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Human Genome & Diseases: Review

Huntington's disease: from huntingtin function and dysfunction to therapeutic strategies

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Abstract. Huntington's disease (HD) is a neurodegenerative disorder that usually starts in middle age and is characterized by involuntary movements (chorea), personality changes and dementia, leading to death within 10–20 years. The defective gene in HD contains a trinucleotide CAG repeat expansion within its coding region that expresses a polyglutamine repeat in the protein huntingtin. Together with the characteristic formation of aggregates in HD, aberrant protein interactions and several post-translational modifications affect huntingtin during disease progression and lead to the dysfunction and death of selective neurons in the brains of patients. The exact molecular mechanisms by which mutant huntingtin induces cell death are not completely understood but may involve the gain of new toxic functions and the loss of the beneficial properties of huntingtin. This review focuses on the cellular functions in which huntingtin is involved and how a better understanding of pathogenic pathways can lead to new therapeutic approaches.

Keywords. CAG expansion, polyglutamine, aggregation, intracellular transport, transcription, signal transduction, therapy.

Introduction

Huntington's disease (HD) is a fatal neurodegenerative disorder characterized by psychiatric, cognitive and motor disorders [1]. HD affects both sexes with the same frequency and is inherited in an autosomal-dominant manner. HD prevalence is highest in Europe and North America, with between 5 and 10 cases per 100,000 individuals. An extremely high occurrence was also found within the 15,000 members of a large group of interrelated families living in fishing villages along the border of Lake Maracaibo in Venezuela [2]. This led to the foundation of the Venezuelan HD project which characterized these family members clinically and genetically. Most are descendents of a woman who suffered from 'el mal de San Vito', the local name for HD, in the early nineteenth century. Linkage analysis of these families led to localization of the HD gene on chromosome 4p16.3 [3], although it was only in 1993 that the causative gene encoding the huntingtin protein was finally isolated [4].

HD symptoms usually appear in middle age. However, disease can start earlier, and about 6% of HD patients develop juvenile forms [5]. The initial symptoms vary from person to person but disease onset is generally marked by involuntary movements of the face, fingers, feet or thorax [6]. Psychiatric symptoms are more heterogeneous but can occur up to 20 years before onset of the choreiform movements. These symptoms are usually recognized later as being part of the disease process and may therefore represent the earliest symptoms of the disease. They include depression, anxiety, apathy and irritability [7]. As HD progresses, the affected person develops overt choreiform movements of the head, neck, arms and legs. Pa-

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tients also show cognitive deficits such as impairments of memory and language comprehension, the severity of which parallels disease progression [8]. Weight loss is a fourth characteristic of the disease and may be due to dysphagia as well as degeneration of hypothalamic orexin-positive neurons [9, 10]. In the late stages of the disease, patients become severely rigid and akinetic. They also present severe dementia, eventually ceasing to talk and becoming unable to care for themselves. The patient usually dies 10–20 years after the first symptoms appear as there is currently no effective treatment to prevent or delay disease progression.

The neuropathology of HD involves the selective dysfunction and death of specific neuronal subpopulations within the central nervous system. The most affected cells are the gamma-aminobutyric acid (GABA)-releasing spiny-projecting neurons of the striatum, the subcortical brain structure that controls body movement and, to a lesser extent, neurons within the cerebral cortex [11]. The first degenerating subpopulation of GABAergic neurons express enkephalin and are enriched in the dopamine receptor D2 [12, 13]. As the disease progresses, there is general neuronal loss in several brain regions such as the globus pallidus, the subthalamic nuclei, the substantia nigra, the cerebellum and the thalamus. Together with the neuronal loss, glial proliferation is observed [11], although whether this proliferation is a cause or a consequence of the disease remains to be determined.

The huntingtin protein

The human HD gene (also called IT15) contains 67 exons spanning more than 200 kb. The translated wild-type huntingtin protein is a 350-kDa protein containing a polymorphic stretch of between 6 and 35 glutamine residues in its N-terminal domain. When the number of glutamine-encoding repeats exceeds 36, the gene encodes a version of huntingtin that leads to disease [4, 14]. Although the gene was discovered 13 years ago, only now is the role of the normal protein becoming understood. This is partly due to the ubiquitous expression of the protein and its localization in many subcellular structures. Also, other than the polyglutamine stretch, huntingtin has no homologies with other proteins.

Huntingtin is widely expressed, the highest levels being found in the testis and brain [15–17]. Within the brain, the main expression sites are the neocortex, the cerebellar cortex, the striatum and the hippocampus. The distribution of huntingtin in the brain and also in the striatum does not explain the cell type specificity of death in HD [18]. Within cells, the huntingtin protein is found in the cytoplasm, within neurites and at synapses. It associates with various organelles and structures, such as clathrin-coated vesicles, endosomal and endoplasmic compartments, mitochondria, microtubules and plasma membrane [15–17, 19]. Although it is mainly found in the cytoplasm, huntingtin is also located in the nucleus [20, 21]. Given its subcellular localization, huntingtin appears to be involved in various cellular functions in the cytoplasm and the nucleus. Consistent with this, huntingtin interacts with numerous proteins involved in gene expression, intracellular transport, intracellular signalling and metabolism (Table 1) [22, 23].

Of its several roles, huntingtin functions in transcription and intracellular transport are well established [24–27]. Huntingtin may regulate transcription by shuttling transcription factors between the nucleus and the cytoplasm and by interacting with spliceosome-related proteins [28]. Although not fully understood, this shuttling between the cytoplasm and the nucleus may involve the nuclear pore protein Tpr [29] and the nuclear export sequence within the protein [30].

The regulation of transcription by huntingtin may involve direct interactions between huntingtin and transcription factors. For example, huntingtin binds to the transcriptional, repressor element-1 transcription/neuron restrictive silencer factors (REST/NRSFs), and therefore sequesters this complex in the cytoplasm [31]. Huntingtin activates transcription by keeping REST/NRSF in the cytoplasm, away from its nuclear target, the neuron restrictive silencer element (NRSE), which is a consensus sequence found in genes such as the gene encoding brain-derived neurotrophic factor (BDNF).

