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Impaired mitochondrial trafficking in Huntington's disease

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Abstract

Impaired mitochondrial function has been well documented in Huntington's disease. Mutant huntingtin is found to affect mitochondria via various mechanisms including the dysregulation of gene transcription and impairment of mitochondrial function or trafficking. The lengthy and highly branched neuronal processes constitute complex neural networks in which there is a large demand for mitochondria-generated energy. Thus, the impaired mitochondria trafficking in neuronal cells may play an important role in the selective neuropathology of Huntington's disease. Here we discuss the evidence for the effect of the Huntington's disease protein huntingtin on the intracellular trafficking of mitochondria and the involvement of this defective trafficking in the pathogenesis of Huntington's disease.

Keywords

Mitochondria; Huntington; trafficking; neurodegeneration

1. Introduction

Huntington's disease (HD) is a dominant, progressive neurodegenerative genetic disease that is caused by a CAG triplet repeat expansion (>35 CAGs) in the first exon of the gene encoding the huntingtin (htt) protein. HD is characterized by uncontrolled movement, dementia, emotional disturbance, and early death, which often occur in middle age. These symptoms are associated with the neuronal loss that occurs preferentially in medium spiny neurons of the striatum and also extends to other brain regions during the late stages. The preferential degeneration of striatal neurons can be reproduced by administration of the mitochondrial toxins in different animal models, leading to the prevalent theory that mitochondrial dysfunction contributes to the pathogenesis of HD. In support of this idea, many recent studies have demonstrated that mutant htt affects the function of mitochondria in various HD cellular and animal models [1]. The negative impact of mutant htt on mitochondria appears to result from the indirect effects of mutant htt on the nuclear expression of genes important for the biogenesis of mitochondria and the direct effects of htt on the respiration function and trafficking of mitochondria. In this review, we focus on the relationship between mutant htt and mitochondria trafficking as well as HD pathogenesis.

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2. Mitochondrial trafficking

Mitochondria are the primary generators of ATP and are important regulators of intracellular calcium homeostasis. Although the human brain comprises 2% of total body mass, it consumes 20% of resting metabolic energy [2]. Neurons are highly specialized cell types and possess lengthy axons and dendrites that are highly branched and constitute complex neural networks via synapses. Synaptic connections are highly plastic and undergo continuous remodeling to modulate information processing [3.4]. Thus, neurons represent a particular anatomical and physiological challenge for mitochondrial trafficking within neuronal processes and nerve terminals.

Mitochondria are dynamically transported along lengthy neuronal processes to provide energy to nerve terminals and maintain the normal neuronal function. Mitochondria are highly dynamic organelles that fuse and divide in neurons. The movement of mitochondria also facilitates its fusion and fission events in neurons and retrieval of damaged mitochondria for degradation by autophagy. Although how mitochondria are transported and regenerated remains to be understood, the failure to move mitochondria or deliver mitochondria to appropriate sites in neurons would result in energy starvation and impairment of neuronal interactions or neural network function.

Mitochondrial movement in neurons is highly diverse and complex. There are stationary and motile mitochondria, which move with different speeds and in different directions [5]. Three major groups of proteins are involved in transporting mitochondria in neurons: (1) cytoskeletal microtubules and actin microfilaments, (2) molecular motors, and (3) adaptor and scaffolding proteins that link cargos to motors and the cytoskeleton. In neurons, microtubules are likely to be tracks for transport over long distances while actin microfilaments mediate travel over short distances. The molecular motors, kinesins and cytoplasmic dynein, which are ATPases, transport mitochondria toward (+)- and (−)-ends of microtubules, respectively. It remains unclear how the cytoskeletal substrates mediate the bidirectional and dynamic transport of mitochondria.

The association of motor proteins with their cargos is largely mediated by adaptor and scaffolding proteins. For example, Milton and syntabulin are implicated as scaffolding proteins for linking mitochondria with kinesin heavy chain [6,7]. Reducing the expression of these proteins leads to abnormal distribution of mitochondria, as expected from disrupted anterograde transport. APLIP1 is another example of a scaffolding protein that may interact with both kinesin and dynein to regulate retrograde transport of mitochondria [8]. Thus, complex mitochondrial movements are likely mediated by various and dynamic interactions between regulatory proteins, adaptors, motors, and cytoskeletal elements.

