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THE ROLE OF MITOPHAGY IN SELECTED NEURODEGENERATIVE DISEASES

ROLA MITOFAGII W WYBRANYCH CHOROBACH NEURODEGENERACYJNYCH

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Abstract

Purpose: Mitophagy is a type of selective autophagy, associated with degradation of inefficient mitochondria. The modulation of mitophagy seems to be one of the most important solutions for key factors in the maintenance of neuronal cell homeostasis. This paper overviews the role of mitochondria and mitophagy in the etiology of the most common age-related neurodegenerative diseases, i.e. Alzheimer's disease (AD) and Parkinson's disease (PD).

Views: In recent years, the role of mitophagy in neurodegenerative diseases has been given more attention. It has been shown that disturbed mitophagy and mitochondrial dysfunction in neurons may contribute to the cell death. In AD and PD, a number of abnormalities related to the expression and function of proteins involved in the process have been revealed. Because mitochondrial dysfunction plays a role in the origin/etiology of those diseases, possible therapeutic strategies aiming to improve quality control systems of mitochondria are also presented. Nowadays, these are mainly strategies improving the energy efficiency and facilitating induction of mitophagy.

Conclusions: Recent reports suggest that abnormal function of proteins involved in mitophagy may be an important etiological factor in neurodegenerative diseases. Furthermore, these findings may become the basis for the development of more effective therapies preventing or alleviating the disease symptoms.

Key words: mitophagy, mitochondria, Alzheimer's disease, Parkinson's disease.

Streszczenie

Cel: Mitofagia jest rodzajem selektywnej autofagii, podczas której degradacji ulegają mało wydajne mitochondria. Modulacja procesu mitofagii wydaje się obecnie jednym z najważniejszych rozwiązań umożliwiających utrzymanie homeostazy komórek nerwowych. Celem niniejszej pracy jest podsumowanie istniejącej wiedzy dotyczącej roli mitochondriów oraz procesu mitofagii w etiologii najbardziej rozpowszechnionych chorób neurodegeneracyjnych związanych z wiekiem, tj. choroby Alzheimera (AD) i choroby Parkinsona (PD).

Poglądy: W ostatnich latach obserwuje się wzrost zainteresowania rolą mechanizmu mitofagii w powstawaniu chorób neurodegeneracyjnych. Wykazano, że zaburzona funkcja mitochondriów i utrata zdolności do mitofagii w komórkach nerwowych może przyczyniać się do ich śmierci. W AD i PD zaobserwowano szereg nieprawidłowości związanych z ekspresją oraz funkcją białek zaangażowanych w ten proces. Ze względu na powiązanie zaburzeń funkcji mitochondrialnych z omawianymi chorobami w niniejszej pracy przedstawiono także możliwe strategie terapeutyczne ukierunkowane na poprawę wewnątrzkomórkowych systemów kontroli jakości tych organelli. Obecnie są to przede wszystkim strategie poprawiające wydajność energetyczną komórek nerwowych i rozwiązania umożliwiające kontrolowane indukowanie procesu mitofagii.

Wnioski: Najnowsze badania wskazują, że nieprawidłowe funkcjonowanie białek zaangażowanych w proces mitofagii może stanowić ważny czynnik etiologiczny chorób neurodegeneracyjnych. Wyniki tych badań mogłyby stać się podstawą do opracowania skuteczniejszych terapii zapobiegających wystąpieniu objawów wspomnianych chorób bądź łagodzących ich przebieg.

Słowa kluczowe: mitofagia, mitochondria, choroba Alzheimera, choroba Parkinsona.

INTRODUCTION

Ageing is one of the most important risk factors for common neurodegenerative disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD). With the increase in life expectancy, new treatments are being intensively searched for. Although general mechanisms behind age-related neurodegeneration have been identified, the complex processes responsible for its development are still not fully understood, and current pharmacotherapy is still based on symptomatic treatment.