Evidence is growing to suggest that huntingtin is also involved in trafficking. Huntingtin interacts with many proteins that regulate intracellular transport or endocytosis, such as huntingtin-associated protein 1 (HAP1), huntingtin-interacting protein 1 and 14 (HIP1 and HIP14), HIP1-related protein (HIP1R), protein kinase C and casein kinase substrate in neurons-1 (PACSIN1) [25, 32–37]. In addition, huntingtin is modified by the HIP14 protein, a palmitoyl transferase involved in the sorting of many proteins from the Golgi region [38]. In *Drosophila,* the reduction of huntingtin expression causes axonal transport defects in larval nerves and neurodegeneration in adult eyes [39]. Moreover, wild-type huntingtin stimulates transport by binding with HAP1 and subsequently interacting with the molecular motors dynein/dynactin and kinesin [40–43]. Huntingtin directly promotes the microtubule-based transport of BDNF in neurons through this interaction. Increasing or decreasing huntingtin levels in cells increases or decreases, respectively, intracellular transport, showing that huntingtin is a processivity factor for the microtubule-dependent transport of vesicles containing BDNF [42].

Finally, huntingtin is an indispensable protein that has anti-apoptotic properties. Studies in huntingtin knockout mice have shown that huntingtin is required for normal embryonic development and neurogenesis:

Table 1. Proteins interacting with and/or modifying huntingtin.

Interactor/modifier	PolyQ length dependence	Region of huntingtin involved	Function	References
α-Adaptin C/HYP-J	yes ↘	NT (aa 1–550)	endocytosis	28
Akt/PKB	no	S421	kinase	148
β-Tubulin	no	unknown	structure, vesicle transport	212, 213
CA150	no	unknown	transcriptional activator	101
Calcineurin	unknown	S421	phosphatase	150
Calmodulin	yes ↗	unknown	calcium-binding regulatory protein	214
Calpain	unknown	aa 430–550	protease	215, 216
Caspase-3	no	aa 513, 530	protease	83
Caspase-6	no	aa 586	protease	217
CBP	yes ↗	NT (aa 1–588)	transcriptional co-activator	93
Cdk5	no	NT (aa 5–56)	kinase	153
CIP4	yes ↗	NT (aa 1–152)	signal transduction	218
CtBP	yes ↘	PLDLS motif (aa 182–186)	transcriptional co-repressor	21
Cystathionine β-synthase	no	NT (aa 1–171)	generation of cystein	219
FIP2/HYP-L	unknown	NT (aa 1–150)	cell morphogenesis	28
GAPDH	yes ↗	PRD	glycolitic enzyme	220
GIT1	unknown	NT (aa 92–170)	G protein-coupled receptor kinase	221
Grb2	unknown	PRD	growth factor receptor-binding protein	222
HAP1	yes ↗	NT (aa 171–230)	membrane traffic	32
HAP40	unknown	CT	endosome motility	77, 119
HIP1	yes ↘	NT (aa 1–540)	endocytosis, proapoptotic	33, 34
HIP14/HYP-H	yes ↘	NT (aa 1–550), C214	traffic, endocytosis	28, 35, 38
HIP2	no	NT (aa 1–540)	ubiquitin-conjugated enzyme	223
HYP-A	yes ↗	PRD	RNA splicing factor	28
HYP-C	yes ↗	PRD	transcription factor	28
IKKγ	yes ↗	PRD and polyQ	kinase inhibitor	224
$InsP_3R1$	yes ↗	NT (aa 1–171)	calcium release channel	225
MLK2	yes ↘	PRD	kinase	137
N-CoR	yes ↗	NT (aa 1–171)	nuclear receptor co-repressor	100
NFκB	unknown	HEAT repeats	transcription factor	226
p53	no	PRD	transcription factor	93
PACSIN1	yes ↗	PRD	endocytosis, actin cytoskeleton	36
PQBP-1	yes ↗	polyQ	transcription repressor	227
PSD-95	yes ↘	PRD	synaptic scaffolding protein	228
RasGAP	unknown	PRD	Ras GTPase activating protein	222
REST/NRSF	yes ↘	unknown	transcription factor repressor element	31
SGK	no	S421	kinase	152
SH3GL3	yes ↗	PRD	endocytosis	229
Sin3a	yes ↗	NT (aa 1–171)	transcription repressor	93
SP1	yes ↗	NT (aa 1–171)	transcription factor	98, 99
SUMO	unknown	K6, K9, K15	post-translational modification	107
TAFII-130	no	NT (aa 1–480)	transcription factor	98
TBP	yes ↗	unknown	transcription factor	230
Tpr	yes ↘	NT (aa 1–17)	nuclear export protein	29
tTG	yes ↗	NT (aa 1–550)	transglutaminase	231
Ubiquitin	yes ↗	K6, K9, K5	post-translational modification	223

The proteins found so far to interact with or modify huntingtin are listed in alphabetical order. Arrows indicate whether these interactions are increased or decreased by the polyQ expansion. NT, N terminal; CT, C terminal.
[Adapted and completed from refs. 22, 51 , 210 , 211].

mice lacking huntingtin show extensive ectoderm cell death at embryonic day 7.5 (E7.5) [44–47]. Huntingtin also plays an essential role postnatally, as the inactivation of the gene in the brain in the adult mouse leads to neurodegeneration [48]. Furthermore, the wild-type protein protects against polyglutamine (polyQ)-huntingtin-induced cell death *in vivo* and against neurodegeneration after ischaemia or NMDA receptor-mediated neurodegeneration [49–54]. Huntingtin overexpression also increases the survival of serum-deprived or 3-nitropropionic acid (3-NP)-treated striatal cells [55]. The anti-apoptotic effect of huntingtin is also supported by the observation that huntingtin downregulates activation of the pro-caspase 8 apoptotic pathway by sequestering HIP-1 [56, 57].