3. Mitochondrial energy impairment in HD

The hypothesis that cellular energy production and metabolism are compromised in HD was originally derived from clinical observations of both peripheral weight loss and central deficits in brain glucose utilization in HD patients [9,10]. Subsequent studies of peripheral tissues from HD patients confirmed the negative effect of mutant htt on the energetic status in various cell types [11]. Analyses of metabolic enzyme activity in post-mortem HD brain tissue have consistently revealed deficits in enzymes of the mitochondrial TCA cycle and OXPHOS system. In particular, decreased complex II/III activity and complex II (SDH) expression are seen in HD striatum but not cortex or cerebellum [12-14].

Systemic administration of SDH inhibitors 3-nitropropionic acid and malonate in rodents and non-human primates causes striatal pathology and behavioral abnormalities reminiscent of HD [15]. Activities of several mitochondrial enzyme, including pyruvate dehydrogenase,

aconitase, SDH, and cytochrome oxidase, are significantly reduced in brain tissue from HD patients [11]. Following the generation of genetic animal models of HD, several more specific deficits in mitochondrial function have been consistently observed. ΔΨm, ATP production, Ca^{2+} handling, reactive oxygen species (ROS) generation, and apoptotic induction are all altered in various HD models [16]. However, the primacy of mitochondrial energetic function in HD pathogenesis remains unclear. Of particular importance is the question of whether mitochondrial function is influenced by the direct effect of mutant htt or via an indirect mechanism (e.g. altered nuclear transcription).

It is known that mutant htt can accumulate in the nucleus to interact with a number of transcription factors, leading to gene transcriptional regulation [17]. Several recent studies highlight the potential relevance of nuclear mutant htt on mitochondrial function. Mutant htt has been shown to alter transcriptional activity of p53 and PGC-1α, two nuclear factors that are known to indirectly regulate mitochondrial function via their transcriptional activity [18-20].

In vitro studies indicate that ΔΨm and mitochondrial Ca^{2+} regulation are directly impaired by mutant htt and that increased ROS generation is the driving force for these alterations [21-23]. Further, these studies demonstrate similar impairments in mitochondria isolated from HD patients or mouse models and normal mitochondria incubated with purified mutant proteins. These studies also suggest that other mitochondrial abnormalities observed in HD patients and model systems could be directly caused by mutant htt.

4. Mutant htt affects mitochondrial trafficking

There is increased evidence that mutant htt can also affect the trafficking of mitochondria in neurons. Cortical neurons transfected with mutant Htt display reduced mitochondrial trafficking specifically to cytoplasmic htt aggregates, and the degree of movement impairment is correlated with the size of aggregates [24]. However, abnormal mitochondrial motility was also observed in HD striatal neurons in the absence of aggregates [25]. The effects of mutant htt on mitochondrial movement support the early studies that htt plays an essential role in axonal transport in Drosophila [26] and that polyQ expanded htt inhibits transport in squid axoplasm [27]. The trafficking function of htt is also indicated by its association with HAP1 [28]. HAP1 is a neuronal protein that is essential for neuronal function and viability, as elimination of HAP1 leads to postnatal death of mice [29,30]. HAP1 interacts with microtubule transporters dynactin p150 [31,32] and kinesin light chain [33]. The complex containing htt and HAP1 may act as a docking platform to modulate vesicular cargo attachment to both dynein/dynactin and kinesin microtubule motors [34]. A HAP1 homolog in Drosophila, Milton, influences mitochondrial distribution in axons through its interaction with the mitochondrial protein Miro [35,36]. Also, htt may directly interact with trafficking proteins and acts as a molecular switch for bidirectional transport in neurons [37].

Although there is compelling evidence that htt and its associated proteins, such as HAP1, are involved in intracellular trafficking, the mechanisms by which mutant htt affects intracellular organelle trafficking remain to be fully understood. It is likely that an abnormal interaction between mutant htt and HAP1 affects the trafficking of organelles in neurons by disrupting the formation of trafficking complexes and impairs vesicular transport in mammalian cells [38]. Mutant htt may also sequester wild type htt and trafficking proteins to impair neuronal trafficking [25,26]. In addition, loss of the normal function of htt can affect vesicular transport in neurons [26,34].

It is also possible that different htt forms differentially affect intracellular trafficking. It is possible that large htt aggregates can physically block the neuronal trafficking if their size exceeds the narrow region of neuronal processes. However, it remains unclear which form of

soluble mutant htt is more harmful to the vesicular transport in neurons. Htt is a large (350 kDa), predominantly cytoplasmic protein that is a substrate for various proteolytic enzymes. Proteolytic cleavage of full length mutant htt yields small N-terminal fragments containing the polyQ domain that readily misfold and aggregate in both neuronal nuclei and processes [39, 40]. The strong toxic property of proteolytically processed mutant htt is evidenced by the more rapid disease progression of HD mice expressing smaller N-terminal mutant htt fragments than that of mice expressing full length mutant htt [41]. This phenomenon has led to extensive study of the proteolysis of htt and the identification of a number cleavage sites in the N-terminal region of htt [42].

