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Review Article

Mitochondrial Movement: A Review

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Abstract

The balance between fusion and division determines most of the functions of mitochondria, controls their bioenergetic function, mitochondrial turnover, and also protects mitochondrial DNA. The division promotes equal segregation of mitochondria into daughter cells during cell division itself and enhances the distribution of mitochondria along the cytoskeletal pathways. In addition, division can help isolate damaged mitochondrial segments and thus promote autophagy. Fusion provides protein complementation, and equal distribution of metabolites. The movement of mitochondria in the dendrites, axons and perikaryons of neurons is an important aspect of the vital activity of nerve cells. Disorders of mitochondrial fusion, division, and mobility can lead to defects in the functioning of the nervous system, which makes it important to study these processes for improving methods of prevention, diagnosis, and correction of neurological diseases.

Keywords: mitochondria; genetic diseases; proteins; mitochondrial fusion and division.

Introduction

Mitochondria are accumulations of free floating organelles in the cytosol. They are known to be called the "powerhouse" of the cell. The main function of mitochondria is to generate energy in the form of adenosine triphosphate (ATP). Mitochondria play many important biological roles, including ATP production, lipid biogenesis, ROS regulation, and calcium clearance. They are very dynamic and have a very complex structure. Mitochondria are involved in the metabolism of lipids and amino acids [26]. They also store the intermediates of pyruvate and Krebs cycle oxidation and play a role in scavenging free radicals and controlling programmed cell death. The mitochondrial matrix carries 10–100 or more copies of circular mitochondrial DNA [35]. Modern research shows that mitochondria undergo constant morphological changes during continuous cycles of fusion and division, resulting in the formation of mitochondria with different morphologies, from fragmented states to continuous networks [3, 7].

The balance between fusion and division determines most of the functions of mitochondria, it controls their bioenergetic function, mitochondrial turnover, and also protects mitochondrial DNA [24]. Mitochondria can change their shape, ranging from discrete isolated organelles to the shape of a large, continuous reticulum. Mitochondrial dynamics and morphological structures have been the subject of extensive research in the past few decades: they are fundamental to the functioning of the cell, in addition, mitochondria are very sensitive to the cellular state and are involved in numerous diseases, including Parkinson's disease, diabetes, cancer and Alzheimer's disease, as well as play a key role in various mitochondrial diseases [4, 13, 14, 18, 23, 29]. Various effects of mitochondrial fusion states have been observed, including increased energy production, protection from apoptotic stress, increased cell proliferation, and regulation of various signaling pathways. Mitochondria are very important for aerobic cells. Neurons, for example, depend on the function of mitochondria, so a violation of these organelles can cause neurological diseases [30]. This vulnerability is explained by the high metabolic requirements of neurons, their dependence on correct communication with calcium and their susceptibility to local proapoptotic and reactive signaling of oxygen species, processes in which mitochondria are critically involved. Moreover, neurons must coordinate the supply, maintenance, and elimination of mitochondria with the various metabolic demands of the perikaryon, synapses, and neurons. Central to this intracellular homeostasis is microtubule-mediated transport, the impairment of which also manifests itself as neuropathology. It is noted that impairment of the mitochondrial function of neurons is associated with the initiation or enhancement of neuronal damage [7, 18, 26, 27].

Neurons are primarily metabolically active cells that require a lot of energy in places far from the cell body. In this regard, cells are particularly dependent on mitochondrial function, which was reflected in the

observation that mitochondrial dysfunction diseases often have a neurodegenerative component. Recent discoveries have shown that neurons are highly dependent on the plastic properties of mitochondria. Type 2A Charcot-Marie-Tooth, peripheral neuropathy and dominant optic atrophy, hereditary optic neuropathy, result from primary mitochondrial fusion deficiency [30]. Moreover, several major neurodegenerative diseases, namely Parkinson's, Alzheimer's and Huntington's disease, are associated with impaired mitochondrial dynamics [4, 5, 7, 11, 13, 14, 23].

Neurons are more extended and complex in shape than other cells, and therefore face a very serious problem in the distribution and maintenance of mitochondria in their branches. Mitochondria need constant rejuvenation, no matter how far from the perikaryon. Axonal transport of mitochondria, as well as mitochondrial division and fusion, contribute to this rejuvenation, while local protein synthesis will also be involved [32]. Maintaining a healthy population of mitochondria requires the removal of damaged proteins and organelles. This includes sequestration in vesicles, degradation of individual proteins derived from mitochondria, degradation of organelles by mitophagy and macroautophagy, and, in some cases, transfer to glial cells. Poetmou, both long-distance transport and local processing, work in achieving mitostasis of neurons: maintaining a properly distributed pool of healthy mitochondria throughout the life of a neuron. Accordingly, defects in the processes that maintain mitostasis contribute significantly to neurodegenerative disorders [6, 10].

Mitochondrial Movement

During development, neurons require a highly integrated metabolic mechanism to meet the enormous energy requirements for growth, differentiation, and synaptic activity in their highly complex cellular structure. Acute depletion of energy will impair mitochondrial dynamics [11, 17, 26, 33].

Since iron deficiency greatly impairs mitochondrial respiration and ATP production, a study was conducted where cultures of hippocampal neurons of mice of different sexes were treated with an iron chelator deferoxamine to simulate chronic energy deficiency and its effect on mitochondrial dynamics during neuronal development [27, 37]. After 11 days in vitro, deferoxamine strongly reduced the mean mitochondrial velocity by increasing the pause rate of individual dendritic mitochondria [11, 17]. The time spent in anterograde movements was reduced, while the retrograde movement, on the contrary, was preserved. From observations of the movement of mitochondria in dendrites and axons in cultured neurons, it is concluded that mitochondria can undergo targeted movement from one destination in the cell to another. The average size of moving mitochondria decreased, and the expression of genes for division was slightly altered, indicating a violation of mitochondrial quality control [33]. The density of mitochondria did not change, which indicates that it is respiratory capacity, rather than localization, that is the key factor in mitochondrial regulation of early growth and branching of dendrites [28]. This study provides new insight into the cross-regulation between energy production and dendritic mitochondrial dynamics during neuronal development and may be important for neuropsychiatric as well as neurodegenerative diseases, many of which are characterized by impaired brain iron homeostasis, energy metabolism, and mitochondrial transport [11, 18, 26, 37].

Regulation of mitochondria occurs through four dynamic processes: fixation, mobility, division and fusion [34]. Mitochondrial movement can be easily assessed by video microscopy of mitochondria that have been fluorescently labeled with either a fluorescent dye such as tetramethylrhodamine or a fluorescent protein intended for import into mitochondria. Note that one population of mitochondria is in motion, while the other is motionless. The difference between these two classes of mitochondria will reflect two different pools: specifically, mobile mitochondria can temporarily stop moving, but they still tend to continue moving forward and will only very rarely change their direction. Thus, it can be concluded that some of the motile mitochondria are specifically designed for anterograde movement down the axon, while others prefer retrograde movement. Interconnected mitochondria will be found in the bodies of nerve cells, but in order to enter the axon, the mitochondrion must first undergo a division reaction that will free it from the reticulum [36]. The division is mediated by a protein, GTPase Drp1, and in almost all cases, contact with the endoplasmic reticulum and actin initiates the process together with the Drp1 receptor MFF is a mitochondrial division factor. When mitochondria meet end-to-end, the opposite fusion reaction is observed [6, 34].

Mechanisms of Movement of Mitochondria

In frogs, in isolated axons, it is indicated that in neurons most of the mitochondria are in motion. In addition, mitochondrial transport will depend on the same microtubules that characterize the axonal transport of other organelles [32]. On the other hand, the detailed characteristics of mitochondrial transport in neurons turned out to be unique: first, there are mitochondria that move in any direction (anterograde and retrograde) with small obvious changes in direction to the middle of the axon [34].

Secondly, there are pauses alternating between phases of stable translocation, which leads to an average speed of 0.25–1 μm/s, which is lower than the average speed of transport of other organelles.

Third, in addition to transport, mitochondria also show other dynamic behavior, fusion and division, which will greatly complicate the analysis of mitochondrial transport, because the identity of a displaced organelle can be removed by interaction with other mitochondria. Thus, in vitro observations were able to paint a step-by-step picture of how the mitochondria of neurons might behave and allowed for fundamental biological and mechanistic analyzes of cells. The good news is that the basic principles of mitochondrial dynamics, obtained as a result of in vitro work, have also been confirmed in vivo [11, 17].

