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REVIEW

Cellular and molecular mechanisms implicated in pathogenesis of selective neurodegeneration in Huntington's disease

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Abstract **Huntington's disease (HD) is one of the most common dominantly-inherited neurodegenerative disorders and is caused by a CAG repeat expansion in the huntingtin gene. HD is characterized by selective degeneration of subpopulations of neurons in the brain, however the precise underlying mechanisms how a ubiquitously expressed disease protein could target specific types of neurons for degeneration remains a critical, yet unanswered question for HD and other major neurodegenerative disorders. In this review, we describe the expanding view of selective neuronal vulnerability in HD, based on recent neuropathological and neuroimaging studies. We will also summarize the systematic effort to define the cell types in which mutant Huntingtin expression is critical for pathogenesis of vulnerable neurons in the striatum and cortex. Finally, we will describe selected, emerging molecular mechanisms that are implicated in selective disease processes in HD. Together, the field has begun to appreciate the distinct molecular pathogenic roles of mutant huntingtin in different cell types that may contribute to the selective neuronal vulnerability, with dissection of such mechanisms likely to yield novel molecular targets for HD therapy.**

Keywords Huntington's disease, neurodegeneration, selective neuronal vulnerability, cortex, striatum, conditional mouse model, cell-autonomous toxicity, pathological cell-cell interaction, pathogenesis, therapeutic targets

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder with typically middle-age onset of motor, psychiatric, and cognitive dysfunction. The disease is relentlessly progressive, with worsening symptoms resulting in death 15–20 years after clinical onset. The HD field has built a large body of literature since George Huntington first described the disease in 1872. Clinically, HD patients exhibit progressive movement disorder including chorea and dystonia, cognitive decline including poor decision making, and psychiatric symptoms including anxiety and depression. One of the striking neurological findings in HD is the profound degeneration of medium-sized spiny neurons in the caudate/putamen (i.e. the striatum) and to a lesser extent the deep layer pyramidal neurons in the cortex. A key advance in the study of HD was the identification of the causal gene mutated in the disease, Huntingtin (Htt), which encodes a very large and nearly ubiquitously expressed protein (The Huntington's Disease Collaborative Research Group, 1993). The HD mutation is a CAG repeat expansion leading to an elongated polyglutamine repeat in the mutant Huntingtin protein (mHtt), expanding from the normal range of < 35 to the pathogenic range of > 39 (The Huntington's Disease Collaborative Research Group, 1993). Similar to the other known neurodegenerative disorders caused by polyglutamine repeat expansion, HD also exhibits an inverse relationship between

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the repeat length and age of disease onset (Orr and Zoghbi, 2007). Mice deficient in murine Htt homolog (Hdh) demonstrate an essential role for Hdh during embryonic development and in the survival of certain adult neurons in the brain (Duyao et al., 1995; White et al., 1997; Zuccato et al., 2010). However, polyglutamine-expanded mHtt still retains these essential functions of Hdh (Hodgson et al., 1999; Gray et al., 2008), so polyglutamine gain-of-function toxicity is thought to be a common triggering mechanism in HD and related polyglutamine disorders (Orