Interaction of misfolded proteins and mitochondria in neurodegenerative disorders

Andrey Y. Abramov[a], Alexey V. Berezhnov[b], Evgeniya I. Fedotova[b], Valery P. Zinchenko[b], Ludmila P. Dolgacheva[b]

[a]Department of Molecular Neuroscience, UCL Institute of Neurology, London WC1N 3BG, United Kingdom

[b]Institute of Cell Biophysics Russian Academy of Sciences, Pushchino 142290, Russia

Corresponding author: Andrey Y Abramov, Department of Molecular Neuroscience, UCL Institute of Neurology, London WC1N 3BG, United Kingdom e-mail: a.abramov@ucl.ac.uk

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Abstract

The number of the people affected by neurodegenerative disorders is growing dramatically due to the aging of population. The major neurodegenerative diseases share some common pathological features including involvement of mitochondria in the mechanism of pathology and misfolding and accumulation of abnormally aggregated proteins. Neurotoxicity of aggregated beta-amyloid, tau, alpha-synuclein and huntingtin is linked to effects of these proteins on mitochondria. All these misfolded aggregates affect mitochondrial energy metabolism by inhibiting diverse mitochondrial complexes and limits ATP availability in neurons. Beta-amyloid, tau, alpha-synuclein and huntingtin are shown to be involved in increased production of reactive oxygen species which can be generated in mitochondria or can target this organelle. Most of these aggregated proteins are able to deregulate mitochondrial calcium handling that in combination with oxidative stress lead to opening of the mitochondrial permeability transition pore. Despite some of the common features, aggregated beta-amyloid, tau, alpha-synuclein and huntingtin have diverse targets in mitochondria that can partially explain neurotoxic effect of these proteins in different brain regions.

Introduction

Aging of the population in the majority of countries leads to increase in the number of people with age-related disorders, including neurodegenerative diseases. Despite the differences in aetiology and different mechanisms of cell loss, most of neurodegenerative disorders share some of common features including the involvement of mitochondrial dysfunction and oxidative stress in development of pathology and, specific for each disease misfolded proteins which aggregates in the brain of patients. Thus, for Alzheimer's disease there are two misfolded proteins – β-amyloid (main component of the senile plaques) and tau protein (aggregates of which form an intracellular tangles) (1). It should be noted that tau aggregates are not specific for Alzheimer's only and appeared in the number of other neurodegenerative disorders. Tau mutations are shown to be linked to familial form of frontotemporal dementia (2, 3). Second most common neurodegenerative disorder – Parkinson's disease is characterised by intracellular occlusions called Lewy bodies, which are formed by aggregated α-synuclein (4). One of the main histopathological features of Huntington disease is an aggregate of huntingtin protein (5). All these aggregates in the brain consist mostly of protein fibrils and for long time are believed to be

the trigger of cellular pathology and neurodegeneration in these diseases. Only recently a number of studies showed that small oligomeric forms of these proteins are more toxic than monomeric or fibril forms.

Mitochondrion is an organelle which is strongly implicated in the mechanisms of neurodegeneration. Being the major energy producer in the cell, mitochondria play important role in the mechanism of cell death, calcium and redox signalling (6). Ability of mitochondria to produce reactive oxygen species (ROS) in the electron transport chain, TCA cycle and some other enzymes has a functional implication in cell signalling, however overproduction of ROS in mitochondria links this organelle to the age-related pathology and neurodegenerative disorders (7, 8). However, some of the mitochondrial enzymes could be specifically linked to functions involved in maintenance of neuronal homeostasis. Thus, the enzyme monoamine oxidase, which is located on the outer membrane of mitochondria, is involved in the homeostasis of neurotransmitters – dopamine, serotonin and norepinephrine (9, 10). Neurons are also dependent on mitochondrial function due to several reasons: a) Neurons predominantly produce ATP via oxidative phosphorylation in the mitochondria, with almost no contribution from glycolysis; b) The brain consumes 10 times more oxygen and glucose than any other organ or tissue that may results in higher probability of ROS production. c) Neurons are long-lived differentiated cells that are therefore more dependent on the processes of mitochondrial dynamics and removal of unwanted mitochondria (mitophagy) compare to cells from other tissues. d) Neurons are excitable cells with high calcium fluxes. Mitochondria play a role of buffering Ca^{2+} that shapes calcium signals and protects cells from calcium excitotoxicity. e) Neuronal processes, that is, axons and dendrites, may be very long and therefore depend on mitochondrial transport for transfer of energy molecules to different parts of the cell. Because of the importance of all mitochondrial functions to neuronal health, it is perhaps understandable why neurons are vulnerable to dysfunction in any mitochondrial pathway. Mitochondrial pathology has been associated with a wide range of neurodegenerative diseases. In primary mitochondrial diseases, that is, diseases caused by mutations in mitochondrial DNA or nuclear DNA encoding mitochondrial proteins, it is clear that perturbation in mitochondrial function alone is sufficient and necessary to trigger neuronal death. It is less clear whether the mitochondrial dysfunction seen in the sporadic late onset neurodegenerative diseases is necessary for pathogenesis or a bystander effect of disease, which is mostly associated with misfolded aggregates.

