

Transgenic animal models for study of the pathogenesis of Huntington's disease and therapy

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Abstract: Huntington's disease (HD) is caused by a genetic mutation that results in polyglutamine expansion in the N-terminal regions of huntingtin. As a result, this polyQ expansion leads to the misfolding and aggregation of mutant huntingtin as well as age-dependent neurodegeneration. The genetic mutation in HD allows for generating a variety of animal models that express different forms of mutant huntingtin and show differential pathology. Studies of these animal models have provided an important insight into the pathogenesis of HD. Mouse models of HD include transgenic mice, which express N-terminal or full-length mutant huntingtin ubiquitously or selectively in different cell types, and knock-in mice that express full-length mutant Htt at the endogenous level. Large animals, such as pig, sheep, and monkeys, have also been used to generate animal HD models. This review focuses on the different features of commonly used transgenic HD mouse models as well as transgenic large animal models of HD, and also discusses how to use them to identify potential therapeutics. Since HD shares many pathological features with other neurodegenerative diseases, identification of therapies for HD would also help to develop effective treatment for different neurodegenerative diseases that are also caused by protein misfolding and occur in an age-dependent manner.

Keywords: transgenic animal models, Huntington's disease, pathogenesis, therapy

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by a polymorphic trinucleotide CAG repeat expansion in exon 1 of the HD gene, and this expansion encodes the polyglutamine (polyQ) repeat in the N-terminal region of the disease protein, huntingtin (Htt).¹ Expanded polyQ in Htt (>36 glutamines) results in HD, and the length of expanded polyQ is inversely correlated with the onset of the disease.^{2,3} The majority of HD patients carry expanded polyQ repeats in the range of 38–55 glutamines and develop late-onset neurological symptoms in mid-life, typically between the ages of 30 and 50 years,⁴ and longer expansions (>60 repeats) may lead to juvenile-onset HD.⁵ HD patients are clinically characterized by cognitive, psychiatric, and motor disturbances,⁶ as well as peripheral phenotypes that include weight loss and muscle wasting.⁷ The pathological feature in patients post mortem is a prominent neuronal loss in the striatum, especially in the caudate putamen region, which is usually accompanied by cell loss in the cerebral cortex and widespread brain atrophy in the brains of patients with grade III–V HD.^{8,9} The neuronal loss occurs in a cell type-specific manner, and the most vulnerable are the GABAergic medium spiny neurons (MSNs) in the striatum and cortical projection neurons (CPNs) in the deep layer cortex.¹⁰

Identification of the genetic mutation in HD lead to generation of a variety of animal models that express expanded-polyQ containing Htt. Different species from *Drosophila*

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and mice, to monkeys have been used to establish animal models of HD.^{9,11,12} The mouse model is by far the most commonly used mammalian genetic model because of its efficiency, economy, and ease of manipulation. These animal models have provided us with important tools to investigate the pathogenesis of the disease and develop therapeutic strategies. There have been a number of excellent reviews about behavioral phenotypes of HD mouse models and drug treatments.^{7,13–19} In this review, we focus on the insights into pathogenesis from HD animal models that will help us to develop therapeutic strategies. Since species-dependent pathology was also seen in large animal models of HD, we also discuss the implications of large HD animal models for future therapeutic applications.

Transgenic mouse models of HD

R6/2 is the first and most extensively studied rodent model of HD. It was generated by expressing exon 1 of human Htt with 144 CAG repeats under the control of 1 kb human Htt promoter.²⁰ R6/2 mice have a severe phenotype, with motor deficits at 5–6 weeks and often cannot survive more than 13 weeks²⁰ without intervention. The early death and severe phenotypes, which make R6/2 mice a plausible model for juvenile-onset HD, indicate the toxicity of the N-terminal fragment of mutant Htt with a large polyQ repeat.^{21,22} Consistently, transgenic N-terminal mutant Htt forms nuclear inclusions and aggregates in R6/2 mice, which led to the discovery of similar inclusions in the post mortem brains of HD patients.^{23–26} Importantly, the aggregates in the brains of HD patients are only labeled by antibodies to the N-terminal region of Htt, validating the idea that only N-terminal mutant Htt is able to misfold and form aggregates.^{23,26} Although R6/2 mimicked human HD pathology in many aspects, it showed no apoptotic neuronal death, which is different from the profound neuronal loss in the striatum and cortex in HD patients.²⁷ These may be due to the early death caused by weight loss or species resistance to damage of mutant Htt.⁹