A cascade of events leading to neuronal cell death

Huntingtin that contains the polyQ expansion induces the formation of neuritic, cytoplasmic and nuclear inclusions, leading to dysfunction and finally death of these neurons (Fig. 1). Many studies have demonstrated a series of events that may participate in the disease process. Huntingtin is primarily found in the cytoplasm and the initial events leading to the disease may take place here. Analysis of post-mortem brains from patients at the early stages of HD revealed the presence of dystrophic neurites before cell death [58, 59]. Early neuropathology has also been detected in mouse models of HD such as electrophysiological and mitochondrial abnormalities and the presence of neuropil aggregates in axons and axon terminals [60–64]. Neuronal dysfunction may also involve alterations in the expression of neurotransmitter receptors [59, 60, 62, 65–67]. Moreover, early in the disease, mutant huntingtin dysregulates mitochondrial homeostasis [68, 69]. The impairment of mitochondrial function disrupts calcium handling [64], thus activating proteases such as calpain [70], and will enhance the p53 pathway [71]. Mitochondrial dysfunction caused by a reduction in ATP levels [72] also causes the release of cytochrome c and the activation of caspases [73]. Furthermore, the dysregulation of Ca^{2+} in medium spiny neurons may involve the abnormal potentiation of NMDA receptors and sensitization of the type 1 inositol 1,4,5-trisphosphate receptor located on the endoplasmic reticulum [74, 75]. These dysregulations may play a central role in HD and could explain the oxidative stress, excitotoxic processes and energy metabolism dysfunction that are observed in HD patients [76]. Other early mechanisms that lead to cell dysfunction and death may involve the HIP-1 protein, which interacts with wild-type huntingtin. When huntingtin contains the polyQ expansion, the huntingtin/HIP-1 interaction is disrupted, releasing HIP-1. HIP-1, which contains a death effector domain, can then bind to its partner, hippi, which then activates caspase-8, leading to apoptosis [56].

Axonal transport deficiencies

Altered intracellular dynamics are likely to participate in the development of the disease. This involves defects in axonal transport but also alterations of the secretory and endocytic pathways. Indeed, as stated earlier, huntingtin interacts with many proteins involved in secretion and endocytosis. A reduction in endosomal motility and endocytic activity in HD fibroblasts and mutant cells was recently reported [77]. This results from the upregulation of HAP40 that acts with huntingtin as a new effector of the small guanosine triphosphatase Rab5. In addition to these defects, dysfunction of huntingtin directly impairs axonal transport. Indeed, wild-type, full-length huntingtin associates with HAP1 and, as part of a protein complex that contains the molecular motors dynein/dynactin and kinesin, stimulates BDNF transport [42]. As shown by RNA interference approaches, the HAP1 protein is likely to play an important role in the huntingtin-mediated transport of organelles along microtubules, and may control not only BDNF trafficking [42] but also the transport of other organelles, such as amyloid precursor protein vesicles, through its direct binding to the kinesin light chain [43, 78]. In disease, polyQ-huntingtin is unable to stimulate transport, resulting in reduced BDNF support and in a higher susceptibility of striatal neurons to death. When huntingtin contains the pathological polyQ expansion, it interacts more strongly with HAP1 and $p150^{Glued}$ [32, 41, 42], leading to detachment of the molecular motors from the microtubules and to a lower processivity of vesicles along the microtubules. As discussed earlier, a reduction in huntingtin levels or the expression of mutant huntingtin both reduce transport [39, 42]. Therefore, the slowing of transport participates in HD pathogenesis and, as seen in other neurodegenerative disorders, the viability of neurons is severely affected by a decrease in intracellular trafficking.

As well as nuclear aggregation, N-terminal huntingtin fragments form aggregates that accumulate in axonal processes and terminals [62]. Several studies have shown that N-terminal huntingtin polypeptide fragments containing the polyQ expansion cause axonal transport defects in cellular and *Drosophila* models of HD [39, 62, 79–81]. These defects subsequently participate in neuronal death. Aggregation is involved in altering axonal transport, with aggregated polyQ-proteins accumulating in axons and titrating motor proteins, particularly $p150^{Glued}$ and kinesin heavy chain (KHC), from other cargoes and pathways. These aggregates also physically block the circulating vesicles or organelles such as mitochondria.