The main pathomechanism of these neurodegenerative diseases is the aggregation of abnormally folded proteins and the associated loss of specific nerve cell populations. In AD, the changes affect areas of the brain that are key to learning and memory processes, i.e. hippocampus, rhinencephalon and frontal cortex [1, 2]. In PD, dopaminergic neurons in substantia nigra of the midbrain are lost [3]. Maintaining the integrity of neuronal networks is dependent on factors involved in the removal of nerve tissue waste products. Among them, autophagy – an evolutionary conservative intracellular mechanism based on the elimination of macromolecular components of cytoplasm, especially proteins with a long half-life and whole organelles – has a great application potential in controlling the processes of neurodegeneration [4-11]. Autophagy is non-selective, when a part of the cytoplasm is digested and the balance between the size and composition of the cytoplasm is being kept. However, this process can be very specific and lead to the degradation of specific structures, such as protein aggregates, cell organelles, as well as bacteria and viruses. A type of selective autophagy important for cell homeostasis is mitophagy – a process of degrading damaged and inefficient mitochondria [12, 13]. Neurons as cells showing a high energy demand dependent on mitochondrial metabolism are particularly sensitive to mitochondrial dysfunction [14-18]. Besides, neurons do not have the ability to proliferate, therefore an efficient system is needed to eliminate damaged mitochondria, which may be a source of reactive oxygen species (ROS) or a factor triggering apoptosis [19].

In recent years, the role of mitophagy in neurodegenerative diseases has been given more attention. It has been shown that disturbed mitophagy and mitochondrial dysfunction in neurons may contribute to the cell death. In AD and PD, a number of abnormalities related to the expression and function of proteins involved in the process have been revealed. Here we review data showing that abnormal function of proteins involved in mitophagy may be an important etiological factor in neurodegenerative diseases. Furthermore, these findings may become the basis for the development of more effective therapies preventing or alleviating the symptoms.

THE MOLECULAR MECHANISM OF MITOPHAGY

Over the last decade, significant progress has been made in the study of molecular mechanisms underlying mitophagy – a process in which autophagosome engulfs damaged mitochondria and directs them towards lysosomal degradation. This research has helped to identify the proteins involved and to understand their role in physiological and pathological conditions. There are two known mechanisms of mitophagy: dependent on and independent of ubiquitin. Ubiquitin is a low molecular weight protein which marks proteins intended for degradation. The addition of ubiquitin molecules to proteins is called ubiquitination. This paper focuses primarily on the ubiquitin-dependent mitophagy, since disturbances in the function of proteins involved in the process have a significant impact on the development of both diseases.

PTEN-induced kinase 1 (PINK1) is a serine-threonine kinase located on the outer mitochondrial membrane (OMM). PINK1 together with the cytoplasmic E3 ubiquitin ligase (Parkin) are important factors involved in the removal of dysfunctional mitochondria on the way of by means of ubiquitin-dependent mitophagy [20].

PINK1 occurs in small amounts in properly functioning mitochondria. PINK1 is transported via TOM/TIM membrane translocases from the outer to the inner mitochondrial membrane (IMM), and is cut by mitochondrial proteases. The remaining part of PINK1 is released into the cytoplasm where it undergoes proteolytic degradation (Figure IA) [21-23]. In dysfunctional mitochondria with a loss of membrane potential, PINK1 degradation is inhibited. It then binds permanently with the TOM subunit of the TOM/TIM complex, which leads to its accumulation in the OMM and initiates mitophagy [23]. The inhibition of PINK1 degradation causes the recruitment of cytoplasmic Parkin and its connection to the mitochondrion with a lost membrane potential [24, 25].

Linked to the mitochondrial surface and activated by PINK1, parkin initiates the ubiquitination of proteins of the OMM, including Mitofusin 1 and Mitofusin 2 (Mfn1 and Mfn2), mitochondrial Rho GTPase 1 (Miro1), voltage-dependent anion-selective channel protein (VDAC1). Mfn1 and Mfn2 preserve mitochondria connections [26]. In a cell, mitochondria connect to each other, forming a spatial and branched network. Probably, such an organisation contributes to the intensification of energy production and facilitates maintaining homeostasis in response to stress conditions [27]. Depending on the needs, the network can be modified by connecting or disconnecting individual mitochondria. Decreased activity of Mfn1 and Mfn2 proteins causes isolation of a dysfunctional mitochondrion from the mitochondrial network [26]. Another substrate for parkin is Miro1 protein,

