Neurotox Res (2017) 32:518–529
DOI 10.1007/s12640-017-9766-1

REVIEW

Huntington's Disease and Mitochondria

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Received: 22 February 2017 / Revised: 28 May 2017 / Accepted: 1 June 2017 / Published online: 21 June 2017

Abstract Huntington's disease (HD) as an inherited neurodegenerative disorder leads to neuronal loss in striatum. Progressive motor dysfunction, cognitive decline, and psychiatric disturbance are the main clinical symptoms of the HD. This disease is caused by expansion of the CAG repeats in exon 1 of the *huntingtin* which encodes Huntingtin protein (Htt). Various cellular and molecular events play role in the pathology of HD. Mitochondria as important organelles play crucial roles in the most of neurodegenerative disorders like HD. Critical roles of the mitochondria in neurons are ATP generation, Ca^{2+} buffering, ROS generation, and antioxidant activity. Neurons as high-demand energy cells closely related to function, maintenance, and dynamic of mitochondria. In the most neurological disorders, mitochondrial activities and dynamic are disrupted which associate with high ROS level, low ATP generation, and apoptosis. Accumulation of mutant huntingtin (mHtt) during this disease may evoke mitochondrial dysfunction. Here, we review recent findings to support this hypothesis that mHtt could cause mitochondrial defects. In addition, by focusing normal huntingtin functions in neurons, we purpose mitochondria and Huntingtin association in normal condition. Moreover, mHtt affects various cellular signaling which ends up to mitochondrial biogenesis. So, it could be a potential candidate to decline ATP level in HD. We conclude how mitochondrial biogenesis plays a central role in the neuronal survival and activity and how mHtt affects mitochondrial trafficking, maintenance, integrity, function, dynamics, and hemostasis and makes neurons vulnerable to degeneration in HD.

Keywords Huntington's disease · Mitochondria · Striatum · Mitochondrial biogenesis · Huntingtin

Abbreviations

ACO	Aconitase
AD	Alzheimer's disease
AMPA	α-Amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
AMPK	AMP-activated protein kinase
B5R	Cytochrome b5 reductase
BDNF	Brain-derived neurotrophic factor
Cat	Catalase
CBP	CREB binding protein
CMT	Charcot–Marie–Tooth disease
CREB	cAMP response element binding protein
DHOH	Dihydroorotate dehydrogenase
DOA	Dominant optic atrophy
Drp	Dynamin-related protein
ERRα	Estrogen-related receptor α
ETC	Electron transport chain
Fis1	Fission 1 protein
GPDH	Glycerol-3-phosphate dehydrogenase
GPX	Glutathione peroxidase
GR	Glutathione reductase
GRX2	Glutaredoxin 2
HAP1	Huntingtin-associated protein 1
HD	Huntington's disease

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1,14 Hip1,14	Htt-interacting proteins
Htt	Huntingtin
KGDH	α-Ketoglutarate dehydrogenase
Mfn1/2	Mitofusin1/2
mHtt	Mutant huntingtin protein
mtDNA	Mitochondrial DNA
MAOA/B	Monoamine oxidases A/B
MnSOD	Manganese superoxide dismutase
mPTP	Mitochondrial permeability transition pore
NE	Nuclear export
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NL	Nuclear localization
NMDA	*N*methyl D-aspartate
NRF1/2	Nuclear respiratory factor 1/2
OPA1	Optic atrophy 1 protein
OXPHOS	Oxidative phosphorylation
PD	Parkinson's disease
PDH	Pyruvate dehydrogenase
PGC1α	Peroxisome proliferator-activated receptor gamma coactivator 1α
PGPX	Phospholipid hydroperoxide glutathione peroxidase
PINK1	PTEN-induced putative kinase 1
PolyQ	Poly glutamine
PPARγ	Peroxisome proliferator-activated receptor γ
PRX3/5	Peroxiredoxins
PSD95	Postsynaptic density protein 95
PSD	Postsynaptic densities
QC	Quality control
ROS	Reactive oxygen species
SIRT1	Sirtuin 1
SOD2	Superoxide dismutase 2
TFAM	Mitochondrial transcription factor A
TR	Thyroid receptor
TrkB	Tyrosine receptor kinase B
TRX2	Thioredoxin 2
TRXR2	Thioredoxin reductase 2
UPS	Ubiquitin proteasome system

