Multiple pathways contribute to the pathogenesis of Huntington disease
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Abstract
Huntington disease (HD) is caused by expansion of a polyglutamine (polyQ) domain in the protein known as huntingtin (htt), and the disease is characterized by selective neurodegeneration. Expansion of the polyQ domain is not exclusive to HD, but occurs in eight other inherited neurodegenerative disorders that show distinct neuropathology. Yet in spite of the clear genetic defects and associated neurodegeneration seen with all the polyQ diseases, their pathogenesis remains elusive. The present review focuses on HD, outlining the effects of mutant htt in the nucleus and neuronal processes as well as the role of cell-cell interactions in HD pathology. The widespread expression and localization of mutant htt and its interactions with a variety of proteins suggest that mutant htt engages multiple pathogenic pathways. Understanding these pathways will help us to elucidate the pathogenesis of HD and to target therapies effectively.

Background
Huntington's disease (HD) was first described by the American physician George Huntington in 1872. The disease is a genetic disorder of the central nervous system, with symptoms usually consisting of uncontrolled movements, emotional disturbances, and mental deterioration [1,2]. Psychiatric abnormalities, including depression, anxiety, apathy, and irritability, are often an early manifestation of HD, appearing before the characteristic neurologic symptoms of overt chorea, or spasmodic movements of the limbs and facial muscles [3,4]. Patients also demonstrate cognitive deficits or dementia as well as weight loss. The age at onset is variable, but most HD patients first show symptoms between the ages of 30 and 40 years [5,6]. Clinical features develop progressively, with an increase in choreic movements, dementia, and other motor deficits including dystonia and rigidity. HD terminates in death within 10–20 years after initial symptoms appear. While there are medications to help manage the signs and symptoms of HD, treatments that can actually prevent the physical and mental decline associated with HD are lacking.

HD is inherited as an autosomal dominant condition and is found in every country of the world. In the United States alone, about 30,000 people have HD, making its prevalence about 1 in every 10,000 persons. At least 150,000 others carry a 50 percent risk of developing the disease, and thousands more of their relatives live with the possibility that they might develop HD.

The hunt for the HD gene involved an intense molecular genetics research effort by investigators cooperating around the globe. For 10 years, scientists were focused on a segment of chromosome 4p16.3, and they succeeded in isolating the HD gene in 1993 [7]. The genetic defect
responsible for the disease is expansion of a CAG repeat in the gene coding for the HD protein, huntingtin (htt). This CAG repeat is an unstable triplet repeat DNA sequence, and its length is inversely correlated with the age at onset of disease, especially in juvenile HD cases, when the repeat length is often >60 CAG units [8-10]. Expanded CAG repeats have been found in 8 other inherited neurodegenerative diseases, as well, including spinocerebellar ataxia (SCA) and spinobulbar muscular atrophy (SBMA) [11-13]. It is now clear that expansion of this repeat in various genes can cause distinct neurodegenerative pathology in different disorders.

The CAG repeat is translated into a polyglutamine (polyQ) domain in the disease proteins. Human htt is a large protein consisting of 3144 amino acids. A normal polyQ domain, which in htt begins at amino acid position 18, typically contains 11–34 glutamine residues in unaffected individuals, but this expands to more than 37 glutamines in HD patients. The length of the polyQ repeat varies among species. For example, mouse htt has 7 glutamines, whereas pufferfish htt contains only 4 [14], which suggests that the polyQ domain may not be essential, but that it can regulate protein function. Consistently, deletion of the CAG repeat in the HD gene only results in subtle behavioral and motor phenotypes in mice [15].

Htt is ubiquitously expressed in the brain and body and distributed in various subcellular regions [16-19]. Its sequences do not show homology to other proteins of known function. One structural feature of htt that has been identified is the presence of HEAT repeats [20], which are sequences of ~40 amino acids that occur multiple times within a given protein and are found in a variety of proteins involved in intracellular transport and chromosomal segregation [21]. Several lines of evidence also suggest that htt is involved in intracellular trafficking and various cellular functions. For example, htt is associated with a number of subcellular organelles [16-18,22]. Consistent with this, htt is known to interact with a variety of proteins that can be grouped according to whether they are involved in gene transcription, intracellular signaling, trafficking, endocytosis, or metabolism [14,19]. Identification of these htt-interacting proteins suggests that htt may function as a scaffold involved in coordinating sets of proteins for signaling processes and intracellular transport.

