ISSN 0006-2979, Biochemistry (Moscow), 2018, Vol. 83, No. 9, pp. 1030-1039. © Pleiades Publishing, Ltd., 2018.
Original Russian Text © S. N. Illarioshkin, S. A. Klyushnikov, V. A. Vigont, Yu. A. Seliverstov, E. V. Kaznacheyeva, 2018, published in Biokhimiya, 2018, Vol. 83, No. 9, pp. 1299-1310.

REVIEW

Molecular Pathogenesis in Huntington's Disease

S. N. Illarioshkin[1,a,b]*, S. A. Klyushnikov[1,2], V. A. Vigont[2,c], Yu. A. Seliverstov[1], and E. V. Kaznacheyeva[2,c]

[1]*Research Center of Neurology, 125367 Moscow, Russia*
[2]*Institute of Cytology, Russian Academy of Sciences, 194064 St. Petersburg, Russia*
[a]*e-mail: snillario@gmail.com*
[b]*e-mail: center@neurology.ru*
[c]*e-mail: cellbio@incras.ru*

Received May 21, 2018
Revision received May 31, 2018

Abstract—Huntington's disease (HD) is a severe autosomal dominant neurodegenerative disorder characterized by a combination of motor, cognitive, and psychiatric symptoms, atrophy of the basal ganglia and the cerebral cortex, and inevitably progressive course resulting in death 5-20 years after manifestation of its symptoms. HD is caused by expansion of CAG repeats in the *HTT* gene, which leads to pathological elongation of the polyglutamine tract within the respective protein – huntingtin. In this review, we present a modern view on molecular biology of HD as a representative of the group of polyglutamine diseases, with an emphasis on conformational changes of mutant huntingtin, disturbances in its cellular processing, and proteolytic stress in degenerating neurons. Main pathogenetic mechanisms of neurodegeneration in HD are discussed in detail, such as systemic failure of transcription, mitochondrial dysfunction and suppression of energy metabolism, abnormalities of cytoskeleton and axonal transport, microglial inflammation, decrease in synthesis of brain-derived neurotrophic factor, etc.

DOI: 10.1134/S0006297918090043

Keywords: Huntington's disease, molecular pathogenesis, polyglutamine expansion, proteolytic stress, transcription dysregulation, mitochondria

Huntington's disease (HD) is a severe autosomal dominant neurodegenerative disorder with the mean age of onset around 30 years. The mean prevalence of HD in the world is 5.5 cases per 100,000 people [1]. Clinically, it is characterized by a combination of inevitably progressing motor (chorea, dystonia, bradykinesia, myoclonus), cognitive, and psychiatric symptoms due to atrophy of the basal ganglia (primarily, striatum) and the cerebral cortex [2, 3]. There is no cure for HD so far, and the death usually occurs 5-20 years after the first clinical signs and symptoms emerge [2].

HD is caused by a pathological increase in the number of copies (expansion) of the glutamine encoding CAG repeats in the exon 1 of the *HTT* gene (4p16.3) [4]. This mutation leads to elongation of the polyglutamine tract within the gene product called "huntingtin", therefore HD is considered as one of the so-called polyglutamine diseases [5]. The pathologically elongated CAG tract is characterized by genetic instability both in gametogenesis (especially in spermatogenesis) and in somatic tissues; the size of the expanded *HTT* allele to high extent determines polymorphism of the HD clinical features [6, 7]. Number of CAG repeats in the mutant allele inversely correlates with the age of disease onset [8-10] and with the age at the time of death [11]. We were the first to show [12] that the number of CAG repeats directly correlates with a rate of HD progression, which was confirmed later by other authors [13, 14]. However, the mutation determines around 66% of variability in the course of HD, which underlines the role of different modifying factors in this disorder [8, 15].

The replication "slippage" is likely to be a possible mechanism of arising of trinucleotide repeat expansion [16]. In meiosis, DNA polymerase, which replicates DNA molecule and moves along the chain of the template, loses orientation of the nucleotide with formation of a "loop" on the complementary chain and continues the synthesis from incorrect position. The probability of such "slippage" greatly increases in replication of DNA

Abbreviations: BDNF, brain-derived neurotrophic factor; CNS, central nervous system; HD, Huntington's disease; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α.

* To whom correspondence should be addressed.

regions containing repeated nucleotide sequences [17]. An aberrant activity of enzymes (MSH2, OGG1) responsible for repair of single-stranded DNA breaks can have a similar result. For example, in transgenic HD mice, inactivation of these enzymes is associated with a significant decrease in the instability of CAG repeats [7].

Homologs of the *HTT* gene were found in many evolutionary distant organisms, beginning from ameba [18], which indicates a highly conservative role of huntingtin in a cell. Huntingtin is supposed to be a molecular "hub" connecting different proteins into complexes or, on the contrary, promoting their dissociation for the fine coordination of cellular processes [19]. Huntingtin is associated with cell membranes and can participate in dynamics of the vesicular transport [7, 20], in synaptic transmission [21], and in regulation of autophagy [22]. It is hypothesized that huntingtin plays a role in the embryogenesis and formation of the nervous system, in control of the neuron survival, signal transduction, and cell adhesion [3, 19]. The final conclusion regarding specific biological role of huntingtin has yet to be formed.

HD AND PROTEOLYTIC STRESS

A universal pathobiochemical mechanism of HD and other polyglutamine diseases has a *conformation-dependent* character. It has been shown that exceeding the number of glutamine residues in a protein above a certain threshold (normally, about 35 copies) leads to a gradual transformation of the protein α-helix into β-folded chains. Those chains get cross-linked into high-molecular-weight antiparallel strands by the mechanism of polar "zippers" and represent a structural basis of amyloid complexes formed in cells [19, 23]. The polyglutamine aggregation in neurons is triggered by the post-translational *N*-terminal proteolysis of huntingtin by caspases, calpains and other endoproteases; in the truncated *N*-terminal fragments, the mutant polyglutamine tract is exposed to surrounding substrates and, therefore, is maximally "aggressive" [24, 25]. In experiments, the truncated molecules of huntingtin form the highest number of polyglutamine-containing aggregates in neurons *in vitro* and lead to the earliest and most severe behavioral disorders in transgenic mice *in vivo* [26]. It should be added that the *N*-terminal fragment of huntingtin may emerge in cells not only as a product of proteolysis of the full-size molecule but also as a result of the aberrant splicing, because the CAG-expansion promotes (i) disturbance of the *HTT* primary transcript processing and (ii) synthesis of a certain amount of mRNA encoding only the *HTT* exon 1 [3].

The neurodegenerative cascade in HD is initiated after translocation of the *N*-terminal fragment into the nucleus of the neuron [27]. Cleavage of polyglutamine proteins facilitates their penetration into the nucleus, because only peptides with molecular mass <46 kDa can be easily transported across the nuclear membrane. The impact of the nuclear localization of the mutant molecules on neuronal death in various polyglutamine diseases was confirmed in experiments: expression of recombinant mutant proteins with the inactivated nuclear signaling epitope (resulting in protein retention in the cytoplasm) or with an inserted additional exporting sequence (stimulating the protein exit from the nucleus into the cytoplasm) significantly decreased protein toxicity [28, 29].