Introduction

Huntington's disease (HD) as one of the prevalent neurodegenerative disorders is characterized by the presence of the aggregated protein, mutant huntingtin (mHtt). *HTT* gene includes 7–35 CAG repeats, which encode glutamine (polyQ), at the 5′ end (Jacobsen et al. 2011). Neuronal loss and dysfunction in basal ganglia contribute to progressive motor dysfunction, cognitive decline, and psychiatric disturbance in the HD (Walker 2007). In addition, neurodegeneration has been identified in other brain regions like cerebral cortex, globus pallidus, thalamus, subthalamic nucleus, nucleus accumbens, substantia nigra, cerebellum, and white matter (Vonsattel and DiFiglia 1998). The prevalence of this disease is 4–10 per 100,000 in the west with the mean age of onset at 40 years (Ross and Tabrizi 2011). HD inherits as autosomal-dominant disorder with >40 CAG repeats in exon 1 of the *HTT* gene (Langbehn et al. 2004). Increasing in the number of CAG repeats elongates glutamine residues, poly glutamine (polyQ), at the amino terminus of protein which leads to aggregation and toxicity (Williams and Paulson 2008). Mutant huntingtin (mHtt) is the main character of the HD, and it can make inclusion and aggregate forms in the nucleus and cytoplasm (DiFiglia et al. 1997). βSheet structures are the most abundant components of the amyloid fibers in the mHtt. Insolubility and toxicity of the aggregate protein, mHtt, in the HD are the main reason of the neuronal death (Soto 2003). Moreover, mHtt has the ability to interact with proteins that participate in the transcription, cell cycle, energy metabolism, and cell signaling. These interactions influence a wide variety of cellular processes which can cause cell death and apoptosis (Shirasaki et al. 2012). mHtt is also capable to alter mitochondrial hemostasis and dynamic (fission and fusion) (Guedes-Dias et al. 2015; Pellman et al. 2015; Brustovetsky 2016). Mitochondria as important organelles in cell survival and death interact with aggregate proteins in many neurodegenerative disorders like Alzheimer's disease (AD), Parkinson's disease (PD), and HD. Any disruption in mitochondrial hemostasis and dynamic activates various signaling pathways to induce cell death and apoptosis.

Normal Huntingtin Function

HTT has high expression in the central nervous system (CNS) and testes. Encoded protein has 3144 amino acids. PolyQ tract (34 glutamines, Q) at the N terminus is followed by proline-enriched domain which helps protein to be soluble (Li and Li 2004; Steffan et al. 2004). Three HEAT repeat domains in Htt structure participate in the protein-protein interactions. A HEAT repeat as tandem structural motif includes two alpha helices linked by a short loop (Andrade and Bork 1995). Nuclear export (NE) and nuclear localization (NL) sequences near carboxy terminal provide the localization of Htt into the nucleus and cytoplasm (Fig. 1). Presence of various sites for the posttranscriptional modifications like phosphorylation and SUMOylation nominates Htt protein to control numerous cellular functions. Presence of the three cleavage sites for proteases in Htt structure generates cleaved protein in cerebral cortex and striatum (Steffan et al. 2004; Warby et al. 2005; Mende-Mueller et al. 2001). By binding the N-terminal to C-terminal, cleaving by proteases is disrupted (El-Daher et al. 2015). After gastrulation, Htt participates in the neurogenesis process. Malformation of the cortex and striatum correlates with the low expression of the *HTT* during

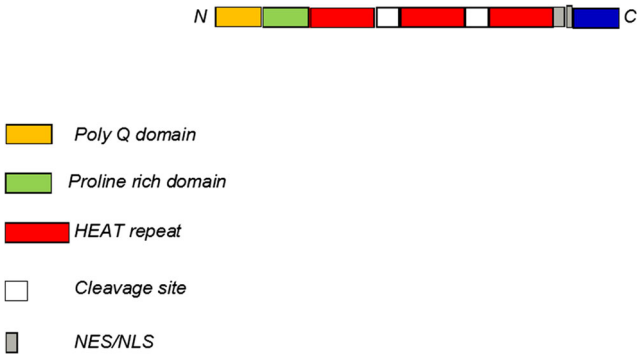

Fig. 1 Schematic diagram of the huntingtin. PolyQ domain at the N-terminal has 34 glutamines, Q, in the normal form. Proline-rich domain has a role in the flexibility of the protein. NE and NL sequences help localization of huntingtin in/out of the nucleus. Cleavage sites make cleaved proteins in the cerebral cortex and striatum

neurogenesis (White et al. 1997). Knocking out of the *HTT* in the embryonic stem cells shows small numbers of neuronal progenitors during differentiation (Metzler et al. 1999). Htt has an antiapoptotic role by influencing caspase-3 and pro-apoptotic Bcl-2 family members like BIK and BAK. In the presence of the normal Htt, neurons are protected against neurotoxins such as 3-nitropropionic acid (3-NP) which inhibits mitochondrial complex II and induces HD-like symptoms (Fig. 2b) (Rigamonti et al. 2000).

Moreover, the neuroprotection character of the Htt could act through transcriptional regulation affair. Brain-derived neurotrophic factor (BDNF) as one of the important neurotrophins with high expression in the CNS regulates neuronal survival, development, and synaptic plasticity (Greenberg et al. 2009; Nakao et al. 1995). Likewise, BDNF increases ATP synthesis and mitochondrial efficacy in the brain (Markham et al. 2004). Ectopic expression of the normal Htt increases BDNF messenger RNA (mRNA) and protein levels in the cultured neurons, while by expressing the mutant form, BDNF level is decreased (Fig. 2a) (Zuccato et al., 2001). In vivo studies showed similar result with in vitro lines of research and confirmed the correlation between normal Htt and BDNF levels in the brain specifically striatum (Hodgson et al. 1999). So, the neuroprotective function of Htt could be related to BDNF expression which has a neuroprotective feature.

BDNF is transported through vesicle trafficking along the axon toward the end and p150 (Glued) as the subunit of the dynactin, helps intracellular transport by binding to dynein and kinesin-2, and interacts with huntingtin-associated protein 1 (HAP1) to complete BDNF transportation. HAP1 intermediates interaction between Htt protein and cellular motors (Fig. 2c) (Gauthier et al. 2004). Htt is related to synaptic transmission by binding to post-synaptic density protein 95 (PSD95). PSD95 in the post-synaptic densities (PSD) can bind to postsynaptic proteins like *N*methyl D-aspartate (NMDA) and α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) and kainite receptors, which are concentrated in the postsynaptic zone (Fig. 2e) (Sheng and Kim 2002). In the presence of the mHtt, the density of the PSD95 is increased and leads to excitotoxicity, which can damage neurons (Leavitt et al. 2001).

