 Fusion/fission activity is also integrated with mitochondrial quality control pathways allowing the detection and removal of aged or damaged mitochondria through a specific form of autophagy, termed mitophagy. The exact mechanism underlying mitophagy, more specifically what triggers mitophagy, remains to be elucidated in more detail.

12 In summary, when mitochondria fuse, they mix their membranes, matrix and inter-membrane space, including all their content (lipids, proteins, metabolites and mtDNA). After this mixing, mitochondria can divide, sharing equally their new content between two daughter organelles. When a damaged mitochondrion is detected, it is eliminated from the fusion/fission cycle by mitophagy, guaranteeing a homogenous and healthy mitochondrial population. Thus, it is not surprising that defects in mitochondrial dynamics and mitochondrial quality control system may lead to cellular impairments, and was proposed to be involved in the process of aging and neurodegeneration.

Conclusions

13 In this review, we aimed to look at brain aging processes from a mitochondrial point of view, and we showed that:

- Mitochondria are at the center of the free radicals theory of aging by being a source and target of ROS. The age-related increase in brain oxidative stress may lead to protein, lipid as well as DNA oxidation, which in turn affects mitochondrial function. When a pathological threshold is passed, this may trigger cell death by apoptosis.
- Mitochondrial dynamics play an important role in maintaining a healthy organelle population. Impairments in this quality control system may lead to the accumulation of defective mitochondria, as well as inefficient mitochondrial transport and distribution, again leading to synaptic and neuronal degeneration.
- Neurons are particularly vulnerable to oxidative insults and mitochondrial dysfunction given that they are post-mitotic differentiated cells relying almost exclusively on the OXPHOS system to sustain their high energy needs. Besides, distinct mitochondrial populations can be observed in different neuronal compartments (e.g., synaptic vs. non-synaptic), highlighting the importance of proper mitochondrial distribution in these highly compartmentalized cells.