In addition to this in vivo study, many other aspects of this disclosure in vitro have been validated, a number of new questions have been raised, and research has opened up in complex developmental and disease contexts that are virtually impossible to simulate in vitro [30]. It is worth noting that there have been conflicting reports on the extent of mitochondrial movement in vivo. A number of studies have shown that about 10-20% of mitochondria in axons near the neuronal perikaryon move at absolutely any point in time, even under conditions where neuronal activity may either be absent due to surgical isolation, or is suppressed by anesthesia. In general, three models can explain the rejuvenation of the stationary pool:

1) The "changing of the guard" model: stationary mitochondria can collect and leave their sentry stations, perhaps every few weeks, to undergo mitophagy.

2) The "space station" model: They are undergoing rejuvenation by merging with a moving pool in much the same way that delivering rockets from Earth can keep the space station resupplied.

3) The “locally produced” model: mitochondria undergo constant low-level rejuvenation from local sources such as axonal protein synthesis. Of course, all these mechanisms can work in parallel, and only a complex and accurate analysis of the rate of remobilization, fusion and protein synthesis will help determine their contribution [25, 34].

A number of proteins are isolated that can be degraded by proteases, which in turn are found in mitochondria. One of the most important classes for the removal of misfolded and denatured proteins are AAA+ mitochondrial proteases. These barrel-shaped proteases are present in the

matrix and in the inner mitochondrial membrane, which faces both the matrix and the intermembrane space. They recognize hydrophobic domains that are exposed on misfolded and oxidized proteins and effectively break down and unwind them. From the neurological phenotypes, the significance of these proteases for the control of the quality of mitochondria associated with mutations in their genes is currently known. Such phenotypes include spastic paraplegia, non-syndromic mental retardation, spinocerebellar and spastic ataxia. In neurons, mitochondrial proteases are usually used for non-mitochondrial quality control, namely, misfolded cytosolic proteins for degradation can also be imported into mitochondria [19].

The Importance of Mitochondrial Movement for Neurons

The axons of the neurons themselves lie quite flat and have a diameter of no more than a micrometer. That is why mitochondria move no further than a plane that will be easily visualized, and as long as the body of the cell itself or the growth cone of an axon can be identified, it will be much easier to distinguish directional movement, and thus to trace and trace the mitochondria at a distance of 100 mm or more. In addition, at the moment when mitochondria form a complex network in almost all types of cells, the mitochondria of axons will be separated from this network. They will be found only in the form of discrete organelles, usually no more than 1-3 mm in length, and in dendrites they tend to be significantly longer than in axons. The areas of the neuron that have the greatest need for the production of mitochondrial ATP, in other words with the greatest energy consumption, in the synapses, are mainly located precisely at the ends of the cell. Most of the mitochondria of myelinated nerves are located in stationary pools in internodes. When mitochondria cross the Ranvier node, electrical activity helps to stop or slow down the movement of these organelles, but with a blockade of electrical activity, everything is different: it increases the mobile fraction. These modulations of movement are a consequence of the change in energy supply, which was caused by the opening of ion channels in the nodes when the action potentials are triggered. Such post-mitotic cells must always be viable, but the lifetime of mitochondrial proteins will be much shorter, amounting to only a few weeks. We conclude that a continuous circulation of mitochondria should take place throughout the cell, including the removal of old and damaged components, as well as the delivery of new materials, most of which are encoded by nuclear genes. This process will be facilitated by three stages [20, 27, 37].

The first is the constant movement of mitochondria in both axons and dendrites [37]. A very important feature of mitochondria in axons is that they distinguish between three classes: those that move mainly anterograde (15%), those that move mainly retrograde (15%), and those that seem to be motionless for a long time period (70%). One half will move anterograde (away from the cell body), and the other half will move retrograde (toward the cell body). This movement probably reflects the main mechanism of exchange and delivery of newly synthesized mitochondrial components. We turn to the second factor, which is designed to maintain peripheral mitochondria - this is the division and fusion of mitochondria itself. The fact that such processes can occur not only in axons and dendrites, but also in all cells, boils down to the fact that they allow the exchange of materials also between mitochondria. Even very minor contacts can involve fusion and extensive exchange with proteins in every mitochondrial compartment, as has been visualized in non-neuronal cells [27]. Consequently, mitochondria may well be renewed in their place due to exchange with proteins that have a mobile fraction, although at first glance they seemed completely immobile. There would be no fusion at all, or it would be insignificant if mitochondrial movement was absent, and this is in fact the case. Mitochondria that are actively moving have a higher fusion rate than stationary mitochondria, and the mechanisms of movement and fusion can generally be linked mechanically. The third factor is the presence of local mitochondrial biogenesis in addition to what happens in the body of the cell itself. Local biogenesis of mitochondria helps maintain the health of mitochondria in axons and dendrites. Moreover, local biogenesis can instantly respond to both local changes and those caused either by increased demand or by damage to mitochondria [34, 37].