In the most neurodegenerative disorders like AD and PD, mitochondria play crucial roles in the progression of the diseases (Martin 2012). Mitochondria have a central role in the HD, but Htt interacts with some of the cellular processes which are eventuated to mitochondrial activity. HAP1 not only controls the vesicle trafficking but also associates with localization of some organelles such as mitochondria and endoplasmic reticulum (Gutekunst et al. 1998). Neurons as polarized cells not have unique disturbance of the mitochondria. Metabolic demands in various parts of the neurons are completely different, and this feature requires a special mechanism to transport the mitochondria. Htt by binding to HAP1 connects with kinesin and dynein. This connection is the main mechanism in trafficking of the mitochondria in neurons (Caviston and Holzbaur 2009). Htt controls both movements of the mitochondria: anterograde (from cell body to axon terminal) and retrograde (from axon ends toward cell body) (Fig. 2d) (Trushina et al. 2004). Transportation, fusion, and fission are the main mechanisms in controlling the mitochondrial hemostasis. Neurons tightly depend on mitochondria transportation, fission, and fusion (dynamic) for maintaining energy demand, morphology, and structure. During fusion, mitochondria attach to each one and exchange their components. Damaged mitochondria could be recovered by taking healthy ingredients from normal mitochondria. But in the fission, damaged mitochondria are divided into daughter ones to eliminate the unhealthy mitochondria. Normal Htt can control fission and fusion processes through Htt-interacting proteins 1,14 (Hip1,14), endophilin3, clathrin, and dynamin (Fig. 2d) (Bossy-Wetzel et al. 2008). Mitochondria transportation could be affected by disruption in the normal Htt (Trushina et al. 2004), but their interaction details are not understood completely. Choo et al. (2004) provide the presence of the normal huntingtin in mitochondrial outer membrane. This localization makes mitochondria vulnerable to any mutations which Htt could have (Choo et al. 2004). In addition to maintenance of the mitochondrial structure and function, Htt has a role in the regulation of mitochondrial membrane potential (Ismailoglu et al. 2014).

Htt–HAP1 complex regulates autophagy and autophagosome transport in the neurons. Autophagy is the cellular degrading mechanism which is mediated by the formation of the autophagosome to clear damage organelles and misfolded