For long time, the role of misfolded proteins in mitochondrial function was disputable due to lack of evidence of location of misfolded aggregates in mitochondria. Recent studies demonstrated that aggregated peptides could be delivered to mitochondria (11).

In this review we discuss the different mechanisms by which misfolded proteins affect mitochondrial function and ROS production and how mitochondrial dysfunction and protein aggregation could be related to progressive neuronal death in different forms of neurodegeneration.

Effects of β-Amyloid on mitochondria

The amyloid precursor protein (APP) is cleaved by β and γ-secretase generating a range of β-amyloid (βA) peptides between 39 and 43 amino acid residues long, where the hydrophobic nature of βA 1-40 and βA 1-42 promotes self-aggregation and neurotoxicity. A series of conformational changes of βA via dimers, oligomers, protofibrils and fibrils leads ultimately to a deposition of amyloid plaques.

βA shown to have a strong effect on mitochondrial enzymes which contains iron-sulphur centre – the most of these enzymes are the complexes of electron transport chain (Figure 1) and TCA cycle - α-ketoglutarate dehydrogenase and aconitase (12-15). In intact cortical and hippocampal neurons, βA reduce ATP levels through inhibition of the complexes I and IV (16) and induces profound mitochondrial depolarisation of two types – slow mitochondrial depolarisation and sharp and transient loss of $\Delta\psi m$ (17, 18). This mitochondrial depolarisation was dependent on the βA-induced calcium signal (17, 19) and induction of ROS overproduction from NADPH oxidase (20, 21). Deregulation of calcium homeostasis has been demonstrated in Alzheimer's disease (AD), with βA causing increased cytoplasmic calcium levels and mitochondrial calcium overload, resulting in increase in ROS production and opening of the PTP (19, 20). βA is able to induce opening of PTP in isolated mitochondria (22, 23) and primary astrocytes (17, 24, 25). Furthermore βA may directly interact with cyclophilin D (a PTP component) forming a complex in the mitochondria that has reduced threshold for opening in the presence of mPTP inducers. Prevention of PTP opening by inducing cyclophilin D deficiency (molecular inhibition of PTP opening) is also able to improve mitochondrial function and learning/memory in an aging AD mouse model (26).

A reduction in complex IV activity has been demonstrated in mitochondria from the hippocampus and platelets of AD patients, as well as in AD animal models and AD cybrid cells (27). Aggregation of βA leads to oxidative stress, mitochondrial dysfunction and energy failure prior to the development of plaque pathology (28). Activation of the DNA repairing enzyme PARP in AD due to overproduction of ROS in NADPH oxidase leads to consumption of NAD and restriction of substrates (Figure 1) for mitochondrial complex I, resulting in collapse in bioenergetics and cell death (29, 30). Provision of mitochondrial substrates can prevent amyloid induced cell death (17, 21). A perturbation in mitochondrial dynamics has also been described in AD human brain and cell models. Fragmented mitochondria are seen in AD hippocampus in association with a downregulation of mitochondrial fusion proteins (MFN-1, MFN-2, OPA-1), with an increase in expression of the mitochondrial fission protein Fis-1 (31).

Mitochondria also can regulate aggregation of βA, tau or alpha-synuclein. Inorganic polyphosphate plays important signalling role in brain (32, 33) and in mammalian cells produced in mitochondria (34). Inorganic polyphosphate accelerates aggregation of βA, tau and alpha-synuclein forming non-toxic fibrils playing role cytoprotective modifier (35).