Selective proteolysis and nuclear translocation of the expanded polyglutamine fragment of huntingtin are now considered the earliest link in the molecular pathogenesis of HD.

Spherical amyloid-like inclusions containing elongated polyglutamine chains and ubiquitin have been detected in nuclei of degenerating neurons, which confirms the role of conformational changes of the mutant huntingtin and/or its fragments in the HD development [30, 31]. Formation of such inclusions is a universal pathological process because it occurs not only in HD patients but also in neurons of transgenic mammals [32] and of drosophila [33], and in cultures of specialized neurons [34] expressing elongated CAG-tracts of *HTT*. Studies on transgenic animals have shown that the formation of intranuclear inclusions precedes the development of the neurological dysfunction [31, 32].

The presence of ubiquitin in the inclusions indicates the role of the extralysosomal selective ubiquitin-proteasomal pathway in mutant huntingtin degradation. It has been shown that huntingtin directly interacts with the ubiquitin-conjugating enzyme E2 [35] and that the proteasomal complex components – the proteolytic 20S nucleus and the regulatory subunit 19S – are associated with the intranuclear inclusions [26]. We [34] and other authors [36] have shown on models of HD and similar disorders that administration of proteasome inhibitors enhances aggregation of mutant molecules in the neurons. However, the efficiency of degradation of polyglutamine aggregates through the ubiquitin-proteasomal mechanism remains low, because the expanded polyglutamines form an energetically stable structure that prevents entry of the molecule into the proteolytic chamber of the 20S subunit [37]. Therefore, binding of the proteasomal components by the intranuclear inclusions is "idle" and results only in exhaustion of proteasomes in the cell leading to further increase of the levels of abnormal huntingtin conformers.

In response to formation of ubiquitinylated aggregates, a system of auxiliary chaperone proteins is activated in the neurons. Thus, expression of the chaperone Hsp70 is increased in $(Glu)_n$-transfected cell lines, and it specifically binds to the polyglutamine aggregates and intranuclear inclusions [5]. However, the level of chaperone proteins in the cell decreases with progression of the disease [38], and impairment of the ability of neurons to

rapidly react to cellular stresses by mobilization of chaperones completes formation of a "vicious circle" and exacerbates the neurodegenerative changes.

The insufficiency of the ubiquitin-proteasomal/chaperone degradation of the mutant huntingtin in HD leads to activation in the cells of the alternative and more conservative proteolytic pathway – the lysosomal autophagy [39]. Activation of autophagy has been shown to be the most important compensatory pathway for preventing the huntingtin toxicity in transgenic models of HD in mice, drosophila, and cell cultures [40, 41]. However, in chronic mutant huntingtin expression in neurons, this pathway becomes compromised with the time. This happens due to impairment of mechanisms for recognition of the mutant huntingtin in cells, dysfunction of endoplasmic reticulum in its interaction with the expanded polyglutamines, as well as due to suggested disturbance in the role of the mutant huntingtin in the immediate regulation of autophagy [22, 39].

Thus, pathological features of the expanded polyglutamine chains in HD and other similar diseases lead to *systemic failure of proteostasis* in neurons [42]. This systemic failure with a final collapse manifests itself on different levels of maintenance of the protein metabolism stability and clearance (the ubiquitin proteasomal pathway, lysosomal autophagy, functioning of the endoplasmic reticulum, the system of molecular chaperones, etc.) [3, 42].

When analyzing neurotoxicity and developing approaches for molecular therapy in HD, it is necessary to clearly differentiate the "early" (the most pathogenic) polyglutamine-containing peptide fragments and their final product – the polyglutamine inclusions formed in cells. Despite the numerous evidences that formation of the intranuclear inclusions is a natural phenomenon in the development of polyglutamine diseases, the interpretation of the cause–effect relationships between the appearance of inclusions and the degeneration of neurons still remains unobvious. Thus, there is no strict correlation between the neurons most prone to degenerative changes and the neurons containing the greatest number of intranuclear inclusions in HD and other polyglutamine diseases [5, 25]. A certain dissociation between the number of inclusions and intensity of neurodegeneration has been observed also in transgenic mice with expression of the mutant huntingtin [32] and in the cell models of HD [28, 43]. All these findings enable an assumption that the formation of intracellular polyglutamine-containing inclusions is only an epiphenomenon, i.e. a by-product of a parallel pathologic process [25]. Moreover, the inclusions can be a kind of a protective reaction of cells to conformational changes of the mutant protein – it is supposed that the polyglutamine aggregates can facilitate binding and thus neutralization of neurotoxic *N*-terminal fragments under conditions of exhaustion of functional abilities of the proteostatic system of a cell [5, 25]. In experiments, inhibition of ubiquitinylation affected the mechanism of detoxification of polyglutamine conformers and suppressed the formation of inclusions concurrently with promoting the neuron death [44].

Regardless of whether polyglutamine-containing inclusions are simple markers or active participants of the pathological process, their appearance is characteristic for the advanced stage of neurodegeneration. However, current knowledge about the course of polyglutamine diseases in humans and transgenic animals suggests a two-stage model of pathogenesis, with the prolonged period of neuronal dysfunction followed by the relatively short period of neuronal loss [3]. Therefore, the major task that determines the development of approaches for treatment of HD and other similar diseases is to discover mechanisms of neurotoxicity of polyglutamine-containing protein molecules during the early stage of their expression in the cell and especially in the cell nucleus. For today, several key mechanisms can be distinguished – transcription dysregulation, disorders in the mitochondria functions and in the energy metabolism, defects of the cytoskeleton and axonal transport, induction of neuroimmune inflammatory reactions, oxidative stress, and loss of own physiological functions of huntingtin.

POLYGLUTAMINES AND SYSTEMIC DISORDERS IN TRANSCRIPTION

To possess its neurotoxicity, the mutant huntingtin has to be localized within the nucleus, and, therefore, it is reasonable to suppose that the molecular pathogenesis of HD is directly related to the processes within the nucleus. Since the glutamine tracts are often found in transcription factors and are responsible for protein–protein interactions at the activation of transcriptional complexes, a hypothesis of *transcriptional dysregulation* has been proposed for polyglutamine diseases. According to this hypothesis, the mutant polyglutamine-containing peptide molecules, being accumulated in the nucleus of neurons, aberrantly interact with different transcription factors and violate their functions [45].

Binding and inactivation of some polyglutamine-containing transcription factors by the mutant huntingtin or by its fragments was directly confirmed in experiments as the neurotoxicity basis. The most studied mechanism of that kind is a pathological interaction of huntingtin with the CREB-binding protein (CBP), which is involved as a transcription co-activator in the activity regulation of multiple genes through acetylation of histones and remodeling of chromatin structure [46]. The strength of this interaction is proportional to the length of the polyglutamine tract [47]. A number of other transcription factors (SP1, NF-κB, NeuroD, p53), transcription activators/repressors (TAFII130, CA150, NCOR, REST/NRSF) and nuclear receptors (LXRα, PPARγ, TRα1)

were also identified as targets for binding to the *N*-terminal domains of huntingtin [19, 48, 49]. Through these interactions, huntingtin can influence an extremely wide spectrum of cell functions on the level of transcriptional networks. For instance, huntingtin can affect the mechanisms of cell cycle control, apoptosis, DNA repair, etc. by interfering the transcription of such a key cellular regulator as p53 [19].