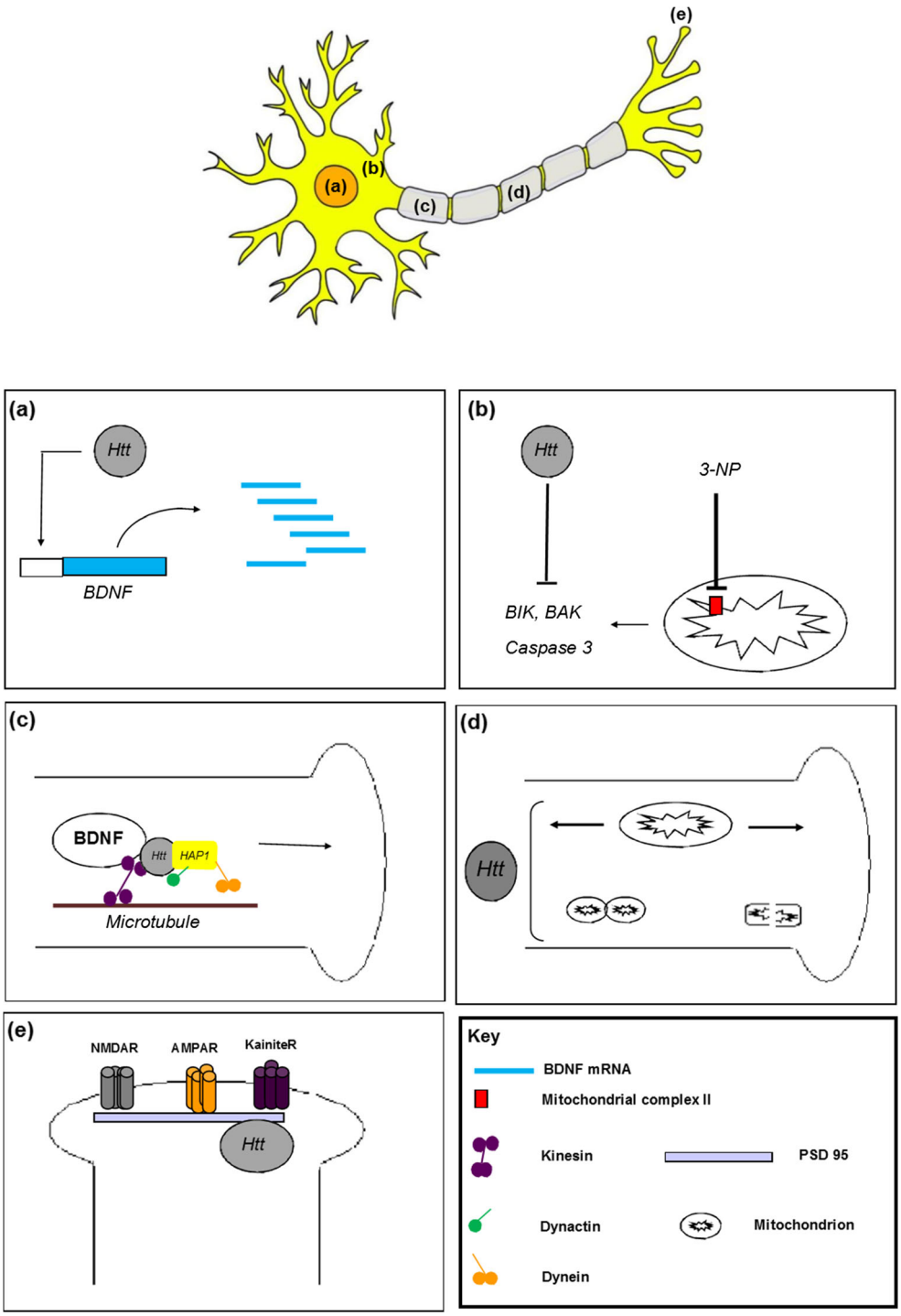

Fig. 2 Major cellular pathways that are controlled by Htt in neuron. **a** Htt can increase the expression of BDNF. **b** 3NP as the chemical for inducing HD-like symptom inhibits mitochondrial complex II and induces BAK, BIK, and caspase-3 activity. Htt inhibits the apoptotic pathway by suppressing BAK, BIK, and caspase-3 activities. **c** Htt by interacting with HAP1, dynactin, dynein, and kinesin helps BDNF transportation through the axon toward axon end. **d** Htt has a role in the mitochondrial trafficking, retrograde and anterograde, and dynamics. **e** Htt binds to PSD-95 at the postsynaptic end. PSD-95 interacts with NMDA, AMPA, and kainite receptors, which are important in excitatory signaling

proteins. Autophagosome follows a retrograde pattern in neurons, and silencing of Htt or HAP1 disrupts this process (Wong and Holzbaur 2014). As well as mitochondrial dynamics, Htt interaction with dynein has a pivotal role in the fusion of the lysosome with autophagosome. Hence, mHtt impairs this fusion and causes accumulation of autophagosomes with non-degraded ingredients in the neurons. Myristoylated Htt controls the formation of autophagosome and autophagy process in the cell. PolyQ expansion at the N terminus promotes Htt to form aggregate and toxic structure. By deposition of the mHtt in the striatum, progress loss of neurons in various parts of the brain is triggered.

Huntingtin in Pathology Form

Not only expansion of CAG repeats in exon 1 but also deletion or inactivation of the Htt can cause HD (O'Kusky et al. 1999; Dragatsis et al. 2000). Amyloid structure of aggregated Htt consists of β sheets with high polyQ domains (Chen et al.

2002; Perutz et al. 1994). mHtt carries more than 40 glutamine residues at the amino terminal. Flexibility of the region between proline-rich domain and polyQ tract is decreased by expansion of CAG repeats. Proline-rich domain inhibits the formation of aggregate protein, but by reducing the flexibility at the N-terminal, protein aggregation is induced (Tam et al. 2009; Caron et al. 2013). In HD, insoluble mHtt could be detected as early hallmark (Orr and Zoghbi 2007). Ubiquitin proteasome system (UPS) is the first stride in the degradation of misfolded proteins and injured organelles, and normal Htt is degraded by this mechanism. The autophagy lysosome system leads to mHtt clearance and deterioration (Ravikumar et al. 2002). We can find large controversies in previous lines of research; some of them believe deficiencies in the UPS system in the HD while other pieces of evidence could not show any disruption in the UPS activity in HD (Bennett et al. 2007; Bett et al. 2006). In HD, autophagosome is increased in number without any ability to bind to substrates, so the autophagy process is affected (Kegel et al. 2000; Martinez-Vicente et al. 2010). mHtt is one of the main reasons that could decrease the axonal transportation of autophagosomes. So, misfolded proteins cannot be cleared and degraded (Jahreiss et al. 2008). Accumulation of mHtt provokes various signaling pathways and influences different cellular activities that all of them cause neuronal death and degeneration.

We outline here some pathological effects of mHtt by focusing particularly on the mitochondria and related signals.