The theory that the N-terminal mutant Htt is toxic is further proved by transgenic mice expressing different N-terminal mutant Htt fragments. For instance, N171-82Q transgenic HD mice, which express the first 171 amino acids with 82 glutamines in the polyQ domain under the control of the mouse prion promoter, also show progressive neurological phenotypes and early death, which often occurs at 4–6 months of age.²⁸ Also, N171-82Q mice show the age-dependent formation of Htt aggregates in neuronal cells, which is consistent with the notion that N-terminal

mutant Htt has altered an conformation that leads to protein aggregation.^{29,30}

Other important evidence indicating the toxicity of N-terminal mutant Htt is derived from transgenic mice expressing full-length mutant Htt with expanded polyQ repeats. BAC and YAC mouse models express full-length human mutant Htt under the human Htt promoter and regulatory elements that provide relatively intact human genomic regulatory elements and protein context within the span of the transgene. Of these HD mice, the most extensively studied are BACHD with 97 CAG/CAA mixed repeats and YAC128 with 128 CAG pure repeats in human Htt.^{31,32} BAC and YAC HD mice show selective atrophy in the striatum and cortex along with progressive motor deficits, thus recapitulating to some extent the regional selectivity of adult-onset HD. These mice present electrophysiological abnormalities suggestive of an alteration at glutamatergic synapses.³³ However, unlike YAC128 mice, BACHD mice express a higher level of Htt but exhibit fewer aggregates. As mixed CAG/CAA repeats lead to more stable polyQ proteins in the rodent brain, the instability of mutant Htt may play a role in aggregate or inclusion formation. A shared phenotype commonly observed in human Htt genomic transgene mice is body weight gain, which is not observed in HD patients and is probably due to the Htt dosage effect, as YAC or BAC mice overexpressing wild-type Htt also show weight gain.³⁴ Another possibility, which remains to be ruled out, is that additional gene expression from the large genomic DNA in BAC and YAC vectors could contribute to the obesity phenotype.

HD knock-in mouse models

Transgenic mouse models of HD using exogenous promoters often raise a concern about the effects of overexpression of the transgene and multiple copies of integrated transgenes.³⁵ In theory, knock-in models should be optimal to reproduce human pathology because they are the most faithful reproduction of the genetic mutations.⁹ A number of knock-in models with expanded CAG repeats or human mutant Htt exon 1 replacing the corresponding sequences in the endogenous murine *htt* gene locus generated.^{13,36–39} Also, a series of mutant Htt-KI models with increasing polyQ length repeats (111,⁴⁰ 140,³⁹ 150,^{38,41,42} and 175^{43,44}) are available for studying HD pathogenesis and therapies. However, all these HD KI mice showed late-onset of phenotype and progressive but mild pathology.^{36,37} Many behavioral abnormalities in this KI model were similar to transgenic mouse models but much milder,⁴² which also supports the idea that N-terminal

mutant Htt could be more toxic. Indeed, mutant Htt also forms aggregates in KI mice, and these aggregates are only labeled by the antibody to N-terminal region of Htt.⁴⁵ In addition, Western blotting of HD KI mouse brain tissue demonstrates the presence of a number of degraded N-terminal mutant Htt that carry an expanded polyQ repeat.⁴⁵ All these observations lead to the theory that proteolysis of full-length mutant Htt is critical for accumulation of N-terminal mutant Htt, which then causes age-dependent neuropathology in HD.^{24,46}