A direct link between transcriptional dysregulation mediated by the mutant huntingtin and the mechanisms, which maintain structural and functional integrity of the brain, is exemplified by the brain-derived neurotrophic factor (BDNF). The normal full-size huntingtin has been shown to facilitate the BDNF expression in the cortical neurons through the binding and inactivation in the cytosol of the repressor peptide REST, which is a negative regulator of transcription. On the contrary, the expanded polyglutamine fragments actively transport REST into the nucleus, where they provide formation of the repressor complex on the *BDNF* gene promoter and thus suppress the expression of this neurotrophic factor in the cerebral cortex [50].

Huntingtin may influence transcription of the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), a regulatory protein, which plays an important role in the modulation of the number and functional properties of mitochondria [51]. It is also supposed that dysfunction of the own transcriptional activity of huntingtin, caused by expression of the pathologically elongated polyglutamine tract, can contribute to the development of HD [19].

The results of numerous studies have shown that the transcriptional dysregulation in HD is systemic in nature and can affect dozens of genes. This has been demonstrated in the post-mortem brains from HD patients and in various tissue specimens from transgenic HD mice [45]. Therefore, from the functional viewpoint, HD and other polyglutamine disorders are sometimes considered as *transcription pathologies* [46].

MITOCHONDRIAL DYSFUNCTION AND DISORDERS OF ENERGY METABOLISM

In 1993, Beal et al. showed that a long-term treatment with 3-nitropropionic acid (a mitochondrial toxin) caused in laboratory animals a selective death of medium-sized spiny neurons of the striatum, i.e. the typical pathology observed in HD [52]. Based on these data, it was proposed for the first time that mitochondrial dysfunction could underlie the pathogenesis of HD, or, at any rate, explain the predilection of the neurodegenerative process to the striatum cells. The subsequent works demonstrated a decrease in the enzymatic activity of the complexes II, III and IV of the mitochondrial chain of oxidative phosphorylation and activity defects of the Ca^{2+}-dependent mitochondrial enzyme aconitase in the striatum neurons solely but not in the cerebellum or fibroblasts of HD patients [53, 54].

The conception of the energy metabolism disruption in HD patients was confirmed by *in vivo* functional neuroimaging studies. For example, study with a positron-emission tomography (PET) found decreased glucose metabolism in some regions of the cerebral cortex and throughout the whole striatum in HD patients, whereas proton MR-spectroscopy study showed an increased level of lactate in the striatum [46, 55]. Clinical observations (a progressive weight loss in HD patients despite a highly caloric nutrition) and morphological data (pathology of the mitochondrial ultrastructure in the cortical neurons, decrease in the number and size of mitochondria in the post-mortem brains) also confirm a bioenergetic insufficiency and mitochondrial dysfunction in HD [54]. In central nervous system (CNS) neurons of both HD patients and transgenic animals expressing constructs based on the mutant huntingtin, various signs of disorders in the mitochondrial dynamics were found, i.e. changes in the mitochondrial gene expression, decrease in the immune reactivity of proteins of the cytochrome system, increase in the level of markers of oxidative damage of DNA [56].

Those defects of the mitochondrial homeostasis in HD can be explained by a direct unfavorable influence of the expanded *N*-terminal fragments of huntingtin on mitochondria [57]. For example, mutant polyglutamine chains can directly bind to the proteins of mitochondrial division/fusion and to the proteins of axonal transport and change their enzymatic activity [54]. Disorders of the mitochondrial dynamics lead to failure of *mitophagy* that is a kind of lysosomal macroautophagy associated with degradation of abnormal mitochondria in cells [58]. All of this is accompanied by accumulation of the impaired mitochondria in the cytoplasm and oxidative damage of cell membranes [59].

Another specific mechanism of negative impact of huntingtin on mitochondria, which has already been described above, is associated with modulation of transcription of a mitochondrial protein PGC-1α, which is being extensively studied by cell biologists [51]. A decrease in the level of PGC-1α mRNA was shown in cell lines of striatum neurons expressing the mutant huntingtin, as well as in the cells of transgenic HD animals and in autopsy brain specimens derived from HD patients [54]. PGC-1α is a unique regulator of the complicated network of transcriptional programs involved in biogenesis and thermoregulation of mitochondria and also in their reaction to caloric load. These functions are realized due to modulation of expression of genes activated by one of peroxisome receptors subtypes – peroxisome proliferator-activated receptor γ (PPARγ) [60].

PGC-1α is highly expressed in the brain where its involvement in biogenesis of mitochondria and in modu-

lation of energy metabolism can be critical for survival and normal functioning of the neurons [46]. This has been confirmed by a severe cerebral pathology observed in mice deprived of PGC-1α (*PGC-1α*$^{-/-}$). Those animals have an impaired thermoregulation, pronounced motor hyperactivity, myoclonus, dystonia and other signs and symptoms with a severe cachectic state which reminds the HD phenotype, as well as degeneration of the cortex, thalamus and basal ganglia (mostly striatum) which is also similar to HD features [61, 62]. Expression of mitochondrial genes in these animals is markedly decreased. Similarly to HD patients, transgenic mice expressing the mutant *N*-terminal fragment of human huntingtin have a significantly decreased expression of the PGC-1α-targeted genes in peripheral tissues and striatum; those genes are involved into regulation of the mitochondrial oxidative metabolism [46]. A number of other transgenic HD models on different biological species confirm the role of pathological interaction of the mutant polyglutamine chains and PGC-1α in the development of neurodegeneration [54].

The polyglutamine-mediated pathology of PGC-1α and its targets illustrates connection between the two key elements of the molecular pathogenesis in HD – the transcriptional dysregulation and mitochondrial dysfunction.

DISORDERS OF CYTOSKELETON AND AXONAL TRANSPORT

Specialized morphology of neurons suggests that the structural and functional integrity should be maintained throughout their unique "cellular geometry" – from the cell body, where gene transcription and protein synthesis occur, to the distal part of axons whose length in humans can be up to 1 m. Therefore, during the evolution the most complicated transport system has been created in neurons. This system is responsible for a permanent flow of proteins and other metabolic substrates, as well as of "building material" (components of ion channels and membrane receptors, precursors of synaptic vesicles, mitochondria, signaling molecules, neurotrophic factors, neurotransmitters) from the cell body to synaptic terminals and backwards. This process depends on the condition of the cytoskeleton microtubules and is directed by proteins from the families of kinesins and dyneins [56]. The anterograde transport towards the synaptic terminals is provided by kinesins, whereas dyneins are responsible for the retrograde delivery of substrates into the body of neurons. Disorders in the axonal transport lead to accumulation of protein complexes and fragments of cellular organelles in neurons that causes their dysfunction and a gradual development of degenerative changes.

There are two main mechanisms which lead to dysfunction of the neuronal transport apparatus in HD [63]. The first mechanism suggests that huntingtin may play an important role in the antero- and retrograde transport of different organelles in axons and dendrites. This can be achieved either directly – through a physical interaction of huntingtin with dynein, or indirectly – through the huntingtin-associated protein 1 (HAP1); this protein is associated with the p150^{Glued}-subunit of dynactin and with a protein KIF5C from the family of kinesins [19, 63]. It is also supposed that huntingtin can act as a molecular carcass for glyceraldehyde phosphate dehydrogenase (GAPDH) and other enzymes involved in energy metabolism, thus optimizing local energy expenditures for the rapid axonal transport and accelerating movement of vesicles along microtubules [64]. It has been shown that expansion of polyglutamine chains or suppression of the normal huntingtin expression through RNA-interference lead to disintegration of the HAP1/p150^{Glued} complex with the microtubules, which is accompanied by suppression of the rapid axonal transport and of subsequent synaptic release of the neuropeptide BDNF [65].