Mitochondria and Neuron

Mitochondria are the major hubs for ATP production in the cells. Moreover, metabolism of the reactive oxygen species (ROS), Ca^{2+} hemostasis, and apoptosis are controlled by mitochondria (Mattson et al. 2008). Neurons as high-demand energy cells need to consume most of the generated ATP for maintaining neuronal activities like neurotransmission and synaptic plasticity (Fontán-Lozano et al. 2008). A wide range of neuronal activities depend on ATP like membrane ion motive ATPase, activities of kinases which are responsible for intracellular signaling, cytoskeleton remodeling, releasing, and recycling neurotransmitters (Chan 2006). Mitochondrial DNA (mtDNA) has a 16.6-Kb size with 13 encoding genes for respiratory chain subunits, 22 tRNA, and 2 rRNA (Larsson and Clayton 1995). Oxidative phosphorylation (OXPHOS) is the process that transfers electrons over electron transport chain (ETC), which includes four complexes (I–IV) in the mitochondrial inner membrane. Complexes I, III, and IV are responsible for relocation of the protons from mitochondrial matrix to the intermembrane space. Potential differences between intermembrane space and matrix as the yield of the proton transferring lead to ATP generation by complex V. Electron transfer during OXPHOS provokes ROS generation specifically super oxide (O^{2-}) (Mailloux 2015). Other sources for mitochondrial ROS are aconitase (ACO), α-ketoglutarate dehydrogenase (KGDH), pyruvate dehydrogenase (PDH), glycerol-3-phosphate dehydrogenase (GPDH), dihydroorotate dehydrogenase (DHOH), monoamine oxidases A and B (MAOA and B), and cytochrome b5 reductase (B5R). But protective strategies against generated ROS such as manganese superoxide dismutase (MnSOD), catalase (Cat), glutathione peroxidase (GPX), phospholipid hydroperoxide glutathione peroxidase (PGPX), glutathione reductase (GR), peroxiredoxins (PRX3/5), glutaredoxin (GRX2), thioredoxin (TRX2), and thioredoxin reductase (TRXR2) are occupied by mitochondria (Winterbourn 1995; Ayala et al. 2014; Lin and Beal 2006). ROS is the principal source of the oxidative stress which is a prevalent circumstance in the neurodegenerative disorders. Superoxide anion radical (O^{2-}), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH–) are the basic elements of the ROS that can oxidize all macromolecules and initiate cell death (Rinnerthaler et al. 2015). Any impairment in the mitochondria increases ROS level in the neurons and triggers neuronal death/degeneration.

Furthermore, mitochondria have essential roles in Ca^{2+} hemostasis by storing it (Gunter et al. 1994). Ca^{2+} stimulates ATP synthesis in the physiological conditions and also works as a stimulator in ROS generation and apoptosis in the pathological state. Ca^{2+} and ROS generation have bidirectional connection (Gordeeva et al. 2003). Ca^{2+} increases respiratory rate, upregulates the OXPHOS system, and elevates ATP synthesis by prompting PDH, isocitrate dehydrogenase, KGDH, and ATP synthase complex (McCormack and Denton 1993; Das and Harris 1990). During mitochondrial ROS generation, Ca^{2+} changes conformation of the ETC complexes and makes more ROS (Brookes et al. 2004). Voltage-dependent anion channel (VDAC) is the main conductor for Ca^{2+} passing through mitochondrial outer membrane (Gincel et al. 2001). Mitochondrial permeability transition pore (mPTP) as a voltage- and Ca^{2+}-dependent channel is responsible for Ca^{2+} inward movement into the mitochondrial matrix through the inner membrane (Crompton 1999). In the presence of the ROS, mPTP is opened and triggers cellular death and apoptosis by releasing cytochrome c (Seidlmayer et al. 2015). The sensitivity of the mPTP to ROS and Ca^{2+} makes amplification loop that causes ROS generation to impair Ca^{2+} entry in a reverse mode (Aon et al. 2003). The importance of the mitochondria to neuronal cells forces cellular mechanisms for quality control (QC) of the mitochondria. Additionally, mitochondria have to move along the axons to provide Ca^{2+} hemostasis and ATP to various parts of the neuron. Numbers of mitochondria and their size are the main concepts of the QC mechanism in the cell. Neuronal cells tightly depend on mitochondrial function and numbers for action potential generation and demanded ATP for metabolism of the neurotransmitters (Sokoloff 1999; Chan 2006). One of the main mechanisms in the QC is mitochondrial fission and fusion. The

functional integrity and density of mitochondria are controlled by monotonous fission and fusion processes. During the fusion process, mitochondria are elongated and connect through outer and inner membrane networking. While during fission, QC acts through removing the damaged mitochondria by mitophagy (mitochondria autophagy) procedure (Gomes et al. 2011). Mitofusin1 (Mfn1), mitofusin2 (Mfn2), and optic atrophy 1 protein (OPA1) are the main factors in the fusion process (Escobar-Henriques and Anton 2013). Fission 1 protein (Fis1) and dynamin-related protein (Drp) 1 are the ingredients of the fission (Elgass et al. 2013). ROS level is the main factor for prompting the fission process. But in the normal conditions and low stress level, fusion is the abundant process in mitochondrial dynamics (Fischer et al. 2012). Joining of mitochondria or fragmentation of them is tightly associated with mitochondrial dysfunction and cell death. In the neurodegenerative disorders and aging-related diseases, disequilibrium between fission and fusion processes plays a central role (Reddy and Reddy 2011). Dominant optic atrophy (DOA) and Charcot–Marie–Tooth disease (CMT) are two neuropathies that associate with mutations in OPA1 and Mfn2 (Delettre et al. 2000; Züchner et al., 2004). Drp1 by having high expression level in the brain plays a pivotal role in the neuron survival. Mutation or posttranscriptional change in the Drp1 causes neuronal death and apoptosis (Kageyama et al. 2012; Cribbs and Strack 2007).

Mitochondria by controlling ATP generation, calcium hemostasis, and ROS level could play central actors in all cells especially neurons. Neurons are postmitotic cells without any ability to regenerate themselves, so disruptions in the activity, integrity, mobility, and hemostasis of the mitochondria have a wide influence on the neuronal function and maintenance.