It is now known that full-length Htt is proteolytically cleaved to N-terminal fragments, and these fragments are ubiquitinated and cleared by the proteasome and autophagy.^{24,46–48} Shorter N-terminal fragments are more stable and prone to aggregation, suggesting that specific proteolysis of full-length Htt into smaller fragments might be one of the initial steps in the disease process.⁹ A number of N-terminal fragments and a subset of the enzymes that generate N-terminal Htt fragments of varying sizes have been determined.²⁴ These include caspase-3, caspase-6,^{49–51} calpain,⁵² matrix metalloproteinase 10,⁵³ and an undefined aspartyl protease.⁵⁴ The presence of caspase cleavage sites in Htt makes the caspase inhibitors promising drugs for HD therapy. YAC transgenic mice expressing human full-length mutant Htt carrying a mutation that blocks caspase-6 cleavage did not show neuropathology or phenotypes when compared with the YAC-128Q model.⁵⁵ However, later studies did not find prevention of generation of the toxic fragment when caspase-6 was knocked out in mice.⁵⁶

Although HD KI mice do not develop phenotypes as robust as those in transgenic mice expressing N-terminal mutant Htt, they recapitulate an important pathological change seen in the brain of the HD patient, which is the preferential accumulation of mutant Htt in striatal neurons that are mostly affected in HD.^{37,38,57} Such important features of HD KI mice provide an avenue to dissect out the mechanism underlying the selective neurodegeneration and early pathology seen in HD.

Conditional HD mouse models expressing N-terminal mutant Htt

The above transgenic and KI HD mice ubiquitously express mutant Htt in both neuronal and non-neuronal tissues, which is also distributed in various subcellular locations, making it difficult to determine the cell type-specific toxicity of mutant Htt. Conditional HD mouse models that express mutant Htt in specific types of cells have been established to address the specific effects of mutant Htt in a cell type-dependent manner.

In brains from HD patients, striatal and cortical neurons are mainly deteriorated. In the striatum, MSNs comprise more than 90% of the total neuronal population,⁵⁸ and in the cortex the large pyramidal neurons in layers III, V, and VI are predominantly affected in HD.¹⁰ Conditional HD mouse models with mutant Htt expression restricted to the striatum or cortex were established.⁵⁹ In conditional BACHD mice, LoxP sequences were inserted into the 5'-untranslated region of mutant Htt and in intron 1 flanking mutant Htt exon 1. Therefore, these two LoxP do not interfere with expression of mutant Htt but do allow BACHD mice to be a conditional inactivation model in which Cre expression can switch off mutant Htt expression. Wang et al crossed BACHD mice with Emx1-Cre (cortex CPN-specific Cre), Rgs9-Cre (striatal MSN-specific Cre), or Emx1-Cre; Rgs9-Cre double-transgenic mice to genetically reduce mutant Htt expression in neuronal populations in the cortex, striatum, or both.⁵⁹ They showed that reduction of cortical mutant Htt expression in BACHD mice partially ameliorates motor and psychiatric-like behavioral deficits, but does not improve brain atrophy, whereas reduction of mutant Htt expression in both cortical and striatal neurons results in the most robust amelioration of all behavioral deficits and selective brain atrophy in BACHD mice.⁵⁹ This study suggests that the optimal therapeutic strategy may require targeting mutant Htt in both cortical and striatal neurons in HD.

The animal brain consists of neurons and glial cells, which comprise more than 90% of the total cell population. Glia can maintain homeostasis, form myelin, and provide support and protection for neurons in the brain. Although mutant Htt is ubiquitously expressed in neuronal and non-neuronal cells, the role of mutant Htt in glial cells remains elusive, despite the fact that white matter degeneration is found in the brains of HD patient.^{60–65} A mouse model (GFAP [glial fibrillary acidic protein]-Htt), which expresses N-terminal mutant Htt in astrocytes, the major type of glial cell, under the control of the human GFAP promoter, also shows age-dependent neurological phenotypes.⁶⁶ These phenotypes are characterized by body weight loss, motor function deficits, and earlier death than wild-type or control transgenic mice. The GFAP-Htt model revealed that mutant Htt binding to Sp1 reduces the associating of Sp1 with the promoter of glutamate transporter, thus resulting in decreased expression of GLT-1 and impaired glutamate uptake.⁶⁶ The findings provide a new mechanistic insight into the excitotoxic damage in HD. Recently, transgenic HD mice expressing mutant Htt in microglial cells are also reported and show some pathological

changes.^{67,68} All these findings imply an important role for non-neuronal mutant Htt in HD pathology.