Role of tau in mitochondrial physiology and pathology

Tau protein (tubulin-associated unit) refers to microtubule-associated proteins. It is a soluble, natively unfolded, and phosphorylated protein, ubiquitously expressed in most tissues and organs. This protein exists as six alternatively spliced isoforms and is encoded by a single gene, *mapt*, that is located on chromosome 17 in humans (36). Tau is found in all cellular and subcellular compartments but is most prominent in the axons of neurons of the central nervous system (37, 38). Tau protein plays an important role in neuronal physiology, in microtubule assembly and dynamics (39), in promoting axonal out growth (40), axonal transport and in signal transduction (41). Physiological and pathological activity of tau is dependent on the phosphorylation (tau is phosphoprotein) and alternative splicing and on the level of aggregation. The soluble prefibrillar aggregates of tau proteins cause the most damage to neurons. In disease, tau dissociates from microtubules and forms large, primarily intracellular, β-sheet rich fibrils (42). Tau protein is involved in the pathogenesis of many neurodegenerative diseases, specifically in Alzheimer's disease and frontotemporal dementia. Pathologies and dementias of the nervous system are associated with tau proteins that have become defective and no longer stabilize

microtubules properly. The abnormal tau function leads to the deficits in fast axonal transport, dystrophic neurites, and abnormal mitochondrial distribution (43-45). This abnormal distribution of mitochondria is more likely to be induced by impairment the fission and fusion of mitochondria by tau (46). It also have been shown that in human tau transgenic mice and flies, F-actin is increased, which disrupts the physical association of mitochondria and the fission protein DRP1 (Figure 1), leading to mitochondrial elongation (46). The resulting neurotoxicity can be rescued either by reducing mitochondrial fusion, or by enhancing fission, or by reversing actin stabilization. The possible effect of tau on mitochondrial complex I have been shown triple knockout Alzheimer's disease mouse mitochondria (47). The 10+16 intronic mutation in MAPT gene, encoding tau increase in the production of 4R tau isoforms, which are more prone to aggregation. Human iPSC derived neurons with this mutation are associated with partially suppressed complex I-driven respiration that lead to F1Fo-ATPase to be switched in reverse mode. This combination increased mitochondrial membrane potential that trigger ROS production in electron transport chain which causes oxidative stress and cell death (48).

Role of α-synuclein in mitochondrial physiology and pathology

α-Synuclein is strongly implicated in pathology of Parkinson's disease as a main component of Lewy body – neuronal aggregated inclusions. Lewy body is one of the major pathological hallmarks of this neurodegenerative disorder. One of autosomal-dominant familial Parkinson's disease can be attributed solely to mutations in the SNCA gene (which encoded α-synuclein) or by genetic duplication or triplication of the wild-type *SCNA* locus (49). Native monomeric form of α-synuclein is soluble protein which aggregates to form insoluble fibrils via a series of conformational changes including most toxic intermediates – oligomeric.

Monomeric α-synuclein plays important physiological roles in synaptic signal transduction (50, 51) and as a regulator ATP production (Figure 1). Thus, monomeric α-synuclein binds F0-F1-ATPsynthase and increase efficiency of this enzyme to produce ATP (52).

Monomeric, oligomeric and fibrillary α-synucleins are able to penetrate through plasma and intracellular membranes (53, 54). The high degree of curvature of mitochondrial membranes and the presence of cardiolipin contribute to the interaction of α-synuclein with this organelle. It is known that α-synuclein preferentially binds to negatively charged lipids

(55-58). Previously, it has been found that α-synuclein specifically binds to mitochondria but no other cell organelles (53, 59).

Parkinson's disease is linked to mitochondrial abnormalities more than any other neurodegenerative disorder. It has been proven by toxins (rotenone and MPTP) and by the fact that most of the familial forms of Parkinson's disease are associated with mitochondria. Pathogenesis of Parkinson's disease is characterized by decreased activity of mitochondrial respiratory chain complex I in the nigrostriatal system by 25-30%. Importantly, oligomeric α-synuclein is able to inhibit complex I (60, 61) or even damage this component of electron transport chain (62). In agreement to this oligomeric α-synuclein had no effect on the neurons with complex I mutation (63). In transgenic mice overexpressing a wild-type α-synuclein occur not only breach morphology, loss of mitochondrial membrane potential (Δψ), and fragmentation of the mitochondria, predisposing to neurodegeneration (64-66).