The essential role of htt has been established using HD gene knockout mice. In this model, the absence of htt causes cell degeneration and embryonic lethality [23-25]. Conditional knockout mice also show degeneration in adult cells [26]. These observations have led to the theory that a loss of htt function may contribute to the neuropathology of HD [27]. However, there is more evidence to support the theory wherein mutant htt gains a toxic function. For example, heterozygous HD knockout mice are known to live normally. Further, identification of the HD gene has allowed for generation of various animal models in which mutant htt is expressed in the presence of endogenous normal htt, and these transgenic mice still develop neurological symptoms and die early, even when endogenous normal htt is expressed at the normal levels [28,29]. In addition, mutant htt can rescue the embryonic lethal phenotype of htt-null mice [30], which also suggests the HD mutation can lead to neuronal toxicity, independent of the essential function of htt.

**Neuropathology of Huntington’s disease**

Despite its widespread distribution, mutant htt causes selective neurodegeneration, which occurs preferentially and most prominently in the striatum and deeper layers of the cortex in the early stages of HD [31]. In advanced stages, other brain regions, such as the hippocampus, hypothalamus, cerebellum, amygdala, and some thalamic nuclei, are also affected. Among these other brain regions, the lateral tuberal nuclei of the hypothalamus exhibits severe atrophy [32].

The neurons that are most severely affected in HD are striatal projection neurons, which send their axons to different brain regions. These are the GABAergic medium-sized spiny neurons (MSNs), and they constitute 95% of all striatal neurons. MSNs receive abundant glutamatergic input from the cortex and primarily innervate the substantia nigra and globus pallidus. Thus, their preferential loss in HD is thought to be the result of glutamate excitotoxicity. Consistently, there is a relative sparing of interneurons that colocalize somatostatin, neuropeptide Y, and NADPH diaphorase, as well as of cholinergic interneurons and a subclass of GABAergic neurons that contain parvalbumin [31,33,34].

Another important pathological feature in the postmortem brains of HD patients is gliosis [35-37]. Reactive glia or gliosis often occurs in response to neuronal injury. For example, neuronal degeneration is evidenced by a dramatic elevation in the density of large glia [38]. Marked astrogliosis and microgliosis were observed in caudate and internal capsule samples of HD patients, but not in normal brain. In the striatum and cortex, reactive microglia also occurred in all grades of pathology, accumulated with increasing grade, and grew in density in relation to the degree of neuronal loss [35,37]. Thus, reactive microglia were considered to be an early response to changes in neuropil [37]. While reactive gliosis does represent an early neuropathological event in HD, glial pathology can also impact neuronal viability. Indeed, gliosis is a pathological feature in several HD mouse models that lack overt neuronal cell degeneration. These models include trans-
Since the discovery of the HD gene, various antibodies to htt have been generated to characterize the distribution of mutant htt. Immunostaining of brains from transgenic mice that express mutant htt revealed nuclear inclusions [28]. Similar nuclear inclusions were then identified in the brains of HD patients [44,45]. Subsequently, the accumulation of expanded polyQ-containing proteins in the nucleus and nuclear inclusions were found to be common pathological features of other polyglutamine diseases [11-13]. The role of these nuclear inclusions in HD remains controversial, since their formation is correlated with disease progression, but is not associated with neuronal degeneration [45-47]. Further, several studies have shown that htt inclusions are protective against htt toxicity in cultured cells [48,49]. Despite the controversy surrounding their exact roles, htt inclusions reflect protein misfolding caused by expanded polyQ domains and represent a pathological hallmark for the accumulation of toxic mutant htt. It is also noteworthy that normal htt is predominantly localized in the cytoplasm, whereas mutant htt with its expanded polyQ domain accumulates in the nucleus. Therefore, nuclear inclusions reflect the aberrant accumulation of mutant htt in the nucleus, as well. Importantly, HD also features abundant cytoplasmic aggregates localized in the neuronal processes (neuropil aggregates), including axons and dendrites [29,45,50-54]. In the early stage of disease, the brains of HD patients contain more dystrophic neurites or neuropil aggregates than nuclear inclusions [44,45]. In addition, the progressive formation of neuropil aggregates is correlated with disease progression in transgenic mice [50-52,54], and neuropil aggregates are associated with axonal degeneration in HD mouse brains [40,52]. Taken together, the localization of htt aggregates in the nucleus and neuronal processes reveals that mutant htt elicits toxicity in both the nucleus and cytoplasm.