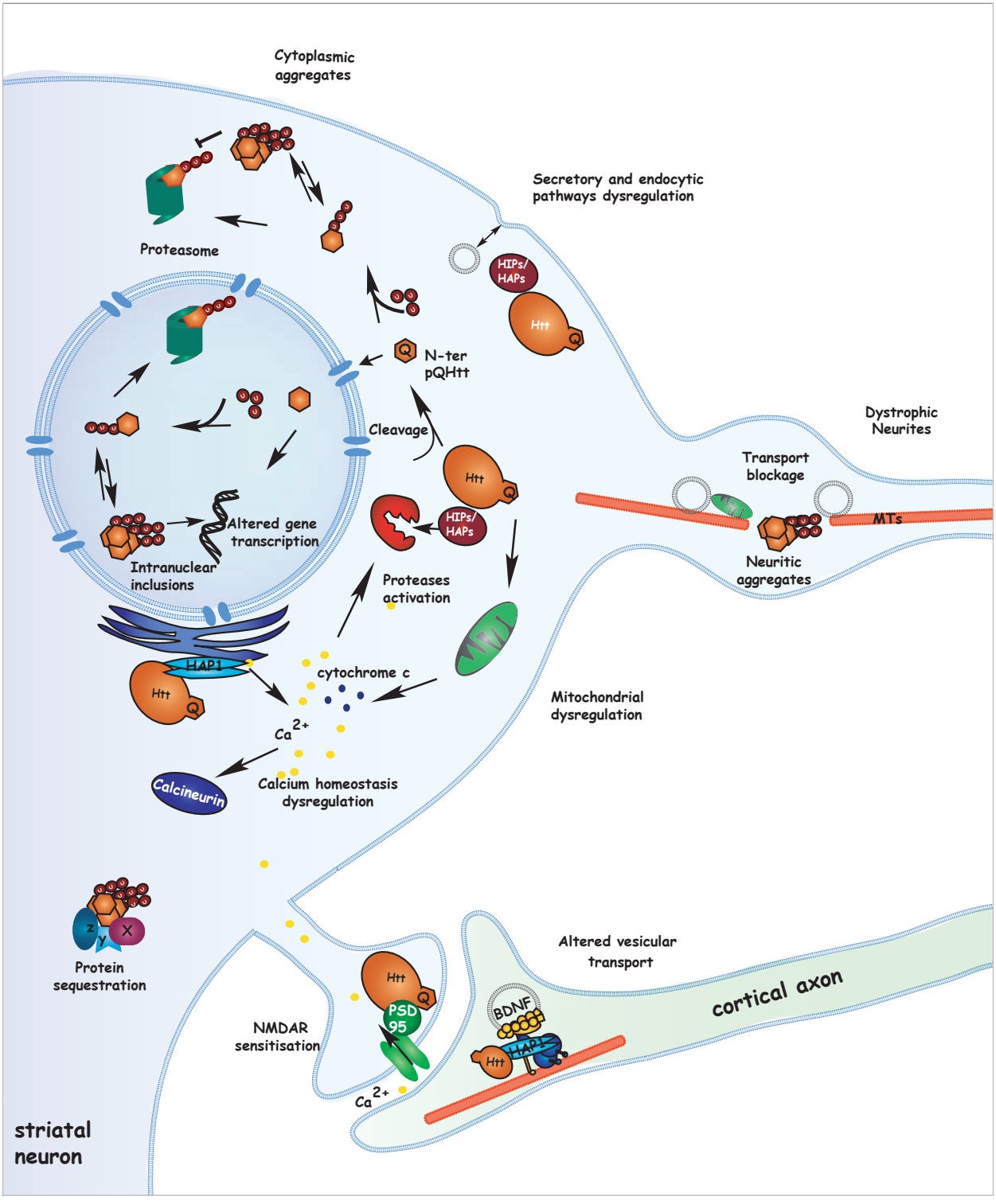

Figure 1. Mutant huntingtin is prone to modifications and induces many intracellular defects. Full-length huntingtin is cleaved by proteases in the cytoplasm, leading to the formation of cytoplasmic and neuritic aggregates. Mutant huntingtin also impairs calcium homeostasis and alters vesicular transport and recycling. Defect in BDNF transport reduces trophic support and increases neuronal death susceptibility. Whereas cytoplasmic and intranuclear aggregates are not directly toxic, neuritic aggregates could physically block transport. N-terminal fragments containing the polyQ strech translocate to the nucleus where they impair transcription and induce neuronal death. In an attempt to eliminate the toxic huntingtin, fragments are ubiquitinated and targeted to the proteasome for degradation. Intranuclear aggregates could represent temporary storage of soluble and oligomeric forms before degradation or when the proteasome becomes less efficient. Htt, Huntingtin; HIPs, huntingtin-interacting proteins; HAPs, huntingtin-associated proteins.

Therefore, in early stages of HD, disruption of the interaction of the soluble form of huntingtin with HAP1 disrupts the role of huntingtin in transport. In later stages of the disease, polyQ-huntingtin forms neuritic aggregates contributing further to a trafficking defect through a gain-of-function mechanism.

Cleavage and nuclear translocation

The proteolytic cleavage of huntingtin into N-terminal fragments containing the polyQ stretch and their subsequent translocation to the nucleus is a key step in the disease. Indeed, nuclear translocation is required to induce neurodegeneration [82], and reducing polyQ-huntingtin cleavage decreases its toxicity and slows disease progression [83, 84]. Several proteases cleave huntingtin *in vitro* and *in vivo*, and the corresponding cleavage products have been found in the brain of patients and in murine models [85]. These proteases include caspase-1, -3, -6, -7 and -8, calpain and non-identified aspartyl-proteases [84, 86–89]. Abnormal activation of these proteases could result from the various insults received by HD neurons such as excessive levels of cytosolic Ca^{2+}, reduced trophic support and activation of the apoptotic machinery. How these proteases contribute to the pathological process is not fully understood but recent studies suggest that not all the N-terminal fragments that result from proteolysis are toxic. Indeed, mutant huntingtin resistant to caspase-6 but not to caspase-3 cleavage is not susceptible to neuronal dysfunction and degeneration, indicating that the nature of the protease involved is critical for disease progression [90].

Once in the nucleus, polyQ-huntingtin induces the death of striatal neurons. Many studies have shown that nuclear polyQ-huntingtin induces the dysregulation of the transcriptional machinery. Microarray studies have revealed that several functional classes of genes are affected by polyQ-huntingtin [66]. Decreased BDNF transcription is particularly relevant to HD [91, 92]. PolyQ-huntingtin dysregulates transcription in several ways. First, polyQ-huntingtin may sequester transcription factors into aggregates, as seen for the CREB-binding protein (CBP), resulting in the inhibition of CBP- and p53-dependent transcription [93, 94]. Second, transcriptional dysregulation occurs *via* the interaction of soluble polyQ-huntingtin with TBP, CBP and p53 [71, 95–97]. Third, the Sp1/TAFII130 pathway is also altered by soluble polyQ-huntingtin, leading to transcriptional down-regulation of the nerve growth factor and dopamine D2 receptors [98, 99]. Finally, dysregulation of transcription may be mediated by the interaction between huntingtin and nuclear repressors or activators such as the nuclear receptor co-repressor N-CoR [100], the transcriptional co-repressor C-terminal binding protein (CtBP) [21] or the activator CA150 [101]. Given the involvement of many transcription factors [102], it will be of importance to dissect their relative contributions to the degenerative process.