Mitochondria and HD

Mitochondria are key organelles in the molecular and cellular basis of neurodegenerative disorders like HD. Strategies for finding all aspects of the mitochondrial biology in neurodegenerative disorders could help to identify therapeutic suggestions that mitigate mitochondrial function and density.

In HD, mitochondrial fission is the prevalent process, Drp1 and Fis1 levels are increased by progression of the disease, but Mfn1/2 show low levels of expression in mRNA level (Kim et al. 2010; Shirendeb et al. 2011). In vivo and in vitro studies showed that binding of the mHtt to Drp1 acts as the main trigger of the fission process in HD models (Song et al. 2011); otherwise, mHtt has the ability to enhance Drp1 activity by posttranscriptional modification (Chang and Blackstone 2010). The presence of the abnormal mitochondria could be the inducer of neuronal death and apoptosis. So, removing the mitochondrial defects is the main strategy that the cell uses to protect themselves against apoptosis. This process is known as mitophagy, and it depends on the activity of PTEN-induced putative kinase 1 (PINK1)/parkin pathway (Pickrell and Youle 2015). Parkin as an ubiquitin ligase promotes degradation of fusion proteins like Mfn1/2 and prevents elongation and connection of mitochondrial defects. PINK1 is essential for recruiting parkin in the initiation of the mitophagy process. The last step in the mitophagy is joining the mitochondria to autophagosome–lysosome complex (Ashrafi and Schwarz 2015; Wang et al. 2011). In the HD models, anomalous mitochondria cannot be engulfed by autophagosomes. The main function of the mHtt is interacting with autophagy receptors and blocking them from binding to damaged mitochondria (Martinez-Vicente et al. 2010). Previous studies showed that PINK1 overexpression can influence the mitophagy process by inhibiting mHtt activity (Khalil et al. 2015). Mitochondria are the main organelles in the management of the apoptosis and cell death. Extrinsic and intrinsic pathways are responsible for inducing mitochondria-dependent apoptosis. Intrinsic pathway is set off by cellular stress or damage. In this process, pro-apoptotic Bcl-2 family induces the formation of pores on the mitochondrial membrane. The development of such pores causes cytochrome c and other apoptotic precursors releasing from intermembrane space into the cytoplasm (Youle and Strasser 2008). The discharged cytochrome c engages caspase-9, which activates caspase-3 and caspase-7 as apoptotic enzymes (Slee et al. 1999). The Bcl-2 family is categorized into three groups: antiapoptotic members (Bcl-2, Bcl-xL, Mcl-1, A1, Bcl-b, and Bcl-w), pro-apoptotic BH3 proteins (Bid, Bad, Bim, Bmf, Bik, BNip3, Noxa, Puma, and Hrk), and pro-apoptotic Bax/Bak proteins. In HD, mHtt induces BNip3 expression and previous studies showed high expression level of BNip3 in the HD patients' muscles (Sassone et al. 2010). Preceding findings displayed that ablation of Drp1 and Fis1 inhibits cytochrome c releasing and apoptosis occurring. mHtt is the main actor in the enhancement of the Drp1 and Fis1 expression (Estaquier and Arnoult 2007; Shirendeb et al. 2011). Therefore, fission proteins like Drp1/Fis1 potentially have apoptotic roles by releasing cytochrome c from the mitochondria into the cytoplasm. But about fusion proteins and apoptosis controversy, lines of evidence have been reported. Some findings reveal this hypothesis that apoptosis and cytochrome c releasing are decreased by overexpression of the Mfn2 (Jahani-Asl et al. 2007), while other studies showed the inhibitory effects of Mfn2 on cytochrome c but not apoptosis (Neuspiel et al. 2005). Sheridan et al. (2008) reported that Mfn1/2 and Opa1 overexpressions never affect apoptosis rate or released cytochrome c. mHtt could be a potent modulator for mitochondrial fission and apoptosis.

Previous studies reported various changes in neurons because of mHtt, which has the ability to amend the expression of some genes and repressor/activators (Sipione et al. 2002). p53, cAMP response element binding protein (CREB), peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α), TAFII130, BDNF, and CREB binding protein

(CBP) are the main targets for mHtt in transcriptional levels (Steffan et al. 2000; Cui et al. 2006; Zhai et al. 2005).

p53 as a tumor suppressor gene is induced during cellular stresses, DNA damage, and activation of oncogenes. In vitro and in vivo studies showed that active p53 increases *HTT* expression. Also, p53 is induced by mHtt. And this bidirectional connection between them causes enhancement of mHtt in the activation of p53 (Jin and Levine 2001; Feng et al. 2006). In addition, p53 has a role in mitochondrial biogenesis (Donahue et al. 2001).

ATP depletion is the main character in the neurodegenerative disorders such as HD. Neurons as high energy demand cells need high ATP level for many functions such as neurotransmission, synaptic function, and axonal maintenance. Mitochondrial biogenesis along fission and fusion is the main regulator for ATP hemostasis. PGC1α is a key regulator of mitochondrial metabolism and maintenance of the energy and lipid hemostasis (Villena 2015). PGC1α has a central role in mitochondrial biogenesis through activation of various factors such as nuclear respiratory factor 1/2 (NRF1/2) (Wu et al. 1999), peroxisome proliferator receptor α and γ (Vega et al. 2000; Mazzucotelli et al. 2007), estrogen-related receptor α (ERRα) (Schreiber et al. 2004), and thyroid receptor (TR) (Zhang et al. 2004). NRF1 and NRF2 regulate mitochondrial transcription factor A (TFAM), which increases mtDNA copy numbers (Kang and Hamasaki 2005). mtDNA encodes most parts of the ETC which generates ATP in the cell. So, by increasing mtDNA and mitochondrial biogenesis, cellular ATP level will be increased. CREB is a potent regulator of PGC1α (Fig. 3) (Wu et al. 2006) and regulated by cellular AMP/ATP ratio (Hardie 2011). Transcriptional level of PGC1α was analyzed in postmortem samples from HD

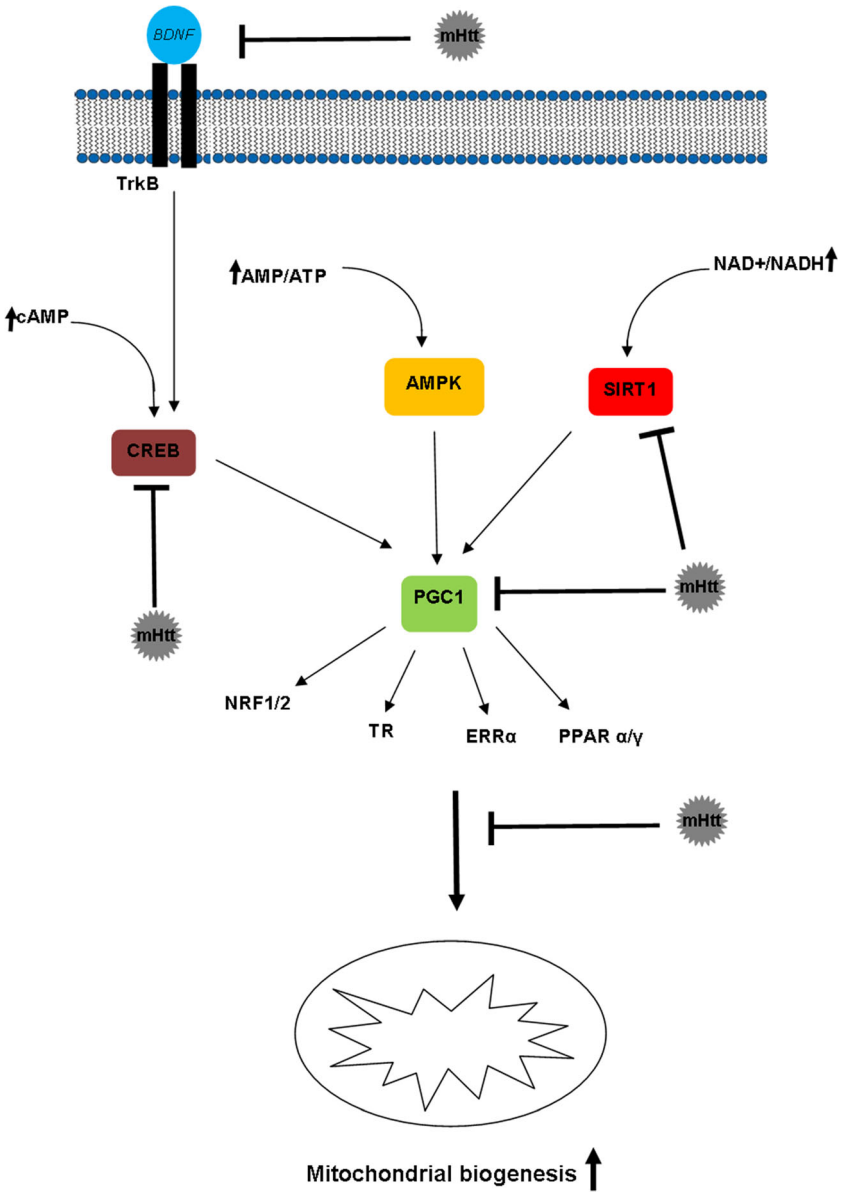

Fig. 3 Mitochondrial biogenesis is induced by AMPK, CREB, SIRT1, and BDNF. In the AMP/ATP high ratio, AMPK is activated and influences PGC1α, which is the main coactivator in the mitochondrial biogenesis. PGC1α increases mitochondria levels through NRF1/2, TR, ERRα, and PPARα/γ. High amount of NAD+ activates SIRT1, which deacetylates PGC1α and induces its activation. CREB is in active form when cAMP level is high in the cell. Moreover, BDNF can induce CREB activity through TrkB receptors. PGC1α is one of the main downstream for CREB. mHtt inhibits most of the signaling, which are responsible in the mitochondrial biogenesis

patients. Their striatum showed low transcriptional and protein levels of PGC1α. mHtt influences PGC1α level through CREB activity (Lin et al. 2004a, b; Cui et al. 2006). Reduction in the PGC1α level declines cytochrome c and complex IV expression in HD (Martin et al. 2011). By decreasing mitochondrial biogenesis through mHtt effects on PGC1α, anaerobic metabolism is increased in the basal ganglia and hippocampus of the HD patients, which leads to lactate generation and accumulation in those regions (Herben-Dekker et al. 2014).

