



In the beginning was the mitochondrion

S.O. Kozlov¹, A.M. Afonin², I.V. Evsykov³, A.B. Bondarenko⁴

¹Research Institute of Experimental Medicine, ²All-Russia Institute for Agricultural Microbiology, ³Saint-Petersburg State University, ⁴Influenza Research Institute, Saint-Petersburg, Russia
stanbiology@gmail.com

Many attempts were made to reveal the main cause of the Alzheimer's disease. The hereditary form of AD is caused by the mutation in one of several genes; etiology of the sporadic form (LOAD) remains a mystery. Both the hereditary form and LOAD are associated with gradual loss of cognitive functions, and share similar sets of neuropathological and molecular manifestations. The amyloid hypothesis, which postulates the key role of AB in AD development, is the most prominent. However this hypothesis does not fully explain all the molecular symptoms, and therefore is heavily criticized. Here we propose a new theory taking into account recent progress in the field.

Mitochondrial DNA has an increased mutation rate due to the lack of histones and proximity to respiratory chain (RC) complexes. With age mutations in mtDNA accumulate, which leads to disturbances in the activity of RC complexes, increased production of reactive oxygen species (ROS) and to decrease in ATP production.

The quality of mitochondria (MC) in cells is tightly controlled. MC could undergo division, and the most damaged organelles are destroyed via autophagy. The loss is offset by the enlargement of the remaining MC and their division.

An exuberance of defective MC containing iron leads to formation of lipofuscin inside autolysosomes. Autolysosomes containing lipofuscin suffer from ROS produced by MC during digestion. ROS, hydrogen and iron are prone to leak into cytoplasm.

Excess of intracellular iron enhances translation of ferritin, APP and ferroportin via iron-responsive elements in their mRNA. Ferroportin exports excessive ferrous ions from neuron. Then these ions are converted to ferric form by APP. Ferric ions could then be trapped by transferrin and transported to other cells or tissues.

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Formation of tau can also be a consequence of decreased ATP production. Tau phosphorylation usually takes place during the preparation to mitosis in cells. Neurons in damaged brains were shown to return to cell cycle and attempt division. However, energy deficiency can lead to interrupted cell cycle thus halting the neuron on the G2 phase leading to formation of tau fibrils and subsequent neuritic degeneration.

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Severe MC dysfunction and intracellular oxidative stress could lead to neuronal apoptosis. AB oligomers could serve as a signal molecules inducing cell cycle re-entry mechanisms in healthier neurons to compensate for neuron loss.

Activity of β -secretase is augmented by decrease in cytoplasmic pH, and, on the contrary, α -secretase activity reduces. It results in increased production of AB peptide, which then can aggregate in oligomers and plaques. AB plaques elicit inflammatory responses, which may serve to amplify degenerative processes.

Increased iron concentration outside the cells could stimulate the production of hepcidin. This peptide binds to ferroportin, leading to its internalization and following proteasomal degradation with consequent reduction in extracellular iron levels. Limited iron efflux and leakage of iron from autolysosomes results in continuing increase of iron level inside the cell, and, therefore, in amplification of APP translation.

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