Aggregation process and toxicity

In the nucleus, N-terminal fragments of polyQ-huntingtin form neuronal intranuclear aggregates (NIIs) (Fig. 1). Although it is well established that the nuclear localization of polyQ-huntingtin is required for neuronal death [82], the toxicity of these nuclear aggregates is still being debated [82, 103, 104]. NIIs are not directly correlated with neuronal death, as the highest percentage of NII-containing neurons are found in non-degenerating regions [60]. Also, NIIs are not correlated with cell death in neuronal models of HD *in vitro* or *in vivo* [82, 105, 106], and the probability that a given neuron will die is lower when it contains inclusion bodies [104]. The formation of NIIs may thus be a protective mechanism of the cell to store temporarily the soluble and toxic products before they are degraded by the proteasome. Consistent with this is the suppression of aggregates but the accelerated polyQ-induced cell death caused by inhibition of the ubiquitination process [82]. Indeed, transfection of a dominant-interfering form of a ubiquitin-conjugating enzyme results in the decrease of ubiquitin-immunopositive inclusions but an increased cell death. The direct role of huntingtin ubiquitination in the regulation of its polyQ-induced toxicity is also supported by experiments in which the three lysines located upstream of the polyQ stretch in the N-terminal fragment of huntingtin regulate survival of photoreceptor cells in *Drosophila* [107] and increase death of striatal neurons *in vitro* [our unpublished data]. Finally, inhibiting the proteasome leads to the accumulation of ubiquitin-immunopositive aggregates and toxicity [108]. Together, this suggests that cells will ubiquitinate the toxic fragment in order to allow its degradation by the proteasome. During these events, the ubiquitinated polyQ-huntingtin fragment might have the propensity to form macro-aggregates as intracellular stores. These aggregates are not stable structures and their formation is dynamically regulated [109–111]. Therefore, compounds that prevent aggregation by inhibiting the ubiquitination process and subsequent degradation might show some toxicity, whereas compounds or enzymes such as chaperones that enhance the degradation of the misfolded protein from the aggregates will show neuroprotection [112, 113]. However, both treatments will lead to a decrease in the formation of inclusions.

Although, ubiquitination is usually seen as a system by which the ubiquitin-proteasome system (UPS) led to polyubiquitination of a given substrate and its subsequent degradation, ubiquitination can occur as a monoubiquitination process or even as multiple monoubiquitination

processes at different sites [114]. In these cases, the resulting post-translational modifications could have a different consequence, such as promoting nuclear translocation of the mutant huntingtin into the nucleus [115, 116].
In addition to the UPS, autophagy also regulates inclusion formation by promoting the clearance of mutant huntingtin through lysosomal-mediated degradation [117–119]. From these data, it appears clear that the mechanisms that regulate huntingtin aggregation and toxicity are far from being completely understood and that further studies are needed. Indeed, although NIIs are not directly linked to cell death, they may play a role in inducing neuronal dysfunction. Transgenic mice carrying huntingtin exon 1 with an expanded polyQ stretch have a very high percentage of intranuclear inclusions, develop progressive behavioural symptoms and neuropathology, but display only little evidence for cell loss [103, 120–122]. Furthermore, the massive aggregation of misfolded huntingtin may disrupt intracellular homeostasis by inhibiting the proteasome, thus inducing neurotoxicity [123–126]. However, the role of the polyQ-containing proteins, whether aggregated or not, in inducing proteasome dysfunction is not clear cut [127–129].

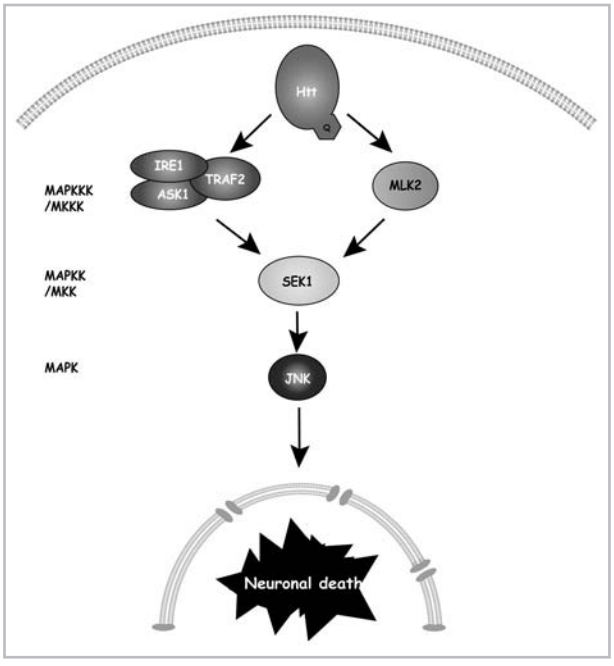

Figure 2. PolyQ-huntingtin activates JNK by phosphorylation of the intermediate proteins MLK2 and SEK1. It also activates the stress response of the endoplasmic reticulum- resident protein IRE1, which, in turn induces the formation of the IRE1-TRAF2-ASK1 complex that activates JNK. UV light, stress and radiation inputs stimulate MEKK1 which can also modulate the activity of JNK.

