Introduction
Different faces of Neurodegeneration

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Progress in medicine increased life expectancy in the most of the countries around the world. Social changes increased proportion of the aged people in society. It brought the age-related problems to the front line. One of the main age-related factors is neurodegenerative disorders. Neurodegenerative diseases are progressive, devastating and incurable, and are becoming increasingly prevalent in aging populations. Two most common diseases – Alzheimer's disease and Parkinson's disease are affecting 5% and 1% of individuals aged 65 and dramatically increased up to 35 % and 5% at age 80 and above [1]. The annual cost in nursing home care for neurodegenerative disorder is billions and with an ageing population worldwide this represents a very substantial cost to society. Nearly 200 years after Parkinson's disease was first described or 100 years from description of Alzheimer's disease, much has been learnt about the pathology and pathogenesis of these diseases, but a number of gaps in our understanding remain [2]. Over the 10-15 years, mutations that mediate familial forms of Parkinson's disease, Alzheimer's disease, frontotemporal dementia, amyotrophic lateral sclerosis and Huntington disease have been identified in number of genes [3]. The progress in medical genetics has allowed creating different cellular and animal models of neurodegenerative disorders. Availability of these models have stimulated a new wave of interest in research understanding the molecular and cellular mechanisms of neurodegeneration, however; much still remains to be discovered. Only by understanding the pathogenic mechanisms that underlie neurodegenerative diseases can therapeutic strategies be designed to halt or at least slow disease progression, rather than merely treat the symptoms.

Currently, the number of possible mechanisms of neurodegeneration has been suggested. Some of them are common for all neurodegenerative diseases – such a neuroinflamation, free radicals production and oxidative stress, mitochondrial dysfunction, some of suggested mechanisms are more specific for each disorder. Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, motor neuron disease, Huntington disease and prion disease all share a common feature such an accumulation of abnormally aggregated proteins termed pathological inclusions [4-5].

This Special Issue of The FEBS Journal provides the reader with various views on the development of neurodegeneration in different pathology and perspective ways for neuronal protection. The present series of reviews are not only summaries of the progress in the specific field of neuroscience but also provides new views on the mechanism of neurodegeneration and associated processes.

Calcium deregulation is known to be one trigger of neurodegeneration. Polina Egorova and Ilya Bezprozvanny attract attention of the readers to component of the calcium signalling system - inositol 1,4,5-trisphosphate receptors (IP3R), their functions and regulation in healthy neurons and in conditions of neurodegeneration. The authors review enhanced activity of the IP_3R was observed in models of Huntington's disease, spinocerebellar ataxias and Alzheimer's disease and suggests IP_3R-mediated signaling as a potential target for treatment of these disorders [6].

Recently identified neurophagy, the process viable synapses, dendrites, axons and whole neurons can be phagocytosed alive, is reviewed by Anna Vilalta and Guy Brown. This process can help to explain the role neuroinflamation in Alzheimer's disease and schizophrenia and the authors in details describing the signals regulating glial phagocytosis of live neurons and synapses, and the involvement of this phagocytosis in development and disease [7].

The transcription factor Nrf2 target genes encode antioxidant enzymes, and proteins involved in detoxification, repair cellular organelles, inflammation, and mitochondrial bioenergetics. Albena Dinkova-Kostova and colleagues provide in depth look of the role of alteration of Nrf2 in pathogenesis of Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and Friedreich's ataxia and how development of small molecules which act as Nrf2 activators can become one of the most promising therapeutic option in treatment of currently incurable neurodegenerative diseases [8].

Mutations in the gene GBA which encodes the lysosomal enzyme glucocerebrosidase are numerically the most important risk factor for developing Parkinson disease accounting for at least 5% of all Parkinson's disease cases. Matthew Gegg and Anthony Schapira focuses on mechanisms of the cellular pathology induced by loss of GCase activity and highlights potential treatments that might be effective in treating GCase deficiency in Parkinson's disease [9].

Aggregation of misfolded proteins such a α-synuclein, β-amyloid makes these protein to be neurotoxic. Kundel et al discuss a range of modern biophysical techniques that have been developed to study protein aggregation, and give an overview of how they can be used for possible diagnostic in the two most common neurodegenerative disorders, Alzheimer's disease and Parkinson's disease [10].

Minee Choi and Sonia Gandhi are also focused on the process of protein misfolding, and the intrinsic and extrinsic processes that cause the native states of the key aggregating proteins to undergo conformational change to form oligomers and ultimately fibrils in Parkinson's disease and Alzheimer's disease. The authors discuss the structural

features of the key toxic intermediate, and describe the putative mechanisms by which oligomers may cause cell toxicity [11].

Astrocytes primarily responsible for homeostasis of the central nervous system and any significant changes in function of astroglia lead to neurodegeneration. The review by Zorec, Papura and Verkhratsky is focused on the role adrenergic astroglial excitation in prevention of neurodegeneration. The authors provide in depth look of how astrocytes integrate neuronal network activity in the brain information processing in health and disease (Zorec et al., 2018).

One of the key questions of the Parkinson's disease is a specific vulnerability of dopaminergic neurons in the substantia nigra pars compacta. Dalton James Surmeier discusses this specificity and providing the evidence that SNc dopaminergic neurons have an anatomical, physiological, and biochemical phenotype that predisposes them to mitochondrial dysfunction and synuclein pathology. Translational opportunities for slowing or stopping Parkinson's disease progression which based on the specificity of dopaminergic neurons are suggested (Surmeier, 2018).