which binds mitochondria to the microtubules and thus provides for each mitochondrion a possibility of movement within the network. Inhibition of Miro1 facilitates isolation and immobilises mitochondrion by disconnecting it from the microtubule [26, 28]. Another protein involved in mitochondrial division is dynamin-related protein 1 (Drp1). PINK1 and parkin can activate Drp1, which results in disconnection of a mitochondrion from the network [29, 30]. In addition, to the proteins of the OMM, polyubiquitin chains are attached which recruit proteins binding microtubule-associated proteins 1A/1B light chain 3 (LC3) present on the surface of a maturing autophagosome. When a damaged mitochondrion is attached to an autophagosome, the autophagosome membrane elongates and closes the mitochondrion inside for the lysis (Figure IB) [31].

The inhibitors of ubiquitin-dependent mitophagy are deubiquitinating enzymes, including USP15, USP30, and USP35, pivotal to maintaining balance between ubiquitination and deubiquitination. Excessive expression of these enzymes may inhibit the mitophagy through increased removal of polyubiquitin chains [32].

MITOCHONDRIAL DISORDERS IN ALZHEIMER'S AND PARKINSON'S DISEASES

Neurodegenerative diseases have different clinical symptoms. However, it is now believed that similar mechanisms leading to neuronal degeneration are responsible for their occurrence. In the nervous tissue of patients with AD and PD, accumulation of neurotoxic and enzyme resistant aggregates is observed. Furthermore, dysfunctional mitochondria have also been found. This indicates faulty mitochondrial function and a diminished ability to mitophagy as a new cause of neurodegeneration [17, 33-36].

Alzheimer's disease

The neuropathological symptoms of AD show extracellular accumulation of β-amyloid (Aβ) plates and formation of intracellular neurofibrillary tangles, which are aggregates of hyperphosphated tau protein [17, 33, 34]. An important role in the pathogenesis of AD is being currently attributed to the interaction of Aβ with mitochon-