The unique structure for neuronal interactions is the synapse. However, how synaptic mutant Htt directly mediates the neuropathology remains unclear. A transgenic HD mouse model was also generated, which selectively expresses mutant Htt in the presynaptic nerve terminal by fusing mutant Htt to synaptosomal-associated protein 25.⁶⁹ Although transgenic Htt is expressed at a lower level than control Htt with a normal polyQ repeat, it causes progressive and age-dependent neurological symptoms and early death. This interaction of mutant Htt with the C-terminal proline-rich domain of synapsin-1 in this mouse model caused a decrease of glutamate release from synapses.⁶⁹ Thus, the transgenic HD mouse models that selectively express mutant Htt in selective types of cells or subcellular regions have provided us with new insight into the pathogenesis of HD (Figure 1).

Transgenic large animal models of HD

Although a variety of mouse models of HD have been extensively studied, none of them show robust neurodegeneration like that seen in the brains of HD patients. This scenario is similar to the transgenic mouse models of Alzheimer's disease and Parkinson's disease, in which there is also a lack of overt neurodegeneration.^{70,71} The failure of transgenic mouse models to replicate striking neurodegeneration in patient brains could be due to biological differences between humans and mice.⁷² Since the aging process is quite different between small and large animals, mutant Htt may accumulate or be cleared differentially in the brains of different species, which could also contribute to differential pathologies in rodents and large animals. Whether larger transgenic animal models can mimic important neurodegenerative features caused by misfolded proteins remains to be rigorously tested. Transgenic non-human primate models