Another mechanism of the polyglutamine-mediated disruption of the axonal transport in HD is thought to be associated with a steric inhibition of the microtubular flow as a result of increasing aggregation of the mutant huntingtin molecules and its fragments in cytosol [66]. It has been shown that accumulation of the mutant huntingtin in neurons is associated with the mitochondria transport inhibition in axons [56]. Impairment of the transporting function of axon in HD may result in accumulation of "intermediate" non-lysed autophagosomes whose maturation is inhibited as the pathology of the lysosomal autophagy gradually progresses [39].

NEUROINFLAMMATION, MICROGLIA, AND OXIDATIVE STRESS

The term "neuroinflammation" is traditionally referred to changes in the CNS associated with infiltration of the brain with peripheral immune cells as the blood-brain barrier (BBB) breaks due to infections, scull-brain injury, stroke, etc. However, at present, neuroinflammation is considered in the broader context as an important component of pathogenesis in a number of neurodegenerative diseases, when in the presence of intact BBB, inflammation in the brain is determined by expression of cytokines and activation of microglia [67]. Microglia is represented by residential immune cells of the CNS similar to peripheral macrophages, which supervise the brain for detecting damages or heterogenous antigens [68].

The microglial activation is accompanied by an increase in the density of benzodiazepine-binding sites on the external mitochondrial membrane, and, therefore, this process can be visualized in both experimental and

clinical conditions by PET using the ^{11}C-labeled ligand of benzodiazepine receptors PK-11195 [69]. The neuroimaging studies showed that the microglial activation was an early sign of the HD pathology, in particular, during the premanifest stage [70, 71]. In premanifest HD mutation carriers, the level of glial activation closely correlated with the predicted age of HD onset, calculated based of the number of CAG repeats. The microglial activation in premanifest HD mutation carriers can be detected even 15 years before the predicted onset of HD symptoms, which approximately coincides with appearance in their blood of interleukin 6 [67]. The autopsy study confirmed the activation of microglia, mainly in the most affected regions of the brain (striatum and cerebral cortex), with a high correlation of the glial activation and severity of the cerebral pathology [70].

Mechanisms of the microglial activation in HD are not completely clear, but such reaction is specific for these cells, because expression of the mutant huntingtin is not accompanied by induction of proinflammatory gene networks both in peripheral macrophages of the transgenic animals or in monocytes of HD patients [72]. It could be speculated, that the polyglutamine tract influences the transcriptional activity of some proinflammatory genes (*PU.1*, *C/EBP*, etc.) in the microglial cells [67]. A direct induction of aseptic inflammation in the extracellular space by the mutant polyglutamine-containing fragments of huntingtin is another possible mechanism. This was confirmed by findings in the transgenic mice selectively expressing the mutant huntingtin in the microglia cells – a stereotaxic injection of a lipopolysaccharide into the striatum, which induced a sterile inflammation, was sufficient for development of neurodegeneration and characteristic HD-like neurological syndrome [67].

Neuroinflammation in the brain in HD is closely related to the development of oxidative stress induced by the mutant huntingtin [73]. Expression of the mutant huntingtin is accompanied by hyperproduction of free radicals in the neurons and other cells [74]. Reactive oxygen and nitrogen species may be considered as a "universal weapon" of the activated microglia aimed at destruction of the trigger that caused the inflammatory reaction [75]. However, if the microglial response goes out of control and gets a chronic course, the developing oxidative stress becomes an independent factor of neurodegeneration that affects DNA, lipids, and proteins. The same scenario applies to HD with pathological iron deposition in the brains of HD patients, given that iron is an inducer of reactive oxygen species; huntingtin is a Fe^{2+}-regulated protein, and the mutant polyglutamine-containing huntingtin inclusions act as Fe^{2+}-depending centers of oxidative stress [76]. Concurrently, in patients with HD, a hyperexpression of antioxidant genes is observed as an adaptive response to the uncontrolled production of free radicals [77].

OTHER MECHANISMS OF MOLECULAR PATHOGENESIS IN HD

The study on transgenic mice expressing the mutant huntingtin showed that the activation of N-methyl-D-aspartate (NMDA) receptors of glutamate was quite an early neurophysiological disturbance in HD. That activation was accompanied by excitotoxicity and an increase in the level of intracellular Ca^{2+} in the affected neurons [77]. On the one hand, the glutamate excitotoxicity is directly associated with the progressive mitochondrial pathology and with oxidative stress and is an unavoidable component of the corresponding molecular cascades [51]. On the other hand, considering a specific influence of the expanded polyglutamines on astrocytes and the decisive role of the astrocytic glia in the glutamate turnover in the brain, this excitotoxicity may have a self-dependent "astrocytic" nature. It has been shown that astrocytes obtained from transgenic HD mice or mice transfected with viral vectors carrying the mutant huntingtin were characterized by a significantly decreased level of the glutamate transporter GLT-1/Slc1a2, a decreased ability to protect the co-cultivated neurons against the glutamate stress, and a disturbance in the regulation of the glutamate–gamma-aminobutyric acid (GABA)–glutamine cycle [46, 78]. Disorders in the regulation of the glutamate reuptake associated with the development of excitotoxicity were also observed in drosophila expressing elongated polyglutamine chains [79].

Expansion of the polyglutamine residues in huntingtin leads to suppression of the BDNF synthesis through mechanism of the translational dysregulation. In addition, the $(CAG)_n$-mutation in the *HTT* gene also affects the postulated BDNF-transporting function of huntingtin. As it is known, BDNF and other neurotrophic factors act as signaling molecules, whose effects are mediated through membrane tyrosine kinase receptors with a subsequent phosphorylation of regulatory proteins and initiation of transcription of genes which control calcium homeostasis, synaptic functions, and survival of neurons. Decreased BDNF levels have also been shown in the brain (mainly in the striatum) and serum of HD patients, as well as in experimental models of this condition *in vivo* and *in vitro* [46, 50]. In HD transgenic mice, an additional inactivation of the *BDNF* gene resulted in the earlier manifestation of the neurological syndrome [80]. Interestingly, the pattern of gene expression in HD mice with the *N*-terminal fragment of the mutant huntingtin inserted into the genome is very similar to disturbances in the expression observed in mice with a knockout of *BDNF* gene [81]. Since normally BDNF is delivered from the cortex into the projection zones of the striatum and plays an important role in the survival and functioning of the striatum neurons, it could be hypothesized that the loss of this function as a result of expansion of the polyglutamine-encoding CAG-repeats is directly associ-

ated with the neuronal loss in striatum. Available experimental and clinical data indicate an important role of the disruption of the neurotrophic support in the development of degeneration in HD.