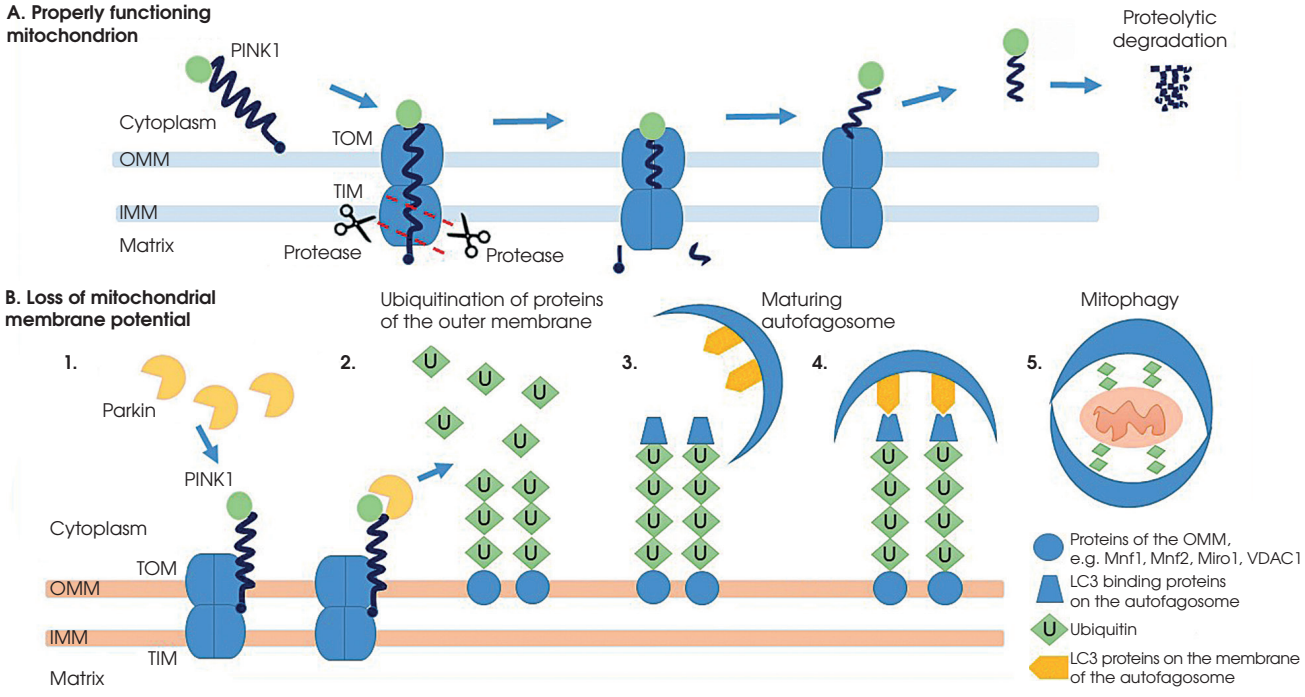

Figure I. The mechanism of ubiquitin-dependent mitophagy. **A.** In properly functioning mitochondria, a PINK1 is transported through the TOM/TIM complex from the OMM to the IMM, where it is cut by mitochondrial proteases. Then the remaining part of the PINK1 is released into the cytoplasm and undergoes proteolytic degradation. **B.** As a result of the loss of membrane potential, the transport of PINK1 by the TOM/TIM complex is inhibited. 1. PINK1 connects to the TOM subunit of the TOM/TIM complex and accumulates on the external surface of the mitochondria. The presence of PINK1 recruits cytoplasmic Parkin and leads to its activation. 2. Activated by PINK1 Parkin initiates the process of ubiquitination of proteins of the OMM, e.g. Mnf1, Mnf2, Miro1, VDAC1. As a result, polyubiquitin chains are attached to mitochondrial proteins. 3. Polyubiquitin chains are recognised by proteins that have the ability to bind to the LC3 proteins present on the autophagosome membrane. 4. The dysfunctional mitochondrion is attached to the membrane of the maturing autophagosome. 5. The autophagosome membrane lengthens and closes the mitochondrion for lysis

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drial matrix proteins, dynamics and distribution of mitochondria in nerve cells, and mitochondrial respiratory chain abnormalities [37-40]. Recent reports also point to the disturbance in the expression of key proteins associated in mitophagy: PINK1 and parkin [41].

It has been revealed that in AD, Aβ and phosphorylated tau protein interact with the Drp1 protein, causing excessive mitochondrial fragmentation [40]. Intensified and prolonged fragmentation causes a decrease in mitochondrial membrane's internal potential and increased permeability disrupting proper function of the electron transport chain [42]. The consequence of abnormal functioning of the respiratory chain complex III and IV is a decrease in ATP production, an increase in oxidative stress, and disruption of calcium homeostasis. Increased Ca^{2+} concentration in neurons may affect both phosphorylation of tau protein and enzymatic treatment of β-amyloid precursor protein (APP), leading to the accumulation of Aβ [43]. It was also shown that Aβ molecules can form pores permeable for Ca^{2+} in the cell membrane and additionally disturb calcium homeostasis, contributing to the formation of free oxygen radicals. Oxidative stress caused by the accumulation of Aβ and calcium excess may contribute to the mitochondrial dysfunction [44]. Early accumulation of structurally abnormal mitochondria was observed in AD patients and a similar change was observed in AD animal models [43, 44].

Although processes preceding the clinical manifestation of AD are being increasingly understood, signal pathways inducing mitophagy in the neurons of patients are still unknown. Recent reports suggest that neurons affected by AD, at first stages, show a strong induction of mitophagy through increased recruitment of parkin to the damaged mitochondria. As the disease progresses, the intensified process of mitophagy leads to a reduction in the cytosolic parkin, which results in accumulation of dysfunctional mitochondria [45]. In the neurons of AD patients with established clinical symptoms, mitophagy impairment associated with a decreased park level and insufficient number of autophagosomes led to accumulation of depolarised mitochondria and PINK1 [41]. Additionally, overexpression of parkin in cell line and mouse AD model caused increased removal of defective mitochondria by intensified synthesis of autophagosomes. This resulted in the recovery of mitochondrial membrane potential and decreased PINK1 accumulation [41, 46].