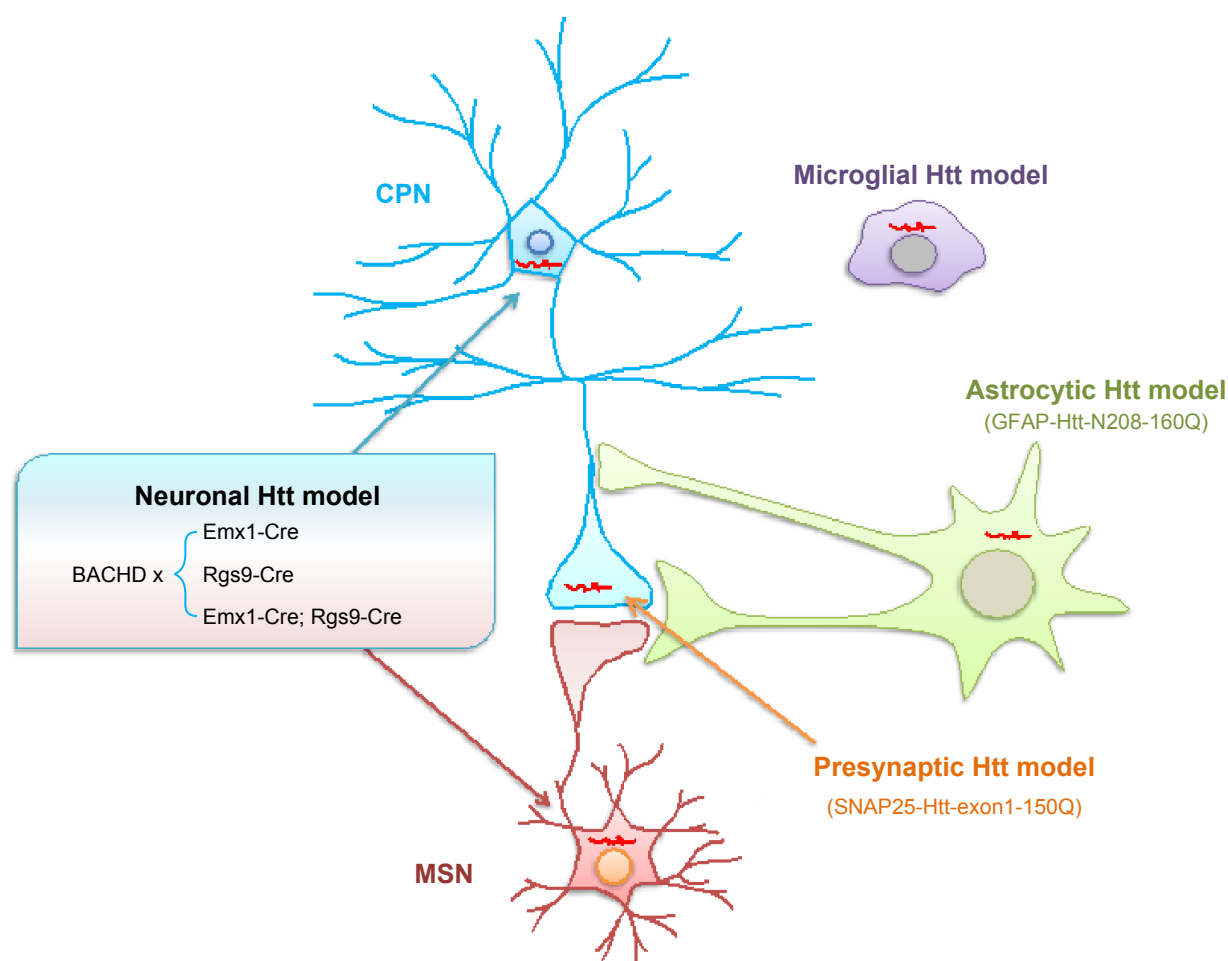


Figure 1 Mouse models expressing mHtt in different types of neurons or glial cells show cell type-specific toxicity and synergistic effects of mHtt, indicating the importance of neuron–neuron and neuron–glia interactions in HD pathogenesis.

Abbreviations: CPN, cortical projection neurons; MSN, medium spiny neurons.

expressing the disease genes were established.^{12,73} Of these large animal models, transgenic HD rhesus monkeys express exon 1 mutant Htt with 84Q under the control of the human ubiquitin promoter.¹² These HD monkeys were generated by injecting lentiviruses into fertilized oocytes to express mutant Htt. Unlike transgenic mice, which can survive after birth when expressing the same exon 1 mutant Htt with an even longer polyQ repeat (150Q),^{30,74} HD transgenic monkeys with 84Q die postnatally, and this early death is associated with the levels of mutant Htt.¹² Despite their early death, some transgenic monkeys developed key clinical HD features including dystonia, chorea, and seizure,¹² which have not been replicated by mouse models or other small animal models. Like the brains of HD mouse models and patients, HD monkey brains also show abundant Htt aggregates in the neuronal nuclei and neuronal processes. More importantly, transgenic HD monkeys display degeneration of axons and neuronal processes in the absence of obvious cell body degeneration,⁴⁵ suggesting that neuronal degeneration in HD may initiate from neuronal processes.

Similarly, transgenic HD pigs that express N-terminal mutant Htt consisting of the first 208 amino acids with 105Q (N208–105Q) were also generated.⁷⁵ The transgenes were expressed under the control of the cytomegalovirus enhancer and chicken beta-actin (CAG) promoter to allow the ubiquitous expression of transgenes in all tissues. Primary porcine fetal fibroblast cells expressing this mutant Htt fragment were used to generate transgenic HD pigs via nuclear transfer. Six early pregnancies were established, and four of them went to term, with five live births. Like transgenic monkey models of HD, most of these transgenic HD piglets die postnatally, and some transgenic HD pigs show a severe chorea phenotype before death. Thus, the postnatal death of transgenic HD piglets also suggests that mutant Htt is more toxic to larger animals. More importantly, in all transgenic pig brains examined, there were apoptotic cells, which have not been reported in any HD mouse models.