The regulation and maintenance of cellular metabolism is a critical issue for the nervous system.

The metabolic costs that are aimed at performing and maintaining basic nerve functions are incredibly high, primarily due to the very complex morphology of neurons, and specifically because of their difficultly regulated transmembrane ion gradients and in particular their constant synapse activity. The human brain is one of the most energy-consuming organs, accounting for approximately 20% of the total energy expenditure. Metabolic homeostasis of the brain involves the activation of metabolism in neurons and glia, which together form a metabolic component to meet all the energy needs of neurons, neural processes. Neural circuits are highly dependent on mitochondrial respiration; it is known that other metabolic pathways also contribute to the bioenergetics of neurons, including glycolysis of neurons [24, 26]. Recently, research has been carried out using the latest techniques, such as optogenetics and real-time metabolic imaging, that have identified the pleiotropic roles of mitochondria ranging from nervous system development to neurodegeneration. These organelles, which were originally recognized as the cell's energy source for ATP production through oxidative phosphorylation, play one of the most important roles in calcium clearance, lipid biogenesis, and ROS regulation [35]. Mitochondria found in mature neurons contribute to synaptic transmission and plasticity through local ATP uptake and calcium buffering. But other types of brain cells, in particular glial cells, also supply important energy metabolites to neurons for nourishing synapses, and their apparent increased metabolic plasticity makes them ideal for regulating multiple forms of interaction not only with neurons, but also with the vasculature [26]. Therefore, we can confidently say that mitochondrial dysfunction and altered mitochondrial dynamics are widely observed in various conditions, from impaired neuronal development to various neurodegenerative diseases [11, 27, 31].

It is known that mitochondrial proteins constitute an important part of locally synthesized proteins in neurons. For example, transcriptome analysis of the synaptic neuropil has shown that many of the dendritically localized mRNA transcripts encode mitochondrial proteins of nuclear origin. Interestingly, cortical neurons exhibit distinct mitochondrial morphology in their dendrites and axons. In dendrites, mitochondria have a more elongated shape, overlapping with a high density, while in axons, mitochondria are rather identical small separate units localized in certain positions [17].

Aware of the high energy requirements of our brains, early research focused on identifying the neural mechanisms that make up most of its energy load. Theoretical calculations have shown that ion homeostasis after the propagation of the action potential is the largest consumer of energy. Due to the high energy consumption for synaptic activity, the mechanisms that carry out the local synthesis of ATP are of particular importance for synaptic function. The use of the previously discussed ATP biosensors in combination with pharmacological manipulations has shown that the generation of ATP in neurons is largely due to the activity-dependent absorption of glucose, which is metabolized both by glycolysis and by oxidative phosphorylation in presynaptic terminals. In dendritic spines, mitochondrial ATP synthesis, rather than glycolysis, mainly feeds protein synthesis-dependent synaptic plasticity. Local dysfunction of mitochondria disrupts both local protein synthesis and morphological plasticity of the spine. These studies only confirm the importance of

mitochondria in the production of ATP at synapses [20, 31, 37]. However, the molecular mechanisms that induce mitochondrial ATP synthesis in response to local synaptic activity are still relatively poorly understood [11, 17, 26].

Fusion of Mitochondria

It is important to mention the proteins involved in the fusion of mammalian mitochondria, there are only three of them, these are GTPases Optic Atrophy 1 (OPA1) and two mitofusins, MFN1 and MFN2. In mitochondrial division, the central protein is a highly conserved protein that is associated with dynamin 1 (Drp1); it also belongs to the family of large GTPases [5, 12, 21, 24].