Disorders in the interactions between expanded polyglutamine chains and proteins responsible for regulation of apoptosis (e.g. caspases), which at some stage lead to initiation of the programmed death of neurons, play a significant role in pathogenesis of HD and other polyglutamine diseases [26]. The induction of apoptosis by polyglutamine-containing protein aggregates due to recruitment of caspases was detected in transgenic animals and in post-mortem specimens of the HD patients' brains [82]. It is necessary to say, that normally huntingtin is able to inhibit processing of procaspase-9, presumably by preventing its interaction with the huntingtin-associated protein 1 (HAP1) [19]. Thus, in HD the mutant huntingtin not only loses its anti-apoptotic properties but becomes an inducer of the apoptosis cascade.

At present, it is generally accepted that neurodegeneration in HD may to some extent be explained by the loss by the mutant huntingtin of its own functions. Thus, the conditional knockout of huntingtin during the post-natal period in transgenic mice leads to degeneration of the striatal neurons [83], whereas inactivation of own huntingtin in mice expressing the mutant fragment of this human protein is accompanied by the more severe course of the degeneration [84]. Examples of suppression of the expanded huntingtin functions during the vesicular transport of BDNF or as part of the control of apoptosis have been already presented above. Moreover, it is highly likely that normally huntingtin is involved in neurotransmission through its interaction with some post-synaptic proteins [85]. The loss of this function in HD leads to dysregulation of homeostasis of synaptic proteins, to abnormalities of dendrites, and to impairment of the synaptic plasticity [21].

Since pathological aggregates and inclusions in neurons contain a variety of cellular proteins which form stable bonds with the expanded polyglutamine chains, disorders in the function of these proteins as a result of their interaction with huntingtin contribute to the pathogenesis of HD. Thus, disorders in functions of the ubiquitin-conjugating protein HIP2 detected within the inclusions can lead to violation of the proteasomal degradation of abnormal aggregates, whereas binding by the polyglutamine chains of acetyltransferase enzymes inhibits the acetylation of chromosomal histone proteins and thus disturbs regulation of the gene expression [19].

During the recent years, epigenetic mechanisms, such as violation of histone acetylation, disorders of the DNA methylation pattern in the regulatory regions of various genes, etc., are thought to play a critical role in the molecular pathogenesis of HD [86]. This is why it is speculated that HD patients have a lower risk of oncological conditions [87, 88]. These epidemiological data, as well as the role of epigenetics in HD, need to be further analyzed.

Thus, disorders in the conformation and processing of the mutant huntingtin represent the core in the molecular pathology of HD. To date, a number of molecular pathways have been identified which either initiate or speed up the progression of the neurodegenerative process. This is important from the standpoint of development of fundamentally new approaches to the treatment of this condition [89].

Funding

The work was supported by the Russian Science Foundation (project no. 17-74-20068).

REFERENCES

1. Baig, S. S., Strong, M., and Quarrell, O. W. (2016) The global prevalence of Huntington's disease: a systematic review and discussion, *Neurodegener. Dis. Manag.*, **6**, 331-343.
2. Hayden, M. R. (1981) *Huntington's Chorea*, Springer-Verlag, Berlin.
3. Bates, G. P., Dorsey, R., Gusella, J. F., Hayden, M. R., Kay, C., Leavitt, B. R., Nance, M., Ross, C. A., Scahill, R. I., Wetzel, R., Wild, E. J., and Tabrizi, S. J. (2015) Huntington's disease, *Nature Rev. Dis. Primers*, **1**, 1-21.
4. The Huntington's Disease Collaborative Research Group (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes, *Cell*, **72**, 971-983.
5. Paulson, H. L. (1999) Protein fate in neurodegenerative proteinopathies: polyglutamine diseases join the (mis)fold, *Am. J. Hum. Genet.*, **64**, 339-345.
6. Wheeler, V. C., Persichetti, F., McNeil, S. M., Mysore, J. S., Mysore, S. S., MacDonald, M. E., Myers, R. H., Gusella, J. F., Wexler, N. S., and The US–Venezuela Collaborative Research Group (2007) Factors associated with HD CAG repeat instability in Huntington's disease, *J. Med. Gen.*, **44**, 695-701.
7. Reiner, A., Dragatsis, I., and Dietrich, P. (2011) Genetics and neuropathology of Huntington's disease, *Int. Rev. Neurobiol.*, **98**, 325-372.
8. Duyao, M., Ambrose, C., Myers, R., Novelletto, A., Persichetti, F., Frontali, M., Folstein, S., Ross, C., Franz, M., Abbott, M., Gray, J., Conneally, P., Young, A., Penney, J., Hollingsworth, Z., Shoulson, I., Lazzarini, A., Falek, A., Koroshetz, W., Sax, D., Bird, E., Vonsattel, J., Bonilla, E., Alvir, J., Bickham Conde, J., Cha, J.-H., Dure, L., Gomez, F., Ramos, M., Sanchez-Ramos, J., Snodgrass, S., de Young, M., Wexler, N., Moscowitz, C., Penchaszadeh, G., MacFarlane, H., Anderson, M., Jenkins, B., Srinidhi, J., Barnes, G., Gusella, J., and MacDonald, M. (1993) Trinucleotide repeat length instability and age of onset in Huntington's disease, *Nat. Genet.*, **4**, 387-392.
9. Andresen, J. M., Javiar, G., Djousse, L., Roberts, S., Brocklebank, D., Cherny, S. S., The US–Venezuela

Collaborative Research Group, HD MAPS Collaborative Research Group, Cardon, L. R., Gusella, J. F., MacDonald, M. E., Myers, R. H., Housman, D. E., and Wexler, N. S. (2006) The relationship between CAG repeat length and age of onset differs for Huntington's disease patients with juvenile onset or adult onset, *Hum. Gen.*, **71**, 295-301.