Studies of transgenic large animals also show that smaller N-terminal mutant Htt is more toxic. This is because transgenic pigs⁷⁶ and sheep⁷⁷ that express much large Htt fragments develop non-detectable or very mild phenotypes. Thus, even in large animals, expression of small N-terminal mutant Htt fragments appears to be necessary to facilitate disease progression.

Current therapeutic strategies

Based on the findings from animal models of HD, it is clear that continuous accumulation of the misfolded mutant Htt

is key to developing HD pathology. Accordingly, several therapeutic strategies have been developed.

Decrease production of mutant Htt

Gene suppression methods provide us with a great tool in HD therapy, and the most popular approach is to use antisense oligonucleotide and RNA interference (RNAi).^{78,79} This approach has been successfully used in HD mouse models and demonstrates favorable effects in alleviating neurological symptoms in HD mice.^{80–83} Because the function of normal Htt is essential for early embryonic development,^{84–86} great effort has been made to develop specific RNAi that only suppresses the expression of mutant Htt.^{87,88} It has been reported that partial lowering of mutant Htt over months in adult rodent models of HD is effective in reducing neuropathology, improving motor behavior, and prolonging survival.^{89–93} However, allele-specific RNAi has to be designed based on polymorphic differences in Htt genes between individuals, and an efficient tool to deliver RNAi and antisense oligonucleotide into human brains remains to be established before their clinical application to suppress expression of mutant Htt in patients.^{83,94}

Enhance clearance of mutant Htt

Misfolded and degraded proteins can be cleared by the ubiquitin-proteasome system (UPS). It has been reported that the activity of the UPS declines with age,^{95–97} which correlates with age-dependent accumulation of mutant Htt in the mouse brain. Also, there is less UPS activity in neuronal cells than in glial cells, suggesting that differential UPS activity contributes to the preferential accumulation of mutant Htt in neuronal cells.⁹⁸ Many *in vitro* studies have demonstrated that inhibiting UPS activity can promote accumulation of mutant Htt in cultured cells.^{99,100} Normally the N-terminal of mutant Htt follows a K48-mediated ubiquitination, which is required for degradation by the proteasome. Degradation of ubiquitinated proteins by the proteasomes requires ubiquitin-conjugating enzymes and ubiquitin-protein ligase E3A. While mutant Htt can be ubiquitinated via K48 in ubiquitin and then targeted via ubiquitin-ligating (E3) enzymes to the proteasome for degradation, the ubiquitin-conjugating (E2) enzyme promotes ubiquitination of mutant Htt via K63 in ubiquitin, resulting in more aggregation of mutant Htt. Reducing ubiquitin-conjugating (E2) or overexpressing ubiquitin-ligating (E3) in the HD mouse brain attenuates Htt aggregation in HD mouse models.^{100,101} These findings suggest that drugs that activate the UPS would be likely to help remove mutant Htt.

The autophagy-lysosomal pathway is another way to degrade mutant Htt.^{47,48} The lipophilic macrolide antibiotic rapamycin was reported to inactivate mammalian target of rapamycin, and this inhibition can induce autophagy to reduce HD symptoms in fly and mouse models.^{102,103} However, rapamycin has broad effects, so its protection is likely due to the combination of its effects on different cellular functions. A more specific drug that only acts on autophagy remains to be developed and may show more specific and efficient clearance of mutant Htt, with less off-target effects.

Reduce gain of toxicity of mutant Htt

PolyQ expansion confers abnormal conformation of Htt, which alters its interactions with other proteins. For example, mutant Htt binds more tightly to Hap1 and Sp1 to alter protein trafficking and transcriptional function.^{104–106} Drugs or small peptides that can prevent this abnormal interaction would possibly reduce the toxicity of mutant Htt. This possibility is supported by expressing engineered intracellular antibodies, known as intrabodies, which were designed to selectively bind to mutant Htt exon 1 in HD mouse brains.

