Mitochondria: old and new target in brain research

Orly Weinreb¹

Published online: 14 December 2015
© Springer-Verlag Wien 2015

Increasing evidence suggests that the deleterious and progressive cellular changes in ageing are associated with the mitochondrion, namely the “Mitochondrial free radical theory of ageing” (Harman 1972, 1981), since the mitochondrion is one of the main sources of endogenous reactive oxygen species (ROS) and its proteins are targets for oxidative alteration and loss of function (Halliwell 2001). This was further extended by Linnane et al. (1989), who proposed that the accumulation of mitochondrial DNA (mtDNA) mutations and subsequent cytoplasmic segregation of these mutations is an important contributor to ageing and neurodegenerative disorders. Over the recent years, the mitochondria became the focus of accumulating research studies of various neuropsychiatric and neurodegenerative diseases, suggesting that abnormalities and deficits in mitochondrial function and structure are having a major role in neuronal dysfunction in these diseases. Based on this, it is becoming a necessity to develop mitochondria-targeted drugs, as novel therapeutic approach in neurodegenerative diseases.

In this special issue, dedicated to ‘mitochondria’, selected authors provided overviews on most up-to-date studies, observations and perspectives regarding the crucial role of mitochondrial dysfunction in neurodegenerative diseases such as, Parkinson’s disease (PD) and Alzheimer’s diseases (AD) and other neurological disorders. Lopert and Patel discuss the role of environmental ROS generation within the mitochondria of dopaminergic neurons by

various Parkinsonian neurotoxins, including methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, paraquat and the endogenous ROS generator 6-hydroxy-dopamine in neurodegeneration. Additional contribution to brain oxidative stress in neurodegenerative diseases arises from the increased activity of the mitochondrial enzymes monoamine oxidase (MAO)-A and -B that catalyze the oxidative deamination of amines. Since MAOs play key role in the inactivation of neurotransmitters, MAO dysfunction is suggested to be responsible for a number of psychiatric and neurological disorders. MAO-A alterations in various molecular levels are implicated particularly in the pathogenesis and phenotypes in neuropsychiatric disorders. In this special issue, Naoi et al. overviewed the recent literature of the involvement of environmental and genetic factors and the regulatory effects of MAO-B inhibitors on MAO-A expression levels in neuropsychiatric function, neuronal survival and death processes. In the context of the effects of genetic factors that stabilize mitochondrial system, on neurodegenerative disorders, Trudler et al. have discussed the potential role of PD genes, such as DJ-1 in mediating brain inflammation. The authors indicate that DJ-1-deficient microglia increase MAO activity, resulting in elevation of the levels intracellular free radicals and proinflammatory cytokines, and eventually lead to increased dopaminergic neurotoxicity.

The evidence for the involvement of biochemical and molecular alterations of the cytosolic aldehyde dehydrogenase (ALDH1) A1 and mitochondrial ALDH2 enzymes that catalyze the oxidation of aldehydes, in particular in PD and AD, are reported in the review of Grunblatt and Riederer. Furthermore, Carvalho et al., have overviewed the vascular and mitochondrial abnormalities occurring in AD, including mitochondrial alterations in vascular endothelial cells in the brain, which is evolving as a common feature

✉ Orly Weinreb
worly@tx.technion.ac.il

¹ Eve Topf Centers of Excellence for Neurodegenerative Diseases Research, Faculty of Medicine, Technion-Israel Institute of Technology, P.O.B. 9697, 31096 Haifa, Israel

that bridges cerebral vasculature and mitochondrial metabolism.

Finally, Bar-Am et al., discuss the potential benefits of novel multimodal neuroprotective brain permeable MAO inhibitors containing propargyl moiety, developed by Youdim and collaborators as a valuable therapeutic strategy in AD treatment. It is suggested that inhibition of MAO-B, reduction of oxidative stress and neuroinflammation, induction of cell survival/neurotrophic factors and subsequent protection of the mitochondrial system might be important targets for developing new approaches of prevention and long-term treatments of age-related neurodegenerative diseases.

The guest editors Orly Weinreb and Moussa B. H. Youdim thank all authors for their excellent contributions, and in particular they would like to acknowledge Peter

Riederer the editor-in-chief of *Journal Neuronal Transmission* for his generous support to gather this special issue of Mitochondria.

References

- Halliwell B (2001) Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment. *Drugs Aging* 18(9):685–716
- Harman D (1972) The biologic clock: the mitochondria? *J Am Geriatr Soc* 20(4):145–147
- Harman D (1981) The aging process. *Proc Natl Acad Sci USA* 78(11):7124–7128
- Linnane AW, Marzuki S, Ozawa T, Tanaka M (1989) Mitochondrial DNA mutations as an important contributor to ageing and degenerative diseases. *Lancet* 1(8639):642–645