A number of mouse models have provided in vivo evidence for the pathology of HD. Several transgenic HD mice were generated using either the human htt promoter or neuronal promoters. For example, transgenic mice R6/2 express exon1 htt with 115–150 glutamine repeats (115–150Q) under the control of the human HD gene promoter [28]. YAC transgenic mice use the human HD gene promoter to drive the expression of full-length mutant htt [55,56]. N171-82Q transgenic mice express the first 171 amino acids with 82Q under the neuronal prion promoter [29]. These transgenic mice have been widely studied and found to have neurological and behavioral phenotypes similar to those of HD patients. There are also HD repeat knock-in mouse models, which are generated by inserting an expanded repeat into the endogenous mouse HD gene [43,57-59]. However, most HD mouse models do not show the overt neurodegeneration seen in human HD patients, even though some models display severe neurological symptoms and early death [28,29]. It is possible that the short life span of the mouse does not allow sufficient time for the development of obvious neurodegeneration, although some earlier pathological events do occur.

HD mouse models also suggest that small htt fragments containing expanded polyQ are more toxic than larger fragments. This fits with the finding that small N-terminal htt fragments are misfolded and form aggregates and inclusions in the brains of HD patients [44,45]. It is evident that proteolysis of htt generates multiple N-terminal htt fragments in HD repeat knock-in mouse brain [60]. A number of protease cleavage sites, including those for caspase-3, cspase-6, calpain, and unknown aspartic protease, have been found within the first 550 amino acids of htt [56,61-64]. However, most studies used transfected proteins to identify these cleavage sites, and the nature of toxic N-terminal htt fragments generated organically in the HD brain is still being explored. It is likely that the proteolysis of full-length htt generates a number of N-terminal htt fragments. The decreased activities of the proteasomes and chaperones, which are responsible for clearing out misfolded and toxic peptides, promote the accumulation of htt fragments in aged neurons. In the meantime, an expanded polyglutamine tract causes them to misfold and aggregate in the nucleus and neuronal processes. The accumulation of mutant htt in the nucleus and neuronal processes therefore suggests that these subcellular regions are the primary sites for mutant htt to elicit its toxicity.

**Nuclear effect of mutant huntingtin**

The nuclear inclusions of mutant htt led investigators to study the mechanisms for this phenomenon. Although some immunostaining and nuclear fractionation studies have shown that normal htt is also localized in the nucleus [65,66], it is clear that the majority remains in the cytoplasm. Moreover, nuclear htt aggregates can only be recognized by antibodies against the N-terminal region of htt [44,45]. Furthermore, isolation of nuclear fractions from HD knock-in mice, which express full-length mutant htt under the endogenous mouse HD gene, provides evidence that multiple N-terminal htt fragments accumulate in the nucleus [60]. The association between nuclear accumulation of mutant htt and disease progression is clear from several HD mouse models. In HD knock-in mouse models, mutant htt accumulates preferentially in the nuclei of striatal neurons and forms more prominent aggregates as the disease progresses [43,58]. A progressive phenotype is also associated with the nuclear accumulation of an amino-terminal cleavage fragment in a transgenic mouse model with inducible expression of full-
length mutant huntingtin [67]. Targeting mutant htt with nuclear localization sequences to direct mutant htt in the nucleus of mouse brains produces neurological phenotypes [68,69]. Furthermore, prevention of htt cleavage by mutating the caspase-6 site can alleviate neurological phenotypes and delay the nuclear accumulation of mutant htt in YAC transgenic mice [56].