Wai Yan Yau et al review importance of DNA repairing pathways in modifying the inherited cerebellar ataxias. The authors highlighted the role of epigenetics and other genetic factors as modifiers in cerebellar ataxias due to trinucleotide repeat expansions (Wai Yan Yau et al. 2018).

We thank the authors for these excellent contributions and we believe that you find these reviews interesting and informative.

References
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9. Gegg ME & Schapira AHV (2018) The role of glucocerebrosidase in Parkinson disease pathogenesis *FEBS J*
10. Kundel F, Tosatto L, Whiten DR, Wirthensohn DC, Horrocks MH & Klenerman D (2018) Shedding light on aberrant interactions – a review of modern tools for studying protein aggregates *FEBS J*
11. Choi ML & Gandhi S (2018) Crucial role of protein oligomerization in the pathogenesis of Alzheimer's and Parkinson's diseases *FEBS J*
12. Zorec R, Parpura V & Verkhratsky A (2018) Preventing neurodegeneration by adrenergic astroglial excitation *FEBS J*
13. Surmeier DJ (2018) Determinants of dopaminergic neuron loss in Parkinson's disease *FEBS J*
14. Yau WY, O'Connor E, Sulliva R, Akijian L & Wood NW (2018) DNA repair in trinucleotide repeat ataxias *FEBS J*

Figure 1. Schematic representation of the cellular mechanisms of neurodegeneration
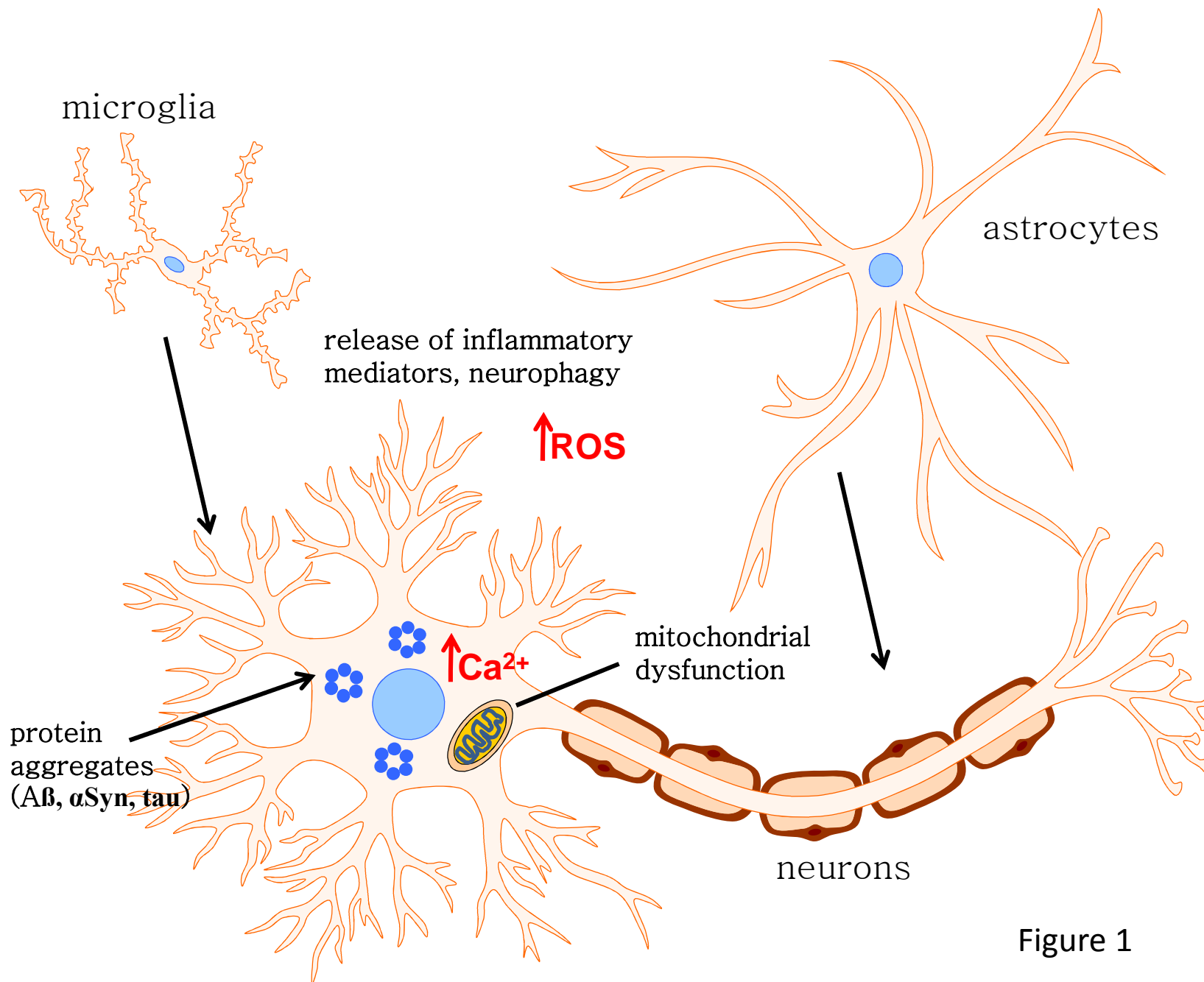
microglia

release of inflammatory
mediators, neurophagy

$\uparrow$ROS

astrocytes

$\uparrow$Ca²⁺

mitochondrial
dysfunction

protein
aggregates
(Aß, αSyn, tau)

neurons

Figure 1