Parkinson's disease

In PD, the presence of neurons with modified α-synuclein protein inclusions in the cytoplasm, called Lewy's bodies, is characteristic [33]. Although the majority of patients are diagnosed with an idiopathic form of PD, the less common family form of this condition has helped to identify genes that are a risk factor. Predominantly, five genes mutations involved in PD development are described. These genes code α-synuclein, parkin, PINK1, protein DJ-1 and kinase 2 [47, 48]. In the pathogenesis of PD, besides α-synuclein, an important role is also played by parkin and PINK1, which are key factors involved in the signal pathway leading to marking and absorption of dysfunctional mitochondria in the mitophagy [49, 50]. The clinical phenotype of PD in patients with those genes mutations is similar to the idiopathic form of the disease. The hereditary form of PD is characterised by earlier manifestation, especially in parkin mutations. Neuropathologically, there are no significant differences [51].

Decreased activity of NADH dehydrogenase, an enzyme present in the IMM of mitochondria, which is a complex of respiratory chain I, is also associated with PD [52]. Mitochondrial toxins, which are inhibitors of this complex, are used in animal models of the disease. A decrease in electron transport chain activity results in an imbalance of calcium homeostasis in the brain and changes in the function of calcium channels (VDCC) type L. It may cause easier end frequent opening of the channel and excessive influx of Ca^{2+} into the neurons, contributing to the formation of free oxygen radicals [53, 54]. Oxidative stress induced by damaged mitochondria causes degeneration of substantia nigra and manifestation of symptoms in experimental animals [55-57]. Interestingly, cells isolated from the brain of mice with PINK-1 knock out gene also showed limited capacity of calcium buffering and increased susceptibility to inflammation-induced oxidative stress [58].

Mitochondrial stress caused by reduced respiratory chain activity causes changes in the organisation of the mitochondrial network. In the rat line of dopaminergic neurons, it has been shown that inhibition of complex I of electron transport chain caused by 1-methyl-4-phenylpridinium neurotoxin (MPP+) and oxidative stress causes fragmentation of mitochondrial network [59]. Similar changes were observed after administration of the complex inhibitor I – rotenone [60, 61]. Intensified division of mitochondria may lead to a decrease in the membrane potential. In that condition, PINK1 does not degrade and accumulates in the OMM, thus initiating the process of mitophagy depending on ubiquitin. Reduced membrane potential, increased Ca^{2+} levels, and excess of ROS in mitochondria of nerve cells were also found in animal knock out of PINK1 and parkin genes [62-64].

IMPROVEMENT OF MITOCHONDRIAL FUNCTION IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE AS A THERAPEUTIC TARGET

Because mitochondrial dysfunctions are believed to be associated with the two neurodegenerative diseases, in recent years the search for methods to improve mitochondrial functions has been given a lot of interest. Nowadays,

the best candidates are drugs supporting mitochondrial mechanisms related to maintaining energy efficiency. These are natural antioxidants, given that oxidative stress plays an important role in the pathophysiology of neurodegenerative diseases. Mitochondria are not only the main production site of ATP, but also an important modulator of oxidative potential in the cell. These organelles constantly generate ROS as a by-product of oxygen metabolism. Mitochondrial DNA mutations (mtDNAs) accumulate in nerve cells with aging. It may lead to changes in the oxidative phosphorylation, the expression of antioxidant enzymes, and an overproduction of ROS [65]. Excessive accumulation of ROS weakens the bioenergetic function of mitochondria, leading to numerous mutations in nuclear and mitochondrial DNA, which decreases the tricarboxylic acid cycle activity and disrupts the respiratory chain function [65]. Therefore, strategies for induction of the mitophagy process seem to be the key to treatment and prevention of neurodegenerative diseases. The solutions described below, allow to partially restore and increase the intensity of endogenous quality control mechanisms.