It is fusion that allows the exchange of mitochondrial components between damaged and healthy mitochondria to mitigate the effects of cellular stressors. Mitochondrial division and fusion are important for the vitality of neuronal mitochondria. Mitofusin mutations cause peripheral neuropathy, and also cause a permanent decrease in mitochondrial DNA preservation and membrane potential. The fusion provides protein complementation, mtDNA repair, and equal distribution of metabolites [1, 15, 26]. Mitochondrial fusion can increase ATP production through several possible mechanisms. The following possible mechanisms of particular interest are: 1) high ATP is caused by fusion-induced changes in the shape of the inner membrane; 2) high ATP is caused by a decrease in proton leakage caused by fusion; 3) high ATP is caused by a decrease in mitochondrial degradation caused by fusion; 4) high ATP is caused by a non-linear response of the rate of ATP synthesis to the membrane potential. We would like to note that the assumption made in all the above hypotheses boils down to the fact that the fusion causes a very high ATP. But it remains to be seen whether mitochondrial fusion is the cause of the geometric increase in ATP, or whether this hyperfusion and high ATP concentrations have a common cause, for example, a recent study showed that an increase in ATP production in general can be observed earlier than mitochondrial fusion [9, 21, 34, 41].

Mitochondrial Fusion Diseases: Fusion Phenotypes

It is for the maintenance of mitochondrial function that fusion and division factors are extremely important. Division, it is assumed, during cell division, promotes equal segregation of mitochondria into daughter cells and enhances the distribution of mitochondria along the cytoskeletal pathways [34]. In addition, it is division that can help isolate damaged mitochondrial segments and thus contribute to their autophagy. In the event that these defense mechanisms do not work, it is mitochondrial division that can promote apoptosis [10, 18]. Mitophagy refers to the degradation of mitochondria through autophagy [6].

Autophagy is a process by which cellular components are destroyed as a result of absorption by autophagosomes. Autophagosomes fuse with lysosomes, which in turn contain hydrolytic enzymes that break down cellular components. During nutrient deficiencies, foods are processed into more essential molecules [10].

Several recent discoveries show that mitophagy can selectively destroy defective mitochondria. From basic autophagy in yeast cells, mitophagy is regulated independently [6, 10].

Mitostasis in Neurons

Neurons often face problems due to their special structure. Long and very branched processes have developed in neurons between the regions of the central nervous system, to and from peripheral organs, this mechanism works for the rapid transmission of electrical signals. It has been established that in humans, peripheral nerves and cortical-spinal tracts can have axons a meter or more in length [38]. Moreover, since information processing requires extensive convergence and decoding of signals, the cytoplasmic volume of highly branched branches, in this position, easily displaces the volume of the neuronal cell body [27]. Neurons are not dividing cells and therefore must be preserved throughout a person's life. The difference between cellular and protein metabolism is especially great. Note that, as in any cell, almost all neuronal proteins are encoded by genes in the nucleus, and this does not depend on how far this nucleus can be from the site of protein action. Mitostasis is a special form of homeostasis, it is a kind of mechanism by which the number of mitochondria is maintained throughout the entire time in each section of the neuron. How is mitostasis achieved? It is known that the mitochondrial DNA of vertebrates encodes no more than 13 proteins, and the rest of the more than a thousand proteins found in mitochondria are encoded exclusively in the nucleus. Since every part of the neuron needs ATP and therefore requires the obligatory presence of mitochondria. Consequently, some mitochondria need to be retained in the perikaryon, while other mitochondria need to be transported and then positioned along axons and dendrites. This is achieved in order to concentrate in energy-intensive areas, for example in presynaptic terminals and near Ranvier nodes [37]. That is why the transport of mitochondria is a difficult task for the neuron: the balance between supply and demand for energy requires special attention to the needs of each area of the neuron [20].

Study of human TRAK1 isoforms causes fatal lencephalopathy. Parkinson's disease is the most common mitostatic disease identified to date. Several forms of familial Parkinson's disease arise from mutations in PINK1 and Parkin, which in turn alter mitochondrial clearance. At the same time, the study of toxins that cause parkinsonism, such as MPTP+ and rotenone, points to a theory about the mitochondrial origin of the disease [29]. Obtained from the study of mitophagy in neurons showed that a slowdown in Miro degradation and, as a consequence, an inability to stop mitochondria, was typical of many cellular movements derived from this disease. That is, it turned out to be typical not only for those with PINK1 and Parkin mutations. This included LRRK2 mutations and controversial cases of unidentified genetic linkage [2, 6, 8]. Parkinson's disease demonstrates the complexity of the relationship between mitochondrial movement and mitochondrial clearance. Adequate mitochondrial movement in healthy cells maintains the axon pool, but if transport is impaired or mitochondrial health is impaired, mitochondrial movement will be significantly reduced [30, 37]. Thus, the condition of the mitochondria can be further affected. But the constant movement of damaged mitochondria in the neurons of Parkinson's disease and the subsequent proliferation of ROS can do as much harm to the cell as insufficient movement [4, 13]. Moreover, spurious activation of the PINK1 Parkin pathway in a healthy context of mitochondrial arrest can be just as dangerous. Mitochondria are also implicated in many other diseases such as Alzheimer's disease, amyotrophic lateral sclerosis and motor neuron diseases, and of course in conditions where bioenergetic substrates are absent, such as hypoxia and stroke [29]. Altered mitochondria are present in neuroinflammatory lesions. In vivo imaging in disease models demonstrates a decrease in mitochondrial transport, which leads to local accumulation of dysfunctional mitochondria and their lack in distal axons [1, 14, 15, 18].