Studies of N-terminal htt fragments have failed to find that these fragments contain nuclear localization sequences. Thus, N-terminal htt fragments may passively enter the nucleus, but expanded polyQ repeats prevent their export from the nucleus [70]. The presence of mutant htt fragments in the nucleus and various cleavage sites in the N-terminal region of htt [61-64,71] also support the notion that proteolysis of htt leads to generation of toxic htt fragments. Consistently, smaller N-terminal htt fragments appear to be more toxic than large-sized fragments in both cultured cells [72] and transgenic animals [28,29,40]. For example, R6/2 mice that express exon1 (1-67 amino acids) with 115–150Q show more severe neurological phenotypes than transgenic mice that express longer-fragment (N171-82Q) or full-length mutant htt [28,29,56]. In addition, transgenic mice expressing smaller htt fragments show more abundant htt inclusions in the nucleus than those expressing longer htt fragments.

The aberrant nuclear accumulation of mutant htt is likely to cause gene transcriptional dysregulation. Indeed, several nuclear transcription factors are found to bind htt [19,73]. Of these, the coactivators cAMP response element-binding protein (CREB)-binding protein (CBP) and specificity protein 1 (Sp1) are particularly important for neuronal function. Deletion of CREB in the brain causes selective neurodegeneration in the hippocampus and striatum [74]. Many neuronal genes that lack a TATA box require Sp1 for their transcription [75]. Dysregulation of gene expression mediated by CBP and Sp1 have been found in HD mouse brains [76].

The interactions of mutant htt with transcription factors may occur at various binding sites. Many transcription factors contain a polyQ-rich domain. Since CBP is recruited into aggregates formed by different polyQ proteins, such as the androgen receptor [77], the SCA3 [78], and the DRPLA [79] proteins, it has been thought that the polyQ domain is the binding site to interact with other polyQ proteins. In support of this idea, a number of transcription factors containing polyQ or proline-rich domains, including CBP [79,80], TBP [81,82], and TAF130 [83], have been found in nuclear polyQ inclusions. However, subsequent studies showed that the acetyltransferase domain in CBP interacts with htt [78,80], which led to the finding that inhibition of histone deacetylase (HDAC) or promotion of histone acetylation ameliorates neurodegeneration in cellular and fly models [80] and motor deficits in a mouse model of HD [84]. The colocalization of some transcription factors in nuclear polyQ inclusions also led to the idea that recruitment of transcription factors into polyQ inclusions reduces the level of these transcription factors. After examining several HD mouse models, however, researchers were unable to find decreased levels of CBP in symptomatic mouse brains [54,85]. In addition, altered expression of a number of genes was not necessarily associated with the formation of htt aggregates in HD mouse brains [76] and could occur in cell models in the absence of nuclear inclusions [86,87]. Thus, it is likely that soluble or misfolded htt may interact with transcription factors to alter transcriptional activity. This idea is further supported by the finding that soluble mutant htt reduces the binding of Sp1 to DNA [88,89].

Several other important transcription factors are also implicated for their interactions with htt in the nucleus. TAF130, which is an important transcription factor that binds TBP and is involved in Sp1 and CREB-dependent gene transcription, binds htt [88] and other polyQ proteins, such as the DRPLA and SCA3 proteins [83]. TBP, which is a basal transcriptional factor containing a polyQ stretch, is also found to colocalize with polyQ inclusions [81,82] and to associate with htt in vitro [90]. In addition, htt interacts with p53 in the nucleus to affect cell viability [91]. Recent studies also show that mutant htt can affect PGC-1alpha (peroxisome proliferator-activated receptor gamma coactivator 1 alpha), which transduces many physiological stimuli into specific metabolic programs by stimulating mitochondrial activity. Lack of this transcription factor causes degeneration in different types of cells, including striatal neurons [92,93]. Cui et al.’s study showed that mutant htt associates with the promoter of the PGC-1alpha gene to affect its expression, thereby mediating striatal degeneration [94]. The interference of PGC-1alpha function is also observed in brown fat tissues in HD transgenic mice [95]. These studies suggest PGC-1alpha as a new therapeutic target in HD. Combined, there is ample evidence that mutant htt acts in the nucleus to affect gene transcription.