10. Brinkman, R. R., Mezei, M. M., Theilmann, J., Almqvist, E., and Hayden, M. R. (1997) The likelihood of being affected with Huntington's disease by a particular age, for a specific CAG size, *Am. J. Hum. Genet.*, **60**, 1202-1210.
11. Persichetti, F., Srinidhi, J., Kanaley, L., Ge, P., Myers, R. H., D'Arrigo, K., Barnes, G. T., MacDonald, M. E., Vonsattel, J. P., Gusella, J. F., and Bird, E. D. (1994) Huntington's disease CAG trinucleotide repeats in pathologically confirmed post-mortem brains, *Neurobiol. Dis.*, **1**, 159-166.
12. Illarioshkin, S. N., Igarashi, S., Onodera, O., Markova, E. D., Nikolskaya, N. N., Tanaka, H., Chabrashwili, T. Z., Insarova, N. G., Endo, K., Ivanova-Smolenskaya, I. A., and Tsuji, S. (1994) Trinucleotide repeat length and rate of progression of Huntington's disease, *Ann. Neurol.*, **36**, 630-635.
13. Brandt, J., Bylsma, F. W., Gross, R., Stine, O. C., Ranen, N., and Ross, C. A. (1996) Trinucleotide repeat length and clinical progression in Huntington's disease, *Neurology*, **46**, 527-531.
14. Rosenblatt, A., Liang, K. Y., Zhou, H., Abbott, M. H., Gourley, L. M., Margolis, R. L., Brandt, J., and Ross, C. A. (2006) The association of CAG repeat length with clinical progression in Huntington's disease, *Neurology*, **66**, 1016-1020.
15. Myers, R. H. (2004) Huntington's disease genetics, *NeuroRx*, **1**, 255-262.
16. Tautz, D., and Schlotterer, C. (1994) Simple sequences, *Curr. Opin. Genet. Dev.*, **4**, 832-837.
17. Klintschar, M., Dauber, E.-M., Ricci, U., Cerri, N., Immel, U. D., Kleiber, M., and Mayr, W. R. (2004) Haplotype studies support slippage as the mechanism of germline mutations in short tandem repeats, *Electrophoresis*, **25**, 3344-3348.
18. Zuccato, C., and Cattaneo, E. (2016) The Huntington's paradox, *Sci. Am.*, **315**, 56-61.
19. Saudou, F., and Humbert, S. (2016) The biology of huntingtin, *Neuron*, **89**, 910-926.
20. Velier, J., Kim, M., Schwarz, C., Kim, T. W., Sapp, E., Chase, K., Aronin, N., and DiFiglia, M. (1998) Wild-type and mutant huntingtins function in vesicle trafficking in the secretory and endocytic pathways, *Exp. Neurol.*, **152**, 34-40.
21. Nithianantharajah, J., and Hannan, A. J. (2013) Dysregulation of synaptic proteins, dendritic spine abnormalities and pathological plasticity of synapses as experience-dependent mediators of cognitive and psychiatric symptoms in Huntington's disease, *Neuroscience*, **251**, 66-74.
22. Martin, D. D. O., Ladha, S., Ehrnhoefer, D. E., and Hayden, M. R. (2014) Autophagy in Huntington's disease and huntingtin in autophagy, *Trends Neurosci.*, **38**, 26-35.
23. Perutz, M. F., Johnson, T., Suzuki, M., and Finch, J. T. (1994) Glutamine repeats as polar zippers: their possible role in inherited neurologic diseases, *Proc. Natl. Acad. Sci. USA*, **91**, 5355-5358.
24. Landles, C., Sathasivam, K., Weiss, A., Woodman, B., Moffitt, H., Finkbeiner, S., Sun, B., Gafni, J., Ellerby, L. M., Trottier, Y., Richards, W. G., Osmand, A., Paganetti, P., and Bates, G. P. (2010) Proteolysis of mutant huntingtin produces an exon 1 fragment that accumulates as an aggregated protein in neuronal nuclei in Huntington's disease, *J. Biol. Chem.*, **285**, 8808-8823.
25. Rubinsztein, D. C., Wyttenbach, A., and Rankin, J. (1999) Intracellular inclusions, pathological markers in diseases caused by expanded polyglutamine tracts? *J. Med. Genet.*, **36**, 265-270.
26. Ross, C. A., Wood, J. D., and Schilling, G. (1999) Polyglutamine pathogenesis, *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, **354**, 1005-1011.
27. Graham, R. K., Deng, Y., and Slow, E. J. (2006) Cleavage at the caspase-6 site is required for neuronal dysfunction and degeneration due to mutant huntingtin, *Cell*, **125**, 1179-1191.
28. Saudou, F., Finkbeiner, S., Devys, D., and Greenberg, M. E. (1998) Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions, *Cell*, **95**, 55-66.
29. Klement, I. A., Skinner, P. A., Kaytor, M. D., Yi, H., Hersch, S. M., Clark, H. B., Zoghbi, H. Y., and Orr, H. T. (1998) Ataxin-1 nuclear localisation and aggregation: role in polyglutamine-induced disease in SCA1 transgenic mice, *Cell*, **95**, 41-53.
30. DiFiglia, M., Sapp, E., Chase, K. O., Davies, S. W., Bates, G. P., Vonsattel, J. P., and Aronin, N. (1997) Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain, *Science*, **277**, 1990-1993.
31. Scherzinger, E., Lurz, R., Turmaine, M., Mangiarini, L., Hollenbach, B., Hasenbank, R., Bates, G. P., Davies, S. W., Lehrach, H., and Wanker, E. E. (1997) Huntingtin-encoded polyglutamine expansions form amyloid-like protein aggregates *in vitro* and *in vivo*, *Cell*, **90**, 549-558.
32. Davies, S. W., Turmaine, M., Cozens, B. A., DiFiglia, M., Sharp, A. H., Ross, C. A., Scherzinger, E., Wanker, E. E., Mangiarini, L., and Bates, G. P. (1997) Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation, *Cell*, **90**, 537-548.
33. Warrick, J. M., Paulson, H. L., Gray-Board, G. L., Bui, Q. T., Fischbeck, K. H., Pittman, R. N., and Bonini, N. M. (1998) Expanded polyglutamine protein forms nuclear inclusions and causes neural degeneration in *Drosophila*, *Cell*, **93**, 939-949.
34. Nekrasov, E. D., Vigont, V. A., Klyushnikov, S. A., Lebedeva, O. S., Vassina, E. M., Bogomazova, A. N., Chestkov, I. V., Semashko, T. A., Kiseleva, E., Suldina, L. A., Bobrovsky, P. A., Zimina, O. A., Ryazantseva, M. A., Skopin, A. Y., Illarioshkin, S. N., Kaznacheyeva, E. V., Lagarkova, M. A., and Kiselev, S. L. (2016) Manifestation of Huntington's disease pathology in human induced pluripotent stem cell-derived neurons, *Mol. Neurodegener.*, **11**, 27.
35. Kalchman, M. A., Graham, R. K., Xia, G., Koide, H. B., Hodgson, J. G., Graham, K. C., Goldberg, Y. P., Gietz, R. D., Pickart, C. M., and Hayden, M. R. (1996) Huntingtin is ubiquitinated and interacts with a specific ubiquitin-conjugating enzyme, *J. Biol. Chem.*, **271**, 19385-19394.
36. Chai, Y., Koppenhafer, S. L., Shoesmith, S. J., Perez, M. K., and Paulson, H. L. (1999) Evidence for proteasome