The expression of such intrabodies can ameliorate motor deficit symptoms in multiple HD mouse models.^{107–109} Similarly, overexpression of Q-rich prion-like proteins suppresses polyQ cytotoxicity via altering the interactions of polyQ proteins with other interactors.¹¹⁰

Improve specific cellular function that can be affected by mutant Htt

Accumulation of mutant Htt can affect a variety of cellular functions. Mutant Htt in the nucleus can affect gene transcription. Cytoplasmic mutant Htt associates with a number of proteins to affect intracellular trafficking, mitochondrial function, and synaptic transmission to induce excitotoxicity, inflammation, and cell death (Figure 2).

Drugs that selectively improve one or more of the above defects caused by mutant Htt have been tested in HD mouse models. For example, histone deacetylase inhibitors, which are known to improve transcriptional activity, have been used in HD mice and show beneficial effects.^{111–113} Neurotrophic factors that can prevent neuronal cells also show protective effects in HD mouse models.^{114–117} Several drugs, such as

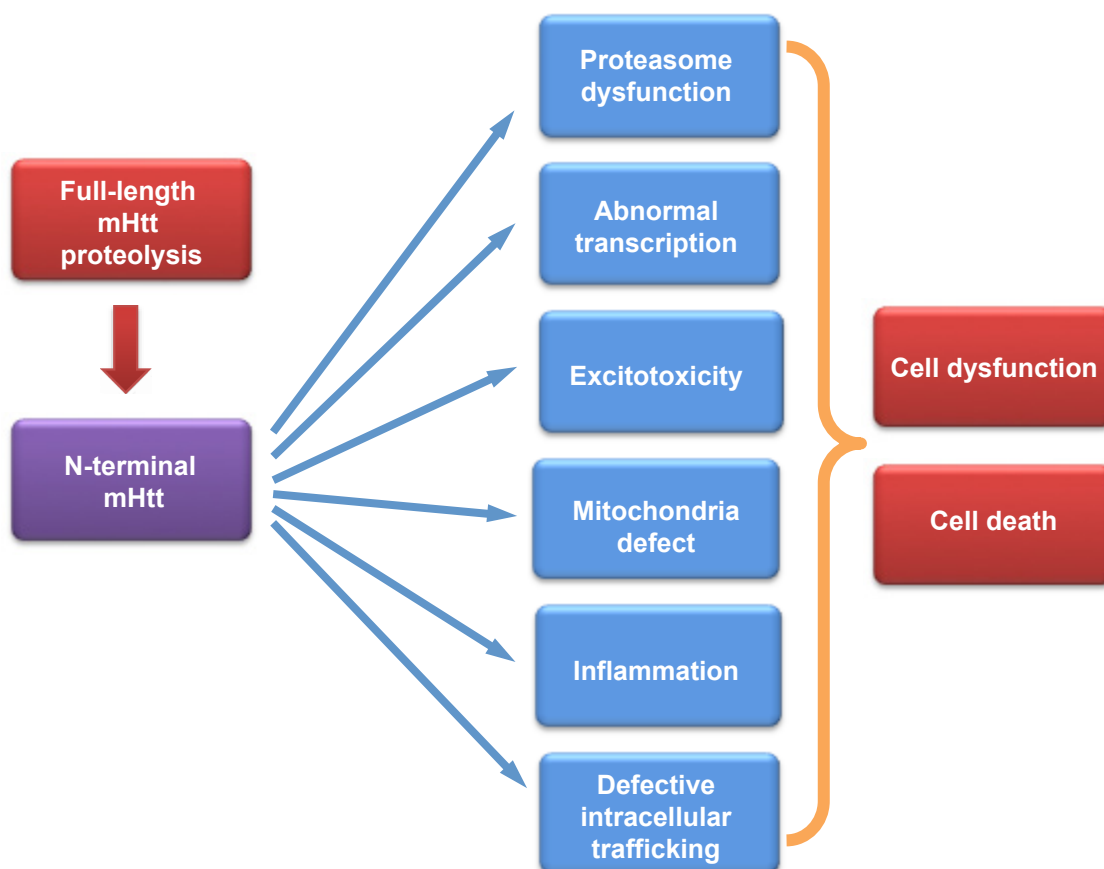


Figure 2 Proteolysis of full-length mutant Htt generates N-terminal mutant Htt that affects multiple cellular functions, leading to excitotoxicity, mitochondrial deficit, inflammation, cellular dysfunction, and cell death, and pointing out a number of potential therapeutic targets.