Lycopene – a carotenoid compound naturally occurring primarily in tomatoes and other red fruits, has a strong ability to remove free radicals. It is suggested that lycopene has a therapeutic potential for neurodegenerative diseases. The beneficial effect of lycopene supplementation has been shown in the PD rat model, where the oxidative stress caused by rotenone was reduced by restoring the level of endogenous antioxidants (glutathione and peroxide dismutase) and by reactivation of the respiratory complex I in mitochondria [57]. Another promising antioxidant is resveratrol – polyphenol naturally occurring mainly in dark grape varieties. Resveratrol not only reduces ROS, but also increases the APP protein degradation, improves the clearance of the neurotoxic protein Aβ and reduces its aggregation [66-68]. It was also found to be a potential inhibitor of proapoptic factors, such as the Bax protein, which takes part in the formation of channels increasing the permeability of the outer mitochondrial membrane [68, 69]. Neuroprotective action of resveratrol is probably also associated with stimulation of sirtuin synthesis, which reduces ROS levels [70]. However, numerous studies have shown that the use of resveratrol may be limited due to low bioavailability and some effort has been made to improve its properties through structural modifications. *In vitro* studies have shown that methylated and butylated resveratrol derivatives have better neuroprotective and anti-inflammatory properties [71].

Another organic chemical with neuroprotective effects is creatine, which after being absorbed into the brain and skeletal muscles is converted into phosphocreatine (PCr) by cytosolic and mitochondrial creatine kinase. PCr is the buffering factor for ATP in tissues with high energy demand, such as skeletal muscles and the brain [72]. Numerous independent studies have shown that creatine blocks the death of neurons and increases neuron vitality in experimental models of animal neurodegenerative disorders [73]. The effectiveness of creatine in treating PD patients has not been demonstrated by a long-term exploratory study conducted by the National Institutes of Health (NIH). Based on the Unified Parkinson's Disease Rating (UPDRS), no significant differences were found between patients receiving creatine monohydrate and those receiving placebo [74]. However, due to promising pre-clinical studies, creatinine could be used in combination therapy. Polytherapy of creatine with ubiquinone (coenzyme Q10) shows additive neuroprotective effect in animal PD models [75]. Ubiquinone is an essential biological cofactor of the electron transport chain, which removes free oxygen radicals in the IMM by interacting with α-tocopherol. Coenzyme Q10 also showed neuroprotective effects in several models of neurodegenerative disorders *in vitro* and *in vivo* [72, 76].

The mitophagy seems to be a key pathway in quality control of these organelles. Unfortunately, compounds currently used to induce mitophagy *in vitro* are very toxic and non-selective. Significant research has led to the development of a new potential inductor of mitophagy – PMI (P62-mediated mitophagy inducer). PMI increases expression and signalling of autophagic adaptive molecule P62/SQSTM1 in mitochondria, activating mitophagy independently of PINK1/parkin pathway, and thus does not cause loss of mitochondrial membrane potential and does not affect mitochondrial network. Thus, the action of PMI does not include non-specific effects associated with a sudden decrease in the membrane potential, characteristic of compounds routinely used to induce mitophagy *in vitro*, and may be a prototype pharmacological tool for the exploration of molecular mechanisms of this process [77].

CONCLUSIONS

The improvement of mitochondria quality control mechanisms, including mitophagy, seems to be one of the most promising therapeutic interventions in PD and AD. The aim is difficult to achieve because the processes responsible for the proper functioning of mitochondria are under control of many complexes and not fully understood cellular mechanisms. Current symptomatic therapies do not allow to solve the problem of progressive neurodegeneration and do not allow to completely abolish the symptoms of the late stage. For this reason, most of the research focuses on the search for neuroprotective, regenerative and replacement therapies. Nowadays, there is no unequivocally effective therapeutic approach able to control the dynamics of mitochondria and the mitophagy. Explaining the interrelation of many molecular mechanisms, metabolic and biochemical processes related to mitochondrial functions, and finding factors activating these processes will facilitate the search for new, effective methods of treating these diseases.

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Conflict of interest/Konflikt interesu

Absent./Nie występuje.

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