Disease-causing proteins and mitochondrial transport.

Literally every year, more and more new evidence appears that it is proteins that are associated with neurodegenerative diseases that can affect the axonal transport of organelles in general and mitochondria in particular. The mechanism by which this can happen is characterized by the formation of aggregates in neuronal processes that block transport [27, 32]. A good example of this mechanism would be neurons that express extended polyglutamine forms of huntingtin, a protein that is responsible for Huntington's disease. The disease is autosomal dominant, characterized by a combination of progressive choreic hyperkinesis with mental disorders. In these neurons, the aggregates were associated with

mitochondria, and the areas of the neurite around the aggregate showed a small, but very noticeable movement of mitochondria. The slow delivery of mitochondria to sites of demand for ATP, which are distant from the aggregated blocked process, provides a mechanism to explain the slowly developing loss of function of neurons in the striatum, which is precisely associated with this disease [27]. Amyotrophic lateral sclerosis, in contrast to Huntington's disease, is largely a sporadic disease [5, 18]. However, the disease was well modeled in mice by overexpression of mutant forms of copper and zinc superoxide dismutase (mtSOD1), which has been identified in less common familial forms of the disease [25]. Deep mitochondrial defects were observed in neurons that emanate from mtSOD1-expressing mice, which coincided with the emergence of motor neuron pathology. In addition, there is evidence of a decrease in mitochondrial penetration into axons beyond the initial segment, as well as a significant decrease in retrograde mitochondrial transport in motor neuron axons from studies in mtSOD1 mice. It is noted that it is mutant SOD1 that will be associated with mitochondria, and it is possible that this disrupts the interaction of mitochondria with motor proteins or their adapters. Like mtHtt, mtSOD1 is also merged, allowing for physical obstruction. It is important to consider that metabolic dysfunction may be a key event, so that impaired ATP delivery to the motors will be implicated in movement cessation [16, 26]. The microtubule-bound tau protein, when hyperphosphorylated, forms neurofibrillary tangles, which are precisely the main distinguishing and visible sign of Alzheimer's disease [30]. The tau protein also has an important effect on mitochondrial movement. Tau inhibits the attachment of weights to kinesin-based motors, so that overexpression of tau leads to accumulation of mitochondria near the minus end of the microtubules in the center of the cell [14, 16, 18].

When abnormalities in mitochondrial fusion, division, mobility and renewal occur, it can lead to characteristic defects in neurons. Note that these defects also overlap significantly, since these four processes are highly interdependent [11, 34].

The process of transferring mitochondria to distant sites that require extremely high energy consumption is a critical component of both normal neurophysiology and pathophysiology, neurodevelopmental disorders and neurodegenerative disorders. Simultaneously with the development of neurons, mitochondria are attracted to the areas of growth and branching of dendrites, as well as to the formation of spines. Violation of this movement will disrupt dendritic branching and, accordingly, the formation of synapses, which in turn will lead to structural abnormalities [29].

As a rule, mitochondria mainly move along microtubules using ATPase-dependent kinesin and dynein motor proteins, as well as dendritic and axon-specific adapter proteins. Note that the anterograde movement of mitochondrial axons is generated by kinesins. Of the large number of possible kinesin families, it is kinesin-1 and kinesin-3 that make a huge contribution to the movement of mitochondria. Kinesins provide anterograde transport, while dyneins provide retrograde transport. In proximal dendrites, the polarity of microtubules is mixed, and motor proteins are not selective for any of the presented transports [6, 11, 26, 37].