coenzyme Q10, which can improve mitochondrial function, have been used clinically.^{118,119} However, to date, there is no effective drug that can be used clinically to stop or reverse progression of HD.

Use of HD animal models to identify therapeutics

The established animal models of HD provide us with important tools to identify therapies for HD. However, these animal models express different forms of mutant Htt and show different neurological phenotypes in various time frames. Thus, it would be important to utilize the unique features of these HD animal models when choosing them for drug studies. Transgenic HD mice, such as R6/2 and N171-82Q, develop severe phenotypes with rapid disease progression. The pathological alterations in these mice are not restricted to neuronal cells in the central nervous system, and may also occur in the peripheral tissues. Thus, drugs that can significantly delay disease progression in these mice are likely to improve the function in the brain and peripheral tissues as well. However, overexpression of small truncated N-terminal mutant Htt may generate pathological events that do not happen when full-length mutant Htt is expressed at the endogenous level. YAC and BAC HD mice are important models for drug studies as they express full-length mutant human Htt. The toxicity of human mutant Htt may be different from transgenic N-terminal Htt, which carries a large polyQ repeat. Human Htt may have specific post-translational modifications that can also influence its toxicity in transgenic mice.

Since these full-length Htt transgenic mice often show the overweight phenotype, which is not seen in HD patients but can influence rotarod test performance, drugs that can improve rotarod performance should also be considered for their potential effects on metabolism and body weight and need to be verified by examining their protective effects on the HD neuropathology in these mice. HD KI mice express expanded-polyQ Htt at the endogenous level and develop neurological symptoms slowly and to much less of an extent than transgenic HD mice. Thus, they are especially useful for identifying initial pathological changes. For example, one can examine how mutant Htt preferentially accumulates in the striatal neurons in HD KI mice, which mirrors the preferential degeneration of striatal neurons in HD patients. Further, transcriptional and proteomic analysis of HD KI mice during the course of disease development may identify molecular targets that are likely to contribute to disease progression. Although HD is an autosomal dominant neurodegenerative disease caused by polyQ expansion in Htt, environment

influences, such as housing and diet, could also influence the age of onset and disease severity in HD animal models. Finally, although HD mice do not show obvious neurodegeneration, use of transgenic large animal models of HD that show similar neuropathology to that in HD patient brains will offer an alternative avenue to identify therapeutics that can reduce or ameliorate neurodegeneration.

Conclusion

A variety of transgenic animal models of HD have been established and provided an important insight into the pathogenesis of HD. Various transgenic mouse models of HD are widely used for identifying therapeutics. Each model possesses unique phenotypes or pathological characteristics of HD, which would allow one to find therapeutics that may have broad protective effects or specific effects in a cell type-dependent manner. Because mutant Htt interacts with a number of proteins and affects multiple cellular functions, the most powerful therapy would be one that selectively suppresses the expression of mutant Htt. Even before we develop such a powerful therapeutic tool, drugs that can selectively target downstream pathways that are impaired in HD can also be beneficial for treating HD. However, combined therapeutics that can synergistically improve the functions of multiple pathways are more likely to achieve the goal of effectively reducing HD pathology and delaying disease progression. Because HD shares many common pathological events with other neurodegenerative diseases that are also caused by accumulation of misfolded proteins, identification of therapeutics using HD animal models could also help find treatment for other neurodegenerative diseases.

Disclosure

The authors report no conflicts of interest in this work.

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