Mitochondria play important role in maintenance of calcium homeostasis in physiology and pathology (67). For monomeric and oligomeric α-synuclein shown ability to stimulate calcium signal (Figure 1) by incorporation into plasma membrane and forming a pore (68, 69). Mitochondrial calcium overload and reactive oxygen species are the major triggers for mitochondrial permeability transition pore (mPTP) (70). Although activation of production of ROS in mitochondria by α-synuclein is disputable it was shown recently that β-sheet-rich α-synuclein oligomers, and to a lesser extent α-synuclein fibrils are initiated of increase ROS production and lipid peroxidation (71, 72) Ability of oligomeric (but not monomeric) α-synuclein to induce both calcium rise and ROS production increases the probability of mPTP opening. However, using of purified recombinant human α-synuclein on isolated mitochondria it has been shown that the addition of oligomeric forms of α-synuclein reduced retention time exogenously added Ca^{2+}, promoted of Ca^{2+} induced swelling and mitochondrial depolarization and accelerated secretion of cytochrome C. Inhibition of mPTP prevented these oligomer-induced changes of mitochondrial parameters (61).

In all eukaryotic cells, endoplasmic reticulum (ER) and mitochondria interact closely using a specific sub-domains of ER and MITO membrane, forming MAM structures (mitochondria-associated membranes, see Figure 1) (73). MAM site of ER has a unique lipid composition, enriched of cholesterol and the anionic phospholipids, with the characteristics of the lipid raft (74). It has been shown that α-synuclein affects a key MAM function - calcium transport between the ER and mitochondria and the wild type α-

synuclein from cell lines and brain tissue of human and mouse is present in MAM structures (73, 75). It was found that pathogenic point mutations in human α-synuclein result in its reduced association with MAM, coincident with a lower degree of apposition of ER with mitochondria, a decrease in MAM function, and an increase in mitochondrial fragmentation compared with wild-type (76).

α-Synuclein can interfere with number of mitochondrial transport proteins including TOM machinery and VDAC (57). Thus, it was shown that certain types of post-translationally modified α-synuclein binds with high affinity to the receptor TOM20, related to mitochondrial protein importing machinery TOM. This binding prevented the interaction of TOM20 with its co-receptor, TOM22, and impaired mitochondrial protein import (77).

Huntingtin protein and mitochondria

Huntington's disease is neurodegenerative disorder caused by mutation of a CAG repeat located in exon 1 of Huntingtin gene. Vulnerability and degeneration of striatal neurons are the first obvious signs of early-grade Huntington's disease. Importantly, a mutation of huntingtin protein (Htt) changes the location of this protein from the nucleus and cytoplasm for wild type Htt to mitochondria for mutant Htt (78, 79). For wild type Htt the role in vesicle trafficking, secretion pathways and apoptosis was demonstrated (80, 81).

The Htt function should affect a multitude of signalling pathways that could be confirmed by lethality of *htt* knockout mouse model (82).

The co-localisation of mutant Htt to the mitochondria leads to inhibition of electron transport chain and reduction of energy levels in Huntington's disease which initiates striatal cell death (Figure 1). Expression of mutant Htt in mice resulted in a reduced mitochondrial membrane potential, suggesting that one or more of the electron transport chain complexes are not working correctly. Thus, in mice with mutated Htt activity of the complex II and complex IV is reduced and expression of mitochondrial complex II is also significantly decreased (83-85). Lower mitochondrial membrane potential in neurons with mutated Htt leads to dramatically reduced calcium buffering capacity (86). Lower mitochondrial buffering capacity in cells with mutated Htt could be the reason for induction of mitochondrial PTP and cell death (87).

Conclusions and future directions

Despite the difference in toxicity between βA, α-synuclein, tau and Htt and their original location (extracellular, intracellular or membranes) all these misfolded proteins and peptides have similarities in the mechanisms of neurodegeneration induced by their aggregates. One of the most important steps is an induction of oligomerisation of these peptides. Considering possible role of monomers (α-synuclein, tau and huntingtin) in cell physiology aggregation of these peptides is the initial step in the mechanism of their toxicity. Although all these misfolded proteins initiate ROS production and inhibit mitochondrial respiration via different mechanisms, it results in induction of cell death through opening of mPTP.