Signalling pathways and disease

As well as modulating the expression of signalling molecules, several studies have suggested that signal transduction pathways involving the phosphorylation of different substrates are modified by polyQ-huntingtin expression (Fig. 2). PolyQ-containing polypeptide expression has been shown to cause cellular stress responses. Among these, the induction of heat shock proteins has been described in several models [130].
Another stress response is the activation of mitogen-activated protein kinase (MAPK)-signalling pathways that initiate an apoptotic program [131, 132]. Among the first MAPKs shown to play a role in HD were the JNKs, which are important transcription regulators for controlling programmed cell death or apoptosis [133]. Expression of polyQ-huntingtin activates JNK in several models [134–136]. This activation involves the mixed-lineage kinase 2 (MLK2), a brain activator of JNK [137–139]. MLK2 binds directly to the MAP kinase kinase 7 (MKK7) and stress-signalling kinase 1 (SEK1) and activates them by phosphorylation. MKK7 and SEK1 then activate JNK thus initiating neuronal apoptosis. In agreement with these results, Yasuda et al. [140] also reported in a rat pheochromocytoma cellular model (PC12) of HD, the inhibition of polyQ-induced cell death by a dominant-negative form of SEK1 [140]. JNK and the transcription factor c-jun, the major target of JNK, are activated in striatal neurons when treated with 3-NP, a chemical that models HD, or when transfected with exon 1 of huntingtin [141].

The JNK pathway may also be modulated through the activation of the endoplasmic reticulum (ER) stress response (Fig. 2). The accumulation of unfolded proteins within the ER lumen induces a stress response whose initial mediators are ER-resident type I transmembrane serine/threonine protein kinases, PERK and IRE1 [142, 143]. The accumulation of unfolded proteins in the ER lumen induces their autophosphorylation, which subsequently activates a cytoplasmic signal transduction. Activated IRE1 recruits TNF receptor associated factor 2 (TRAF2) [144]. The mammalian MAPK kinase kinase, called the apoptosis signal-regulating kinase (ASK1), interacts directly with TRAF2, which then induces the cascade activations of SEK1 and JNK. This cascade is important in polyQ-induced ER stress because the polyQ fragments cause neuronal ER stress through ASK1 activation by the formation of an IRE1-TRAF2-ASK1 complex [145]. Several studies have now shown that polyQ impairs proteasomal activity [124, 145]. Proteasome inhibition also induces ER chaperones and activation of IRE1/PERK. As misfolded proteins are exported from the ER to the cytoplasm, where they are degraded by the ubiquitin-proteasome complex, the inhibition of the ubiquitin-proteasome system by polyQ may trigger ER stress by inducing the accumulation of misfolded proteins in the ER [145].

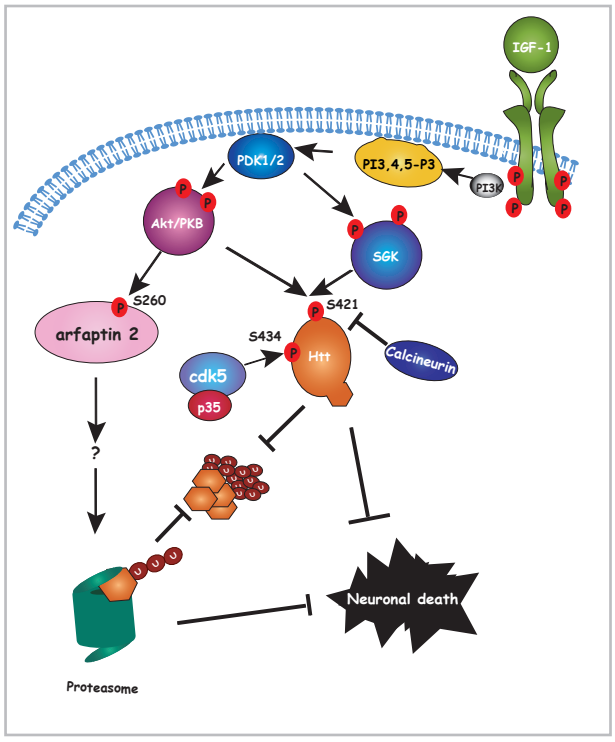

Figure 3. Several signalling pathways directly regulate polyQ-huntingtin-induced toxicity. The survival factor IGF-1, by activating protein kinases such as Akt and SGK, blocks polyQ-huntingtin-induced neuronal death. Akt and SGK act by phosphorylating huntingtin at serine 421 and other substrates such as arfaptin 2 that regulates proteosomal activity. Huntingtin phosphorylation is decreased by the phosphatase calcineurin that becomes activated upon high intracellular levels of Ca^{2+}. The kinase p35/Cdk5 regulates cleavage and toxicity of polyQ-huntingtin by phosphorylation at serine 434.

Other stressful treatments such as UV irradiation and cytokines have been linked with the activation of another kinase, MAPK kinase kinase 1 (MEKK1). As with MLK2, MEKK1 acts upstream from the MAPKs and regulates the JNK, ERK, p38 and NF-κB pathways [146]. MEKK1 and stressful treatments such as UV irradiation increase the intracellular aggregation of polyQ-containing peptides by reducing their solubility in transfected cells [147].

Huntingtin itself is a phosphoprotein (Fig. 3). This suggests that, as for many other proteins, phosphorylation could be a key for regulating wild-type and polyQ-huntingtin function/dysfunction. Huntingtin is phosphorylated at serine 421 by the serine-threonine kinase Akt, which is a potent prosurvival kinase [148–150] (Fig. 3). This phosphorylation blocks polyQ-huntingtin-induced toxicity in striatal neurons. In addition, the IGF-1/Akt pathway is altered during pathogenesis [151]. Consistent with this is the reduction in the phosphorylation of serine 421 of huntingtin in the presence of polyQ expansion [149, 150]. Serine 421 is also phosphorylated by the serum and glucocorticoid-induced kinase, SGK [152]. SGK levels are increased in disease. This dysregulation occurs through the MAPK/p38 pathway and may reflect a stress response to the presence of polyQ-huntingtin. Dephosphorylation by the calcium/calmodulin-regulated protein phosphatase, calcineurin, dynamically regulates serine 421 [150]. Calcineurin decreases the phosphorylation at serine 421 thus increasing polyQ-induced toxicity of striatal neurons. Huntingtin is also phosphorylated at serine 434 by Cdk5, a member of the serine/threonine cyclin-dependent kinase (Cdk) family [153]. Phosphorylation of serine 434 reduces mutant huntingtin cleavage, which attenuates aggregate formation and cell death. Furthermore, the activity of Cdk5 is lower in the brains of HD transgenic mice than in controls. Together, these results show that the phosphorylation state of polyQ-huntingtin can determinate its toxicity. Huntingtin is clearly the substrate of many other kinases and phosphatases and, therefore, cells have access to a large panel of as yet unknown modifications that can specifically regulate huntingtin function/dysfunction.