Using a knock-in mouse model of HD, we show that specific N-terminal fragments, likely smaller than the first 500 amino acids, of mutant htt preferentially associate with mitochondria *in vivo* and that N-terminal mutant htt fragments affect the trafficking of mitochondria [43]. This biochemical finding supports the recent subcellular localization evidence that the first 17 amino acids of htt are required for localization of exon1 htt to mitochondria [44]. We also found age-dependent accumulation of mutant htt on mitochondria and that this accumulation directly correlates with disease progression. Finally, we demonstrate that mitochondrial function can be disrupted by soluble N-terminal mutant htt fragments independent of their nuclear accumulation or aggregation [43]. Our observation of impaired mitochondrial trafficking and decreased ATP level in synaptosomes caused by mutant htt suggests that impaired trafficking of mitochondria in neuronal processes can decrease mitochondrial ATP supply in nerve terminals [45]. The decreased ATP level can also affect the transport of mitochondria in neuronal processes. Together, these findings suggest that abnormal interaction between mutant htt and mitochondria may represent a cytoplasmic pathological event that can serve as a therapeutic target for HD.

5. Impaired mitochondrial trafficking and HD pathogenesis

Impaired mitochondrial transport probably has multiple consequences that increase in severity with the duration of impaired transport. Poor ATP distribution in nerve terminals is likely to be an initial outcome and can affect the cellular processes that require mitochondria in a rapid and dynamic manner. These processes include specific synaptic sites undergoing morphogenesis or potentiation and are likely to actively recruit mitochondria under normal conditions. Consistent with this idea, there are a reduced synaptic ATP level and impaired activity of ubiquitin-proteasomal system (UPS) in synapses of HD mice [43.45]. It is known that the UPS function is largely dependent on ATP. Synaptic UPS may be more vulnerable to impaired mitochondrial function or deficient ATP supplies in nerve terminals. Similarly, other nerve terminal functions, such as neurotransmitter release and synaptic vesicle biogenesis, could also be affected if mitochondria transport to nerve terminal is reduced by mutant htt. In addition, impairment of mitochondrial movement may impede fusion-mediated mtDNA complementation and autophagic degradation of damaged mitochondria [46,47].

As discussed above, neuronal function is particularly dependent on the intracellular trafficking of organelles and molecules over the long distance of axons or neuronal processes. The unique anatomic structures of neuronal processes may make neurons more vulnerable to the impaired trafficking caused by mutant htt, which also contributes to the selective neurodegeneration in HD. However, other polyglutamine disease proteins that largely accumulate in the nucleus can also cause selective neurodegeneration via different mechanisms. Because misfolded proteins preferentially accumulates, in an age-dependent manner, in neuronal cells than in other types of cells in all polyQ diseases, neuronal ability to remove misfolded polyQ proteins is likely decreased by aging related factors. Indeed, age-dependent decrease of UPS activity is more pronounced in neurons than in glial cells [48]. It is also possible that the clearance of mutant htt or damaged mitochondria by autophagy is decreased with age. Once the cellular capacity

to clear mutant polyQ proteins is decreased, misfolded proteins can accumulate in the nucleus to affect gene expression and in the neuronal processes to cause cytoplasmic toxicity. In the case of HD, mutant htt has additional adverse effects on intracellular trafficking. Thus, the impaired trafficking of mitochondria in neuronal processes and reduced ATP supply to nerve terminals can lead to specific dysfunction of neurons.

6. Conclusion

Recent studies have suggested several mechanisms for mitochondrial dysfunction in HD. These mechanisms can be classified as the indirect effects of mutant htt via transcriptional dysregulation of genes important for mitochondrial biogenesis and the direct effects of mutant htt on mitochondria. Biochemical and cell biology studies have provided strong evidence for the negative impact of mutant htt on mitochondrial movement. Moreover, inhibition of the distribution of mutant htt in neuronal processes by an intracellular antibody can alleviate HD neurological symptoms in HD transgenic mice [49]. Because neuronal function is largely dependent on intracellular trafficking in lengthy processes and nerve terminals, the impaired intracellular trafficking in HD neurons is likely to contribute to the specific neuropathology in HD. In addition, given that htt is predominantly distributed in the cytoplasm, the cytoplasmic toxicity of mutant htt could play an important role in HD pathology. Understanding how mutant htt affects the transport of mitochondria will help us to find an effective means to reduce the selective neuropathology in HD.

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