involvement in polyglutamine disease: localization to nuclear inclusions in SCA3/MJD and suppression of polyglutamine aggregation *in vitro*, *Hum. Mol. Genet.*, **8**, 673-682.
37. Holmberg, C. I., Staniszewski, K. E., Mensah, K. N., Matouschek, A., and Morimoto, R. I. (2004) Inefficient degradation of truncated polyglutamine proteins by the proteasome, *EMBO J.*, **23**, 4307-4318.
38. Labbadia, J., and Morimoto, R. I. (2013) Huntington's disease: underlying molecular mechanisms and emerging concepts, *Trends Biochem. Sci.*, **38**, 378-385.
39. Zhao, T., Hong, Y., Li, X.-J., and Li, S.-H. (2016) Subcellular clearance and accumulation of Huntington's disease protein: a mini-review, *Front. Mol. Neurosci.*, **9**, 27.
40. Ravikumar, B., Vacher, C., Berger, Z., Davies, J. E., Luo, S., Oroz, L. G., Scaravilli, F., Easton, D. F., Duden, R., O'Kane, C. J., and Rubinsztein, D. C. (2004) Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington's disease, *Nat. Genet.*, **36**, 585-595.
41. Ravikumar, B., Acevedo-Arozena, A., Imarisio, S., Berger, Z., Vacher, C., O'Kane, C. J., Brown, S. D., and Rubinsztein, D. C. (2005) Dynein mutations impair autophagic clearance of aggregate-prone proteins, *Nat. Genet.*, **37**, 771-776.
42. Harding, R. J., and Tong, Y. F. (2018) Proteostasis in Huntington's disease: disease mechanisms and therapeutic opportunities, *Acta Pharmacol. Sin.*, **39**, 754-769.
43. Kim, M., Lee, H.-S., LaForet, G., McIntyre, C., Martin, E. J., Chang, P., Kim, T. W., Williams, M., Reddy, P. H., Tagle, D., Boyce, F. M., Won, L., Heller, A., Aronin, N., and DiFiglia, M. (1999) Mutant huntingtin expression in clonal striatal cells: dissociation of inclusion formation and neuronal survival by caspase inhibition, *J. Neurosci.*, **19**, 964-973.
44. Cummings, C. J., Reinstein, E., Sun, Y., Antalffy, B., Jiang, Y., Ciechanover, A., Orr, H. T., Beaudet, A. L., and Zoghbi, H. Y. (1999) Mutation of the E6-AP ubiquitin ligase reduces nuclear inclusion frequency while accelerating polyglutamine-induced pathology in SCA1 mice, *Neuron*, **24**, 879-892.
45. Valor, L. M. (2015) Transcription, epigenetics and ameliorative strategies in Huntington's disease: a genome-wide perspective, *Mol. Neurobiol.*, **51**, 406-423.
46. La Spada, A. R., Weydt, P., and Pineda, V. V. (2011) Huntington's disease pathogenesis: mechanisms and pathways, in *Neurobiology of Huntington's Disease: Applications to Drug Discovery* (Lo, D. C., and Hughes, R. E., eds.), Chap. 2, Taylor & Francis, Boca Raton.
47. Cong, S. Y., Pepers, B. A., Evert, B. O., Rubinsztein, D. C., Roos, R. A., van Ommen, G. J., and Dorsman, J. C. (2005) Mutant huntingtin represses CBP, but not p300, by binding and protein degradation, *Mol. Cell. Neurosci.*, **30**, 560-571.
48. Qiu, Z., Norflus, F., Singh, B., Swindell, M. K., Buzescu, R., Bejarano, M., Chopra, R., Zucker, B., Benn, C. L., DiRocco, D. P., Cha, J. H., Ferrante, R. J., and Hersch, S. M. (2006) Sp1 is up-regulated in cellular and transgenic models of Huntington's disease, and its reduction is neuroprotective, *J. Biol. Chem.*, **281**, 16672-16680.
49. Futter, M., Diekmann, H., Schoenmakers, E., Sadiq, O., Chatterjee, K., and Rubinsztein, D. C. (2009) Wild-type but not mutant huntingtin modulates the transcriptional activity of liver X receptors, *J. Med. Genet.*, **46**, 438-446.
50. Zuccato, C., and Cattaneo, E. (2007) Role of brain-derived neurotrophic factor in Huntington's disease, *Prog. Neurobiol.*, **81**, 294-330.
51. Kelly, D. P., and Scarpulla, R. C. (2004) Transcriptional regulatory circuits controlling mitochondrial biogenesis and function, *Genes Dev.*, **18**, 357-368.
52. Beal, M. F., Brouillet, E., Jenkins, B. G., Ferrante, R. J., Kowall, N. W., Miller, J. M., Storey, E., Srivastava, R., Rosen, B. R., and Hyman, B. T. (1993) Neurochemical and histologic characterization of striatal excitotoxic lesions produced by the mitochondrial toxin 3-nitropropionic acid, *J. Neurosci.*, **13**, 4181-4189.
53. Tabrizi, S. J., Cleeter, M. W., Xuereb, J., Taanman, J. W., Cooper, J. M., and Schapira, A. H. (1999) Biochemical abnormalities and excitotoxicity in Huntington's disease brain, *Ann. Neurol.*, **45**, 25-32.
54. Johri, A., Chandra, A., and Beal, M. F. (2013) PGC-1α, mitochondrial dysfunction, and Huntington's disease, *Free Radic. Biol. Med.*, **62**, 37-46.
55. Harms, L., Meierkord, H., Timm, G., Pfeiffer, L., and Ludolph, A. C. (1997) Decreased N-acetylaspartate/choline ratio and increased lactate in the frontal lobe of patients with Huntington's disease: a proton magnetic resonance spectroscopy study, *J. Neurol. Neurosurg. Psychiatry*, **62**, 27-30.
56. Reddy, P. H., and Shirendeb, U. P. (2012) Mutant huntingtin, abnormal mitochondrial dynamics, defective axonal transport of mitochondria, and selective synaptic degeneration in Huntington's disease, *Biochim. Biophys. Acta*, **1822**, 101-110.
57. Orr, A. L., Li, S., Wang, C. E., Li, H., Wang, J., Rong, J., Xu, X., Mastroberardino, P. G., Greenamyre, J. T., and Li, X. J. (2008) N-terminal mutant huntingtin associates with mitochondria and impairs mitochondrial trafficking, *J. Neurosci.*, **28**, 2783-2792.
58. Twig, G., and Shirihai, O. S. (2011) The interplay between mitochondrial dynamics and mitophagy, *Antioxid. Redox Signal.*, **14**, 1939-1951.
59. Martinez-Vicente, M., Talloczy, Z., Wong, E., Tang, G., Koga, H., Kaushik, S., de Vries, R., Arias, E., Harris, S., Sulzer, D., and Cuervo, A. M. (2010) Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease, *Nat. Neurosci.*, **13**, 567-576.
60. Puigserver, P., and Spiegelman, B. M. (2003) Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1 alpha): transcriptional coactivator and metabolic regulator, *Endocr. Rev.*, **24**, 78-90.
61. Lin, J., Wu, P. H., Tarr, P. T., Lindenberg, K. S., St.-Pierre, J., Zhang, C. Y., Mootha, V. K., Jager, S., Vianna, C. R., Reznick, R. M., Cui, L., Manieri, M., Donovan, M. X., Wu, Z., Cooper, M. P., Fan, M. C., Rohas, L. M., Zavacki, A. M., Cinti, S., Shulman, G. I., Lowell, B. B., Krainc, D., and Spiegelman, B. M. (2004) Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1alpha null mice, *Cell*, **119**, 121-123.
62. Leone, T. C., Lehman, J. J., and Finck, B. N. (2005) PGC-1alpha deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis, *PLoS Biol.*, **3**, e101.
63. Gunawardena, S., and Goldstein, L. S. (2005) Polyglutamine diseases and transport problems: deadly traffic jams on neuronal highways, *Arch. Neurol.*, **62**, 46-51.