Neurons depend on mitochondrial transport for their survival much more than any other type of cell. Recent research has identified a motor adapter complex on the surface of mitochondria that is common between neurons and other animal cells. In addition to kinesin and dynein, this complex contains the proteins Miro (also known as RhoT1 2) and milton (called TRAK1 2), which are responsible for the movement of mitochondria. The identification of this complex gave an idea of how exactly this movement is regulated by a huge number of intracellular signals. Regulation of mitochondrial movement can cover and fully meet the energy needs to supply all the unusual architecture of these cells, and can also control the replenishment of mitochondria in the periphery and their cleansing [22].

Conclusions

The movement of mitochondria in the dendrites, axons and perikaryons of neurons is an important aspect of the vital activity of nerve cells. Disorders of mitochondrial fusion, division, and mobility can lead to defects in the functioning of the nervous system, which makes it important to study these processes for improving methods of prevention, diagnosis, and correction of neurological diseases.

References

1. Alicia M., Richard J. (2015). The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease. Journal of Neuron. N2:257-273.
2. Alpana S, Lianteng Z, Hui Zh. (2019). LRRK2 and mitochondria: Recent advances and current views. Journal of Brain Research. N1:96-104.
3. Bertholet A,Delerue T,Millet A,Moulis M. (2016). Mitochondrial fusion/fission dynamics in neurodegeneration and neuronal plasticity. Journal of Neurobiology of Disease. N9:3-19.
4. Bose A., Beal M. (2016). Mitochondrial dysfunction in Parkinson's disease. Journal of Neurochemistry. N139:216–231.
5. Catarina C, Luana N, Carla L, Cristina R. (2018). Mitochondrial Dysfunction in Huntington's disease. Journal of Advances in Experimental Medicine and Biology. N6:59-83.
6. Chen H, Chan D. (2009). Mitochondrial dynamics–fusion, fission, movement, and mitophagy in neurodegenerative diseases. Journal of Human Molecular Genetics. N18:1–8.
7. Faustini G, Marchesan E, Zonta L, Bono F., Bottani E. (2019). Alpha-Synuclein Preserves Mitochondrial Fusion and Function in Neuronal Cells. The Journal of Hindawi. N1:1-11.
8. Fieke W., Tom C., Dorien I., Shaun M. (2020). LRRK2 mutations impair depolarization-induced mitophagy through inhibition of mitochondrial accumulation of RAB10.Journal of Autophagy. N2:203-222.
9. Hanne H., Iain G. J., Jones N. What is the function of mitochondrial networks? A theoretical assessment of hypotheses and proposal for future research. Journal of Problems & Paradigms. N37:687-700.
10. Hemachandra R, XiangLing ., Manczak M, Kumar S, Pradeepkiran J, Vijayan M. (2018). Mutant APP and amyloid beta-induced defective autophagy, mitophagy, mitochondrial structural and functional changes and synaptic damage in hippocampal neurons from Alzheimer's disease. Journal of Human Molecular Genetics. N14:2502-2516.
11. Hong-Min N,Jessica A,Wen-X. (2015). Mitochondrial dynamics and mitochondrial quality control. Journal of Redox Biology. N4:6-13.
12. Iraselia G, Fredy C, Patrick D, Shaynah S. (2015). Mitochondrial OPA1 cleavage is reversibly activated by differentiation of H9c2 cardiomyoblasts. Journal of Mitochondrion. – 2021. – N57:88-96.
13. Jannik P, Ryan L, Kishore R. (2021). Targeting Mitochondrial Impairment in Parkinson's Disease: Challenges and Opportunities. Journal of Cell and Developmental Biology. N1:6-8.
14. Kandimalla R, Manczak M, Yin X, Wang R, Hemachandra P. (2018). Hippocampal phosphorylated tau induced cognitive decline, dendritic spine loss and mitochondrial abnormalities in a mouse model of Alzheimer's disease. Journal of Human Molecular Genetics.N1:l30-40.