**Cytoplasmic effect of mutant huntingtin**

Earlier studies have reported that mutant htt increases caspase activity [96-99] and affects various signaling pathways [100-104]. These findings suggest that mutant htt also acts in the cytoplasm to affect cellular functions. Thus began an intensive search to reveal the interactions between htt and cytoplasmic proteins. By means of the yeast two-hybrid screen and in vitro binding assays, a number of cytoplasmic proteins were found to interact with htt [14,18,105]. Of these, htt-associated protein 1...
transport cultured neurons shows that mutant htt can affect axonal body aggregates. Also, expressing polyQ proteins in expression of full-length mutant htt impaired vesicular anterogradely and retrogradely, and mutant htt disrupts portion of brain-derived neurotrophic factor (BDNF) both neurites, htt is involved in HAP1-associated axonal trans- soluble pool of these proteins in axons. In cultured microtubule transporter proteins, thereby reducing the cytoskeleton and endocytosis [118] and binds clathrin and alpha-adaptin subunit AP-2 [119-121]. The interactions of HIP1 with these proteins may constitute a protein complex involved in clathrin-mediated endocytosis. Unlike HAP1, HIP1 binds mutant htt weakly [118]. This suggests that HIP1 requires interaction with htt for normal function, whereas dissociation from mutant htt may impair its function.

Although the interactions of htt with HAP1, HIP1, and other cytoplasmic proteins suggest that htt is involved in intracellular trafficking, more compelling evidence has come from the studies of trafficking function in cells that express mutant htt. Recent studies show that normal Drosophila htt functions in the axonal transport pathway and that polyQ expansion causes soluble htt to recruit more microtubule transporter proteins, thereby reducing the soluble pool of these proteins in axons [122]. In cultured neurons, htt is involved in HAP1-associated axonal transport of brain-derived neurotrophic factor (BDNF) both anterogradely and retrogradely, and mutant htt disrupts this transport [107]. Trushina et al (2004) also found that expression of full-length mutant htt impaired vesicular and mitochondrial trafficking in mouse neurons [123]. Similarly, expanded polyQ in the first exon of htt can cause axonal abnormalities prior to cell body degeneration in Caenorhabditis elegans, even in the absence of cell body aggregates [124]. Also, expressing polyQ proteins in cultured neurons shows that mutant htt can affect axonal transport [125].

Because of the limited space of neuronal processes, neuropil aggregates themselves may physically impair trafficking or affect neurotransmitter release [126,127]. Recently, htt aggregates were found to affect the trafficking of mitochondria [128], suggesting that neuropil aggregates could also impair the trafficking of other organelles. There is strong evidence for the pathological role of polyQ aggregates in axonal degeneration. As mentioned previously, abundant dystrophic neurites are evident in pre-symptomatic postmortem HD patient brains in the cortex and the striatum, the two areas most affected in HD [44,45]. Dystrophic neurites are abnormal structures outside the cell body and are potentially derived from degenerated axons or dendrites. In HD repeat knock-in mice, which do not show obvious neurological phenotypes, large htt aggregates are found in degenerating axons and axonal terminals [40,52].

The finding of axonal dysfunction or degeneration in various HD models provides a compelling argument that axonal dysfunction is an early neuropathological event in HD [52,122,125,129]. Degeneration of axons often precedes the death of the cell body and is commonly associated with a variety of neurodegenerative disorders, including Wallerian degeneration, Alzheimer's disease, and Parkinson's disease [130,131]. The degeneration of the distal ends of axons can lead to defective neuronal interaction, abnormal synaptic transmission, and an impaired supply of growth factors to the cell body, eventually causing the loss of the neuronal body.

**Cell-cell interactions and Huntington's disease**

Cell-cell interactions constitute the complex circuitry that regulates the normal function of neurons in various brain regions. Previous studies have focused on the autonomic effect of mutant htt on neuronal function, while scant attention has been paid to the role of cell-cell interactions in HD pathogenesis. Gu et al created conditional HD mice that express exon1 mutant htt in discrete neuronal populations. They found that mutant htt forms aggregates in a cell-autonomous manner. However, progressive motor deficits and cortical neuropathology are observed only when mutant htt is expressed in multiple neuronal types, not when mutant htt is restricted to cortical pyramidal neurons [41]. Since the transgenic htt is expressed under a neuronal promoter in their study, their findings provide compelling evidence for involvement of neuronal cell interactions in HD pathology.