64. Zala, D., Hinckelmann, M. V., Yu, H., Lyra da Cunha, M. M., Liot, G., Cordelieres, F. P., Marco, S., and Saudou, F. (2013) Vesicular glycolysis provides on-board energy for fast axonal transport, *Cell*, **152**, 479-491.
65. Gauthier, L. R., Charrin, B. C., Borrell-Pages, M., Dompierre, J. P., Rangone, H., Cordelieres, F. P., De Mey, J., MacDonald, M. E., Lessmann, V., Humbert, S., and Saudou, F. (2004) Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules, *Cell*, **118**, 127-138.
66. Trushina, E., Dyer, R. B., Badger, J. D., Ure, D., Eide, L., Tran, D. D., Vrieze, B. T., Legendre-Guillemin, V., McPherson, P. S., Mandavilli, B. S., Van Houten, B., Zeitlin, S., McNiven, M., Aebersold, R., Hayden, M., Parisi, J. E., Seeberg, E., Dragatsis, I., Doyle, K., Bender, A., Chacko, C., and McMurray, C. T. (2004) Mutant huntingtin impairs axonal trafficking in mammalian neurons *in vivo* and *in vitro*, *Mol. Cell. Biol.*, **24**, 8195-8209.
67. Crotti, A., and Glass, C. K. (2015) The choreography of neuroinflammation in Huntington's disease, *Trends Immunol.*, **36**, 364-373.
68. Nimmerjahn, A., Kirchhoff, F., and Helmchen, F. (2005) Resting microglial cells are highly dynamic surveillants of brain parenchyma *in vivo*, *Science*, **308**, 1314-1318.
69. Banati, R. B. (2002) Visualizing microglial activation *in vivo*, *Glia*, **40**, 206-217.
70. Sapp, E., Kegel, K. B., Aronin, N., Hashikawa, T., Uchiyama, Y., Tohyama, K., Bhide, P. G., Vonsattel, J. P., and DiFiglia, M. (2001) Early and progressive accumulation of reactive microglia in the Huntington's disease brain, *J. Neuropathol. Exp. Neurol.*, **60**, 161-172.
71. Tai, Y. F., Pavese, N., Gerhard, A., Tabrizi, S. J., Barker, R. A., Brooks, D. J., and Piccini, P. (2007) Microglial activation in presymptomatic Huntington's disease gene carriers, *Brain*, **130**, 1759-1766.
72. Crotti, A., Benner, C., Kerman, B. E., Lagier-Tourenne, C., Zuccato, C., Cattaneo, E., Gage, F. H., Cleveland, D. W., and Glass, C. K. (2014) Mutant Huntingtin promotes autonomous microglia activation via myeloid lineage-determining factors, *Nat. Neurosci.*, **4**, 513-521.
73. Kumar, A., and Ratan, R. R. (2016) Oxidative stress and Huntington's disease: the good, the bad, and the ugly, *J. Huntington's Dis.*, **5**, 217-237.
74. Hands, S., Sajjad, M. U., Newton, M. J., and Wyttenbach, A. (2011) *In vitro* and *in vivo* aggregation of a fragment of huntingtin protein directly causes free radical production, *J. Biol. Chem.*, **286**, 44512-44520.
75. Block, M. L., Zecca, L., and Hong, J. S. (2007) Microglia-mediated neurotoxicity: uncovering the molecular mechanisms, *Nat. Rev. Neurosci.*, **8**, 57-69.
76. Firdaus, W. J., Wyttenbach, A., Giuliano, P., Kretz-Remy, C., Currie, R. W., and Arrigo, A. P. (2006) Huntingtin inclusion bodies are iron-dependent centers of oxidative events, *FEBS J.*, **273**, 5428-5441.
77. Hodgson, J. G., Agopyan, N., Gutekunst, C.-A., Leavitt, B. R., LePiane, F., Singaraja, R., Smith, D. J., Bissada, N., McCutcheon, K., Nasir, J., Jamot, L., Li, X. J., Stevens, M. E., Rosemond, E., Roder, J. C., Phillips, A. G., Rubin, E. M., Hersch, S. M., and Hayden, M. R. (1999) A YAC mouse model for Huntington's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration, *Neuron*, **23**, 181-192.
78. Skotte, N. H., Andersen, J. V., Santos, A., Aldana, B. I., Willert, C. W., Norremolle, A., Waagepetersen, H. S., and Nielsen, M. L. (2018) Integrative characterization of the R6/2 mouse model of Huntington's disease reveals dysfunctional astrocyte metabolism, *Cell Rep.*, **23**, 2211-2224.
79. Lievens, J. C., Rival, T., Iche, M., Chneiweiss, H., and Birman, S. (2005) Expanded polyglutamine peptides disrupt EGF receptor signaling and glutamate transporter expression in *Drosophila*, *Hum. Mol. Genet.*, **14**, 713-724.
80. Canals, J. M., Pineda, J. R., Torres-Peraza, J. F., Bosch, M., Martin-Ibanez, R., Munoz, M. T., Mengod, G., Ernfors, P., and Alberch, J. (2004) Brain-derived neurotrophic factor regulates the onset and severity of motor dysfunction associated with enkephalinergic neuronal degeneration in Huntington's disease, *J. Neurosci.*, **24**, 7727-7739.
81. Strand, A. D., Baquet, Z. C., Aragaki, A. K., Holmans, P., Yang, L., Cleren, C., Beal, M. F., Jones, L., Kooperberg, C., Olson, J. M., and Jones, K. R. (2007) Expression profiling of Huntington's disease models suggests that brain-derived neurotrophic factor depletion plays a major role in striatal degeneration, *J. Neurosci.*, **27**, 11758-11768.
82. Sanchez, I., Xu, C.-J., Juo, P., Kakizaka, A., Blenis, J., and Yuan, J. (1999) Caspase-8 is required for cell death induced by expanded polyglutamine repeats, *Neuron*, **22**, 623-633.
83. Dragatsis, I., Levine, M. S., and Zeitlin, S. (2000) Inactivation of Hdh in the brain and testis results in progressive neurodegeneration and sterility in mice, *Nat. Genet.*, **26**, 300-306.
84. Van Raamsdonk, J. M., Pearson, J., Rogers, D. A., Bissada, N., Vogl, A. W., Hayden, M. R., and Leavitt, B. R. (2005) Loss of wild-type huntingtin influences motor dysfunction and survival in the YAC128 mouse model of Huntington's disease, *Hum. Mol. Genet.*, **14**, 1379-1392.
85. Sun, Y., Savanenin, A., Reddy, P. H., and Liu, Y. F. (2001) Polyglutamine-expanded huntingtin promotes sensitization of N-methyl-D-aspartate receptors via post-synaptic density 95, *J. Biol. Chem.*, **276**, 24713-24718.
86. Francelle, L., Lotz, C., Outeiro, T., Brouillet, E., and Merienne, K. (2017) Contribution of neuroepigenetics to Huntington's disease, *Front. Hum. Neurosci.*, **11**, 17.
87. Coarelli, G., Diallo, A., Thion, M. S., Rinaldi, D., Calvas, F., Boukbiza, O. L., Tataru, A., Charles, P., Tranchant, C., Marelli, C., Ewenczyk, C., Tchikviladze, M., Monin, M. L., Carlander, B., Anheim, M., Brice, A., Mochel, F., Tezenas du Montcel, S., Humbert, S., and Durr, A. (2017) Low cancer prevalence in polyglutamine expansion diseases, *Neurology*, **88**, 1114-1119.
88. Sorensen, S. A., Fenger, K., and Olsen, J. H. (1999) Significantly lower incidence of cancer among patients with Huntington's disease: an apoptotic effect of an expanded polyglutamine tract? *Cancer*, **86**, 1342-1346.
89. Mestre, T. A., and Sampaio, C. (2017) Huntington's disease: linking pathogenesis to the development of experimental therapeutics, *Curr. Neurol. Neurosci. Rep.*, **17**, 18.