Towards therapies for HD

Therapeutic research in HD is a major issue as there is currently no treatment for preventing or delaying the progression of the disease. Currently, patients are given general symptomatic and non-specific HD treatments, such as antidepressants or neuroleptics but different approaches for achieving reliable, satisfactory and specific HD treatments that could interfere with HD pathogenic mechanisms are currently being studied. For these treatments to be satisfactory, they need to reduce the symptoms such as involuntary movements and also have neuroprotective effects.

To date the only approach showing beneficial results is a transplantation strategy that is replacing dead neurons with ones phenotypically similar to those lost [154]. The graft is performed by stereotaxic injections of fetal neuroblasts into the striatum of patients [155–157]. Patients show motor, functional and cognitive improvement [158], and the transplanted neurons partially rescue the cortico-striatal loop [159]. Although this is a promising approach, precautions are needed because there are still not enough data to judge the final fate of the transplanted neurons. Furthermore, clinical improvement might not be permanent [160], and this approach poses complex ethical questions and is limited to a very few patients.

Another ongoing approach is the testing of candidate drugs based on the study of the molecular causes of the disease (Table 2). This is now possible as the pathways by which polyQ-huntingtin induces neuronal death are better understood and should allow compounds that interfere with the toxicity of polyQ-huntingtin to be developed. As the mutant protein in HD misfolds and accumulates into

Table 2. Possible therapeutic compounds for HD.

Candidate drug	Tested in HD	Mechanism of action	FDA approved	References
Coenzyme Q10	mouse, rat, human clinical phase I	antioxidant	Yes	188, 189, 232
Creatine	mouse, rat, human clinical phase I	maintains the energy balance in the brain	yes	187, 233–235
Cystamine	fly, mouse	TGase and caspase-3 inhibitor, antioxidant, increases BDNF	no	42, 185, 195, 196, 236
Cysteamine (Cystagon)	neuronal cells, mouse, monkey, human phase I	TGase and caspase-3 inhibitor, antioxidant, increases BDNF	yes	185, 237
Geldanamycin	mouse neurons and organotypic sclices	activates heat shock response	no	113, 238
Lithium	fly, mouse, rat, human phase I	authophagy inducer	yes	239–242
Memantine	rat, human clinical phase I	NMDA receptor agonist	yes	243, 244
Minocycline	mouse, rat human	antiapoptotic	yes	172, 173, 245, 246
Mithramycin	mouse, rat	transcription regulator	yes	247, 248
Paroxetine	mouse	serotonin endocytosis inhibitor	yes	184
Rapamycin	fly, mouse	authopagy inducer	yes	176, 249, 250
Remacemide	mouse, human clinical phase I	NMDA receptor agonist	yes	167, 232, 251
Resveratrol	nematode	antioxidant	no	252
Sodium/phenyl butyrate	mouse	transcription regulator	no	167
Suberoylanilide hydroxamic acid	fly, mouse	transcription regulator	yes	166, 168
Tacrolimus (FK506)	neuronal cells, neurons	calcineurin inhibitor	yes	150
Tauroursodeoxycholic acid	mouse, rat	antiapoptotic	yes	253
Trehalose	mouse	protein aggregation inhibitor	yes	161

aggregates, promoting the degradation of the toxic protein may be a therapeutic strategy. This involves activating chaperone proteins by compounds such as geldanamycin, which induces expression of Hsp70, Hsp40 and Hsp90 [113]. Hsp70, Hsp40 and Hsp90 then promote the heat shock response leading to the unfolding of misfolded proteins and their degradation through the proteasome. Although it is unclear how disaccharide trehalose mediates neuroprotection, it reduces the amount of mutant huntingtin aggregates in brain and liver and extends the lifespan of treated HD mice [161]. Another approach is to directly target the proteasome to promote the degradation of toxic products and to remove aggregates or to inhibit the shock to proteasome induced by the presence of aggregated and misfolded proteins [162]. Although some proteins such as arfaptin 2 could play a role in promoting proteasome activity [163], this strategy has yet to show promise and more research is needed [164].

We have discussed the transcription dysregulation that occurs in HD. This observation led to the discovery that histone deacetylase (HDAC) inhibitors may be therapeutically interesting [165]. HDAC inhibitors increase the acetylation of histones, which could compensate for the decrease in acetylation and repressed gene transcription caused by the polyQ expansion [166]. Recent studies using mouse models of HD have shown that treatment with HDAC inhibitors such as suberoylanilide hydroxamic acid, sodium butyrate or phenylbutyrate increases body weight, improves motor performance and delays the appearance of neuropathological symptoms in these mice [167–169].

Increased apoptosis has been detected in post mortem brains from HD patients [170] and there is evidence from cellular and mouse models [82, 171] to suggest that compounds that can inhibit apoptosis may be therapeutically interesting in HD. In particular, the antibiotic minocycline, which possesses anti-apoptotic and anti-inflammatory properties, may prove beneficial in HD [172]. Although some studies showed opposing results [173, 174], clinical trials are ongoing and may validate the use of this drug in patients [175]. Other strategies could involve the activation of autophagy which promotes the clearance of accumulated and/or aggregated toxic proteins in HD. Rapamycin, by inhibiting the mammalian target of rapamycin and activating autophagy, shows some neuroprotective effect in fly and mouse models of HD [176].