Sirtuin 1 (SIRT1) as a NAD-dependent deacetylase protein is activated in the high NAD^+/NADH ratio (Lin et al. 2004a, b). SIRT1 deacetylates histones H3 and H4 likewise transcription factors or their coactivators such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), p53, peroxisome proliferator-activated receptor γ (PPARγ), and PGC1α (Saunders and Verdin 2007; Picard et al. 2004). Deacetylation by SIRT1 is one of the mechanisms that activates PGC1α (Lagouge et al. 2006). NAD+ as the main inducer of the SIRT1 protects axons against degeneration (Araki et al. 2004). Therefore, we can conclude that SIRT1 activation could protect neurons against degenerative mechanisms. mHtt has the ability to increase acetylation of the SIRT1 substrates. Additionally, mHtt interferes with the deacetylation activity of the SIRT1 and decreases the deacetylation of the targets (Jiang et al. 2011). In HD, modulation of the SIRT1 could alter energy metabolism through modification of mitochondrial biogenesis and function (Fig. 3).

AMP-activated protein kinase (AMPK) is the main sensor for cellular energy content, and its activation depends on cellular AMP/ATP ratio. AMPK reduces cellular anabolism in the presence of the high AMP level. By increasing the activity of the AMPK, PGC1α expression is increased (Terada et al. 2002). So, PGC1α can play a mediator role in mitochondrial biogenesis through AMPK (Fig. 3). Activation of the AMPK shows neuroprotective effects in HD mouse models (Ma et al. 2007). AMPK localization into the nucleus was observed in the striatal neurons of the HD in human and mouse model (Chou et al. 2005). mHtt is the main cause of AMPK localization into the nucleus. In this situation, AMPK downregulates the Bcl-2 family which leads to apoptosis (Ju et al. 2011). Moreover, PGC1α overexpression protects neurons across degeneration in HD models by increasing the ATP level and mitochondrial biogenesis (McGill and Beal 2006). SIRT1 and AMPK are upstream factors in the expression of PGC1α. mHtt also decreases ATP synthesis and mitochondria bioenergetic activities through disrupting structural integrity of mitochondria (Ismailoglu et al. 2014).

BDNF has a key role in the development and survival of the neurons. Tropomyosin receptor kinase B (TrkB) acts as a BDNF receptor and is highly expressed in the adult brain (Murer et al. 2001). TrkB activates various small G proteins after binding to BDNF. In one of the main downstream in the BDNF/TrkB signaling pathways, CREB has a central role and activates PGC1α (Pizzorusso et al. 2000; Volakakis et al. 2010). Therefore, BDNF not only controls neuronal development and maintenance but also has a role in mitochondrial biogenesis through CREB. mHtt influences BDNF level and transportation along the axon (Fig. 3) (Zuccato et al. 2001; Gauthier et al. 2004). By decreasing the transportation of the BDNF, neuronal survival, maintenance, and energy hemostasis will be altered. In HD patients, BDNF level is decreased in striatum and it could be a reason for progression of the disease (Zuccato and Cattaneo 2007).

Alteration in mitochondrial function and integrity influences Ca^{2+} hemostasis in neurons. mHtt increases Ca^{2+} influx into the mitochondria, which leads to apoptosis and ATP synthesis impairment. mHtt induces opening of the mPTP channels, which are important in Ca^{2+} buffering and cytochrome c releasing. HD patients and mouse models show impairment in Ca^{2+} hemostasis, which may be induced directly or indirectly by mHtt (Bernardi 1999; Panov et al. 2002).

Recent studies showed that alteration in mitochondrial activity and biogenesis has the abilities to protect striatal neurons against mHtt toxicity. For example, restoring mitochondria complex IV activity in HD transgenic mice acts as a neuroprotective agent (Bae et al. 2005). PGC-1α overexpression in in vitro and in vivo models of HD ameliorates toxicity of mHtt and protects striatal neurons against degeneration (Weydt et al. 2006; Cui et al. 2006). In addition, upregulation of superoxide dismutase 2 (SOD2), mitochondrial form of the superoxide dismutase, can protect neurons in HD model (Madhavan et al. 2008). Khalil et al. (2015) reported that PINK1/parkin pathway has the ability to alleviate mitochondrial defects in HD model. In summary, some pieces of evidence support this hypothesis that modulation of mitochondrial activity and related signaling pathways could slow the progression of HD.

Conclusion

Neurodegenerative diseases such as HD tightly correlate with mitochondrial activity and biogenesis. Mitochondrial dysfunction and ATP depletion are the main characteristic markers in neurodegeneration. Mitochondria in neurons as highly dynamic organelles in structures and functions have crucial roles in the various neuronal activities. Transportation of the neurotransmitters, releasing of cargos in the synaptic cleft, and maintenance of ATP level for neurons depend on mitochondrial activity and integrity. mHtt influences mitochondrial dynamics and biogenesis in HD models. OXPHOS dysfunction, fragmentation of mitochondria, and decline in the biogenesis are the important factors that are modified by mHtt. Increasing cellular ATP level could be a potential therapeutic

target in neurodegenerative disease especially HD. By modulation of mitochondria in neurons, mHtt may not be able to influence mitochondrial dynamic and function vastly in the cell.

Enhancement in mitochondrial biogenesis affects various signaling pathways which leads to neuroprotection. In HD, mitochondria are the main targets for mHtt, which easily modulates dynamic and biogenesis of them. Therefore, manipulation of the mitochondria dynamics and density could be candidate for therapeutic approaches in HD.

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