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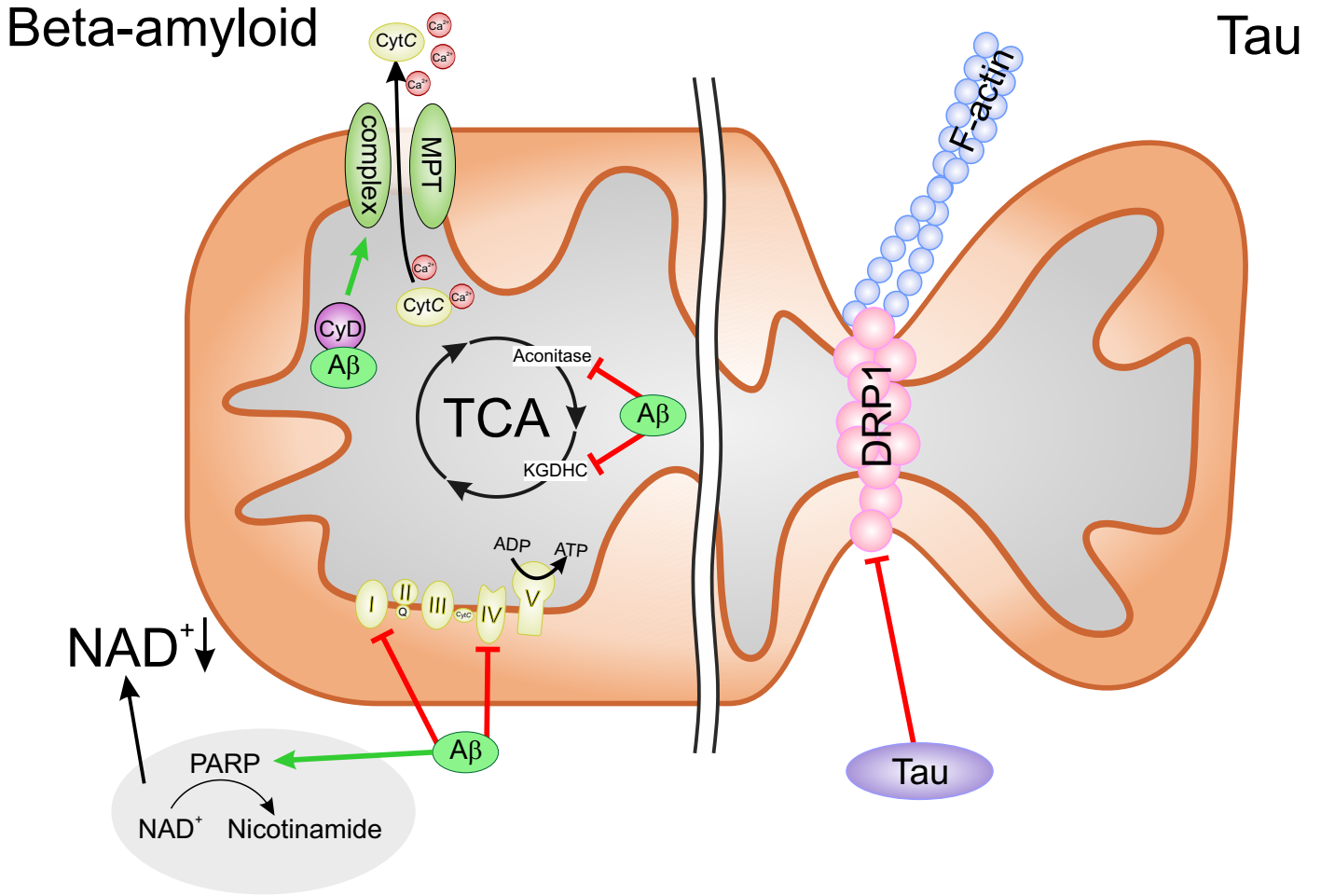
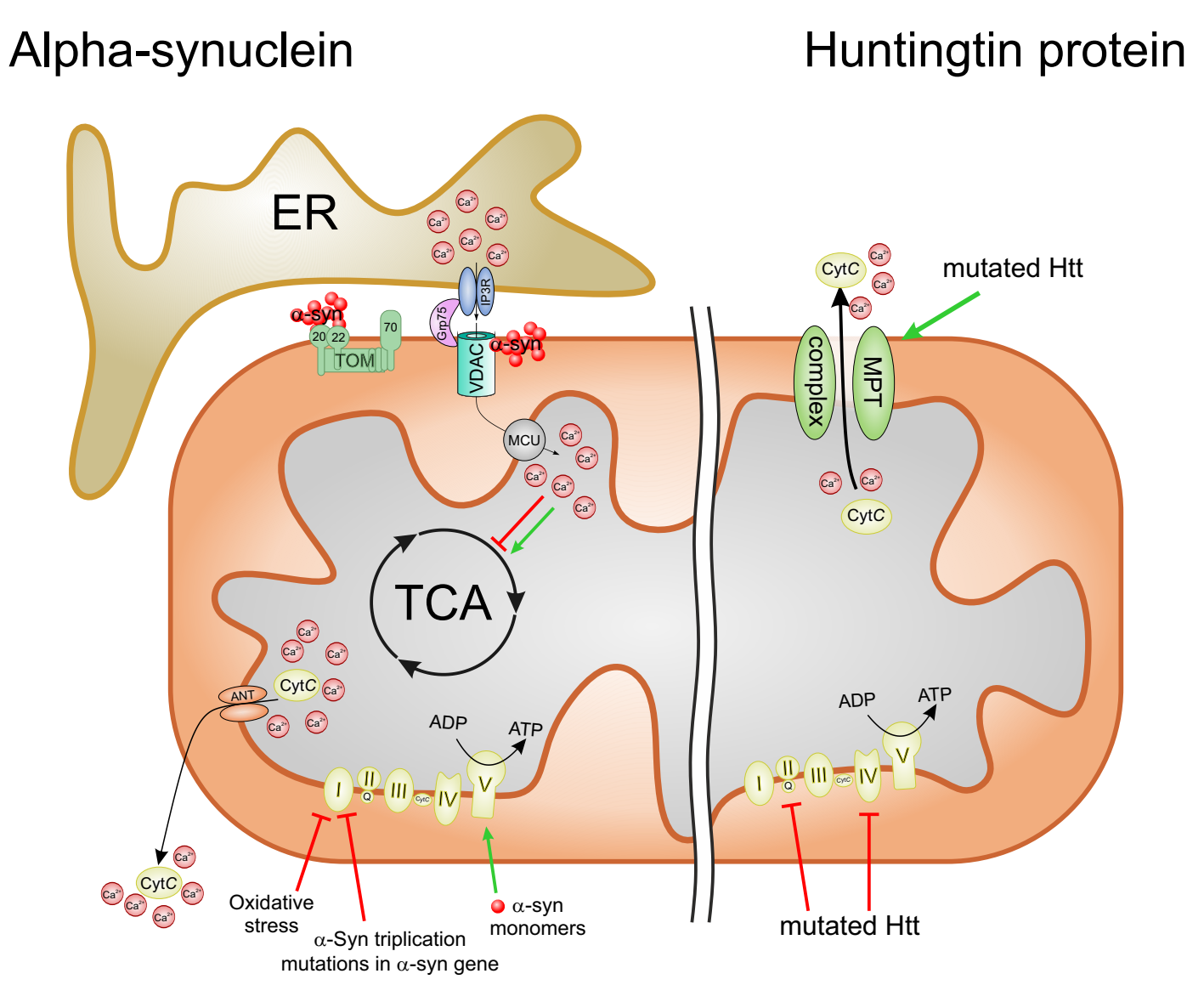
Figure legend

Figure 1. Effects of the major misfolded proteins on mitochondria. Beta-amyloid, tau, alpha-synuclein and huntingtin protein have a direct effect on mitochondria. Oligomeric beta-amyloid, alpha-synuclein and huntingtin protein inhibit complexes of electron transport chain, tau play important role in mitochondrial dynamics. Mitochondrial dysfunction induced by aggregated proteins lead to neuronal cell death


Beta-amyloid
Tau
CytC
complex
MPT
CytC
CyD
Aβ
Aconitase
TCA
Aβ
KGDHC
ADP
ATP
F-actin
DRP1
NAD+
Aβ
PARP
NAD+
Nicotinamide
Tau


Alpha-synuclein
Huntingtin protein
ER
α-syn
20
22
TOM
70
Grp75
IP3R
VDAC
α-syn
MCU
mutated Htt
CytC
complex
MPT
CytC
TCA
ANT
CytC
ADP
ATP
ADP
ATP
Oxidative stress
α-Syn triplication mutations in α-syn gene
α-syn monomers
mutated Htt