A lack of neurotrophic factors, especially BDNF, has been demonstrated in HD [42, 91, 177]. Therefore, compounds that increase neurotrophic factor production, transport and release may also be potentially interesting in HD treatment. For these strategies to be efficient, one has to consider the possible downregulation of the receptors for

these trophic factors, as was recently shown for TrkB, the receptor for BDNF [178]. Nevertheless, trophic factors have been shown to have neuroprotective effects on different neuronal populations of the striatum [179]. Indeed, ciliar neurotrophic factor (CNTF) has shown a high rescue potential in several mouse models and has been tested in clinical trials [180]. BDNF may be particularly potent in the case of HD as it rescues neuronal death *in vitro* and regulates the onset of the disease *in vivo* in mouse models of HD [82, 181]. Trophic factors need to be delivered in the brain, and therefore approaches that use encapsulated cells producing the trophic factor or lentiviral-mediated gene expression are being actively developed and tested [180, 182, 183]. Other strategies could involve identifying compounds that enhance the production or secretion of BDNF, such as the antidepressant paroxetine [184]. Interestingly, cysteamine, one candidate drug for HD, has recently been shown to increase BDNF levels in brain and to induce neuroprotection in HD mouse models through this mechanism (see below) [185]. In addition to deprivation in trophic support, HD is characterized by a severe energy deficit and by impaired mitochondria [186]. These findings led to the first clinical trials in HD of drugs that improve mitochondrial function, such as coenzyme Q10 and creatine [187–189].

Another promising candidate for HD treatment is the transglutaminase (TGase) inhibitor cystamine. TGase is a calcium-dependent enzyme that catalyses the formation of $\varepsilon(\gamma$-glutamyl)lysine isopeptide bonds between a polypeptide-bound glutamine and a lysine of the protein substrate [190, 191]. TGase is thought to participate in HD pathogenesis [192] and is upregulated in the brains of HD patients and HD mice [193–196]. HD mice lacking TGase 2 and HD mice treated with cystamine show less neuronal death, improved motor performance and prolonged survival [195–199]. As well as an inhibitor of TGase, cystamine may also have pleiotropic effects, as it inhibits caspase-3 activity [200], prevents mitochondrial depolarization [201] and increases the levels of antioxidants such as glutathione and L-cysteine [200, 202]. One important mechanism by which cystamine is neuroprotective involves the upregulation of the brain chaperone, HSJ1b, and the inhibition of TGase. Interestingly, both proteins are located on the Golgi apparatus and regulate secretion of clathrin-coated vesicles that contain BDNF; their upregulation increases the secretion and release of BDNF [185]. Cysteamine, the FDA-approved reduced form of cystamine, was shown to be as efficient as cystamine in increasing BDNF levels in mouse brains and is neuroprotective in HD mouse models through a BDNF-dependent mechanism. Interestingly, cysteamine increases serum levels of BDNF in mouse and primate models of HD, reinforcing the rationale of cysteamine as a potential treatment for HD, and indicating that serum BDNF levels can be used as a biomarker for drug efficacy [185].

Another possible candidate drug is the immunophilin ligand drug FK506 (Tacrolimus). It was initially identified as an immunosuppressant by binding to appropriate receptors (immunophilins) [203]. Drugs such as FK506 and cyclosporin A are potentially interesting for the treatment of neurological disorders, such as cerebral ischaemia, and chronic neurodegenerative disorders, such as Parkinson's disease and amyotrophic lateral sclerosis, because they can inhibit the protein phosphatase 2B, calcineurin [204]. We recently demonstrated that calcineurin dephosphorylates huntingtin at S421 and that calcineurin inhibition by FK506 abrogates mutant huntingtin-induced toxicity in neurons and promotes phosphorylation of huntingtin at S421 in HD mouse models [150]. In HD, Akt activity and the resulting S421 phosphorylation is reduced [149, 151]. Moreover, neurodegeneration *in vitro* and *in vivo* is increased by decreasing huntingtin phosphorylation [148, 150]. Therefore, FK506, a drug routinely used in transplantation surgery and that crosses the blood-brain barrier may be a new therapeutic strategy for treating HD patients.

Conclusion and perspectives

Although intense research in HD has led in recent years to a better understanding of the molecular cascade leading to death, several questions remain unanswered. The specificity of striatal death in disease is not understood, i.e. why huntingtin, a ubiquitous protein, kills only striatal neurons, although some contributing factors, such as the loss of BDNF trophic support from the cortico-striatal projecting neurons, have been identified [42, 91, 205]. Microarray studies have identified many genes that are selectively increased or decreased in specific neurons during disease [66, 206, 207]. There is now a need for the physiological validation of these genes *in vivo.* Similarly, yeast two-hybrid studies have led to the characterization of a large number of huntingtin-interacting proteins, but how these proteins function in an interacting network in normal situation and how dysregulation of these interactions affects the physiology of the whole organism is unknown.

In HD, the CAG repeat is the major determinant of age of onset. However, a significant variability in the age of onset exists for individuals with the same CAG repeat [208] suggesting that modifying factors exist. Indeed, extensive study of the Venezuelan kindreds has revealed that genetic factors contribute significantly to this variability [209]. Identification and characterization of these modifiers, be they genetic or environmental, is important, because their modulation could slow down effectively the appearance of the symptoms or their progression. Hopefully, a combination of molecular approaches in cellular and animal models with genetic studies of HD patients

might lead to the validation of these important regulators of huntingtin toxicity.

A better understanding of huntingtin biology has allowed the emergence of new concepts for the disease. First, HD should not simply be considered as only a disease of neuronal death. Indeed, neuronal dysfunction plays an important role in the appearance and progression of the clinical symptoms. Second, both a gain of a new toxic function of the mutant protein and the loss of the protective functions of wild-type huntingtin participate to the disease mechanisms that ultimately lead to the death of neurons in the brain. Given the importance of not only the polyQ stretch but also the proper function of huntingtin and its influence on polyQ-induced toxicity, therapeutic strategies should focus on both the inhibition of neuronal dysfunction and death but also on restoring normal huntingtin function.

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