15. Kim B. (2018). Mitochondria: The needless PINK. Journal of Nature Reviews Molecular Cell Biology. N2:75-76.
16. Lijun W, Brian P, Raymond P. (2014). An enhanced integrated stress response ameliorates mutant SOD1-induced ALS.Journal of Human Molecular Genetics. N10:2629-2638.
17. Lisa T, Shun N, Vincent P, Julien P. (2018). Mitochondrial dynamics: overview of molecular mechanisms. Journal of Essays in Biochemistry. N3P:341-360.
18. Madhavika N., Jerry E. (2017). Mitochondrial Fission in Human Diseases. Handbook of Experimental Pharmacology. N240:159-188.
19. Maria Gomez-Fabra G., Friederike-Nora V. (2021). Mitochondrial proteases in human diseases // Journal of FEBS Letters. N8:1205-1222.
20. Michael J., Josef T. (2018). Mitochondria at the neuronal presynapse in health and disease. Journal of Nature Reviews Neuroscience. N2:63-80.
21. Michelle H,Julia H, Kathryn O, Moyra S., Virginia K. (2019). Meta-analysis of genotype-phenotype analysis of OPA1 mutations in autosomal dominant optic atrophy. Journal of Mitochondrion. N46: 262-269.
22. Misgeld T, Schwarz T. (2017). Mitostasis in neurons: Maintaining mitochondria in an extended cellular architecture. Journal of Neuronscience. N3:651–666.
23. Padraig J., Trushina E. (2019). Mitochondrial Dynamics and Transport in Alzheimer's Disease. Journal of Molecular and Cellular Neuroscience. N98:109–120.
24. Peter J. Mitochondria. (2017). Bioenergetics and Apoptosis in Cancer. Journal of Trends in Cancer. N12:857-870.
25. Plucin G, Paquet D, Hruscha A, Godinho L, Haass C, Schmid B, Misgeld T. (2012). In Vivo Imaging of Disease-Related Mitochondrial Dynamics in a Vertebrate Model System. Journal o f Neuroscience. N32: 16203-16212.
26. Prashant M., David C. Metabolic regulation of mitochondrial dynamics. (2016). Journal of Cell Biology. N4:379-387.
27. Rangaraju , Lewis J, Hirabayashi X, Bergami X, Motori E, Cartoni ., Kwon S, Courchet J. (2019). Pleiotropic Mitochondria: The Influence of Mitochondria on Neuronal Development and Disease. Journal of Neuroscience. N39:8200–8208.
28. Rintoul G., Reynolds. I. (2010). Mitochondrial trafficking and morphology in neuronal injury. Journal of Biochimica et Biophysica. N1:143–150.
29. Ruby M, Katy B, Christopher H, Heather M. (2018). Mitochondrial abnormalities in Parkinson's disease and Alzheimer's disease: can mitochondria be targeted therapeutically. N4:891-909.
30. Ryan L, Christina L, Carolyn M. (2018). Mitochondrial diseases. Journal of Current Biology. N2. – P. 125-141.
31. Satish S, Manti G, Anna K, N. (2017). Mitochondrial dysfunction and mitochondrial dynamics. The cancer connection. Journal of Biochimica et Biophysica. N8:602-614.
32. Saxton W., Hollenbeck P. (2012). The axonal transport of mitochondria. Journal of Cell Science. N125:2095–2104.
33. Schwarz T. (2021). Mitochondrial Trafficking in Neurons. Journal of Neuronscience. N1:1–16.
34. Song G., Junjie H. (2021). Mitochondrial Fusion: The Machineries In and Out. Journal of Trends in Cell Biology. N1:62-74.
35. Sudhakar R, Marie-Francoise Ch. (2013).Mitochondrial dysfunction and oxidative stress in Parkinson's disease. Journal of Progress in Neurobiology. N9:106-107.
36. Thomas L. Mitochondrial trafficking in neurons. (2013).Journal of Cold Spring Harbor Perspectives in Biology. 1-2.
37. Thomas W. B, Hohenberg W, Georgieff M, Lanier L. (2019). Chronic Energy Depletion due to Iron Deficiency Impairs Dendritic Mitochondrial Motility during Hippocampal Neuron Development Journal of Neuroscience. N5:802-813.
38. Tommy L, Lewis J, Gergely F, Turi, S-K K, Attila L, Polleux F. (2016). Progressive decrease of mitochondrial motility during maturation of cortical axons in vitro and in vivo. Journal of Current Biology. N26:2602-2608.
39. Trey F, Naava N, Steve C. (2018).Tying trafficking to fusion and fission at the mighty mitochondria. Journal of Traffic. N8:569-577.
40. Valentina B, Elena M, Caterina P, Joy Ch. (2019). Regulation of ER-mitochondria contacts by Parkin via Mfn2. Journal of Pharmacological Research. N12:43-56.

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