Glial cells constitute 90% of the cells in the brain and provide nutrition, growth factors, and structural support for neurons to survive and function normally. They also protect against excitotoxicity by removing excess excitatory neurotransmitters from the extracellular space [132-134]. This protective function may be particularly relevant to
the neuropathology of HD, since excitotoxicity has been a long-standing theory to account for the pathogenesis of HD [135-137]. As discussed above, MSNs in the striatum are largely innervated by glutamatergic axons and are preferentially degenerated in HD. Glutamate activates ionotropic glutamate receptors, specifically the N-methyl-D-aspartate (NMDA) and non-NMDA receptors (ie, AMPA/kainate). Overstimulation of glutamate receptors by high levels of extracellular glutamate induces excitotoxicity [138]. Administration of NMDA receptor agonists to the striatum of animals causes a selective loss of MSNs and produces neurological symptoms similar to those seen in HD patients [136,139], whereas NMDA receptor antagonists effectively reduce excitotoxicity in HD animal models [140]. Furthermore, HD transgenic mouse models show increased NMDA receptor activity in neurons [102,141,142]. Because of the abundant glutamatergic innervation to MSNs, cell-cell interactions may be particularly important for the vulnerability of MSNs to extracellular glutamate.

Clearance of extracellular excitatory neurotransmitters is largely carried out by astrocytes, which are the major subtype of glia. These cells contain membrane receptors (GLT-1 and GLAST) that transport extracellular glutamate into the cytoplasm, where glutamate is subsequently metabolized by glutamine synthase [143]. Some studies have suggested that the function of GLT-1 is impaired in HD. HD mouse brains have an increased extracellular glutamate concentration and a reduced expression level of GLT-1 [144,145]. Transgenic mutant htt in Drosophila glia reduces the expression of glutamate transporter and shortens the life span of the fly [146]. Shin et al provided evidence that mutant htt is also expressed in glial cells in the brains of both HD mice and HD patients. They further demonstrated that mutant htt reduces glial glutamate uptake, as well as the protection it confers against high-mediated neurotoxicity [147]. These studies suggest that glia-neuron interactions also play important roles in the pathogenesis of HD.

Summary

Since the discovery of the gene mutation in HD, there have been great strides towards elucidating the pathogenesis of this disease. It has become clear that polyQ expansion can cause mutant htt to misfold and to aggregate. Misfolded htt abnormally interacts with a variety of proteins and also accumulates in the nucleus and neuronal processes. Furthermore, it is evident that proteolysis of htt is required for the aggregation and misfolding of mutant htt. Accordingly, many cleavage sites have been found in the N-terminal region of htt, and tremendous efforts have been put forth to find a means of blocking the generation of toxic htt fragments. The present review focuses on the effects of mutant htt in the nucleus and cytoplasm. Given its localization in both the nucleus and neuronal processes and its interactions with a variety of proteins, mutant htt is likely to affect a number of targets. Thus, it is conceivable that mutant htt engages multiple pathogenic pathways.

An important issue facing researchers is how to sort out the major pathogenic pathways as targets for developing therapeutic strategies. For example, which is the more critical for neuronal dysfunction and neurodegeneration, the nuclear or the cytoplasmic effect of mutant htt? Answering this question would require a better understanding than we currently possess of mutant htt's effects in different types of cells and at different stages of the disease. The preferential localization of mutant htt in the nucleus of striatal neurons suggests that the nuclear effect of mutant htt or gene transcriptional dysregulation may affect neuronal function at the early stage of the disease. In other types of cells, mutant htt in the cytoplasm could also impair neuronal function without showing nuclear accumulation. In the case of mitochondrial dysfunction and excitotoxicity, which represent an early theory of HD pathogenesis, mutant htt may act in the nucleus to affect the expression of mitochondrial proteins. It can also directly impair mitochondrial function in the cytoplasm. In addition, cell-cell interactions and circuitry are critical for the selective toxicity of mutant htt. For example, the function of medium spiny neurons in the striatum is regulated to a great extent by BDNF and glutamate input from cortical neurons. Their vulnerability is also influenced by the ability of glial cells to protect against excitotoxicity as well as the effect of mutant htt on NMDA receptors. It is therefore likely that mutant htt affects multiple targets at different levels, leading to the selective neurodegeneration of HD. Understanding how mutant htt mediates these pathological pathways would help us to find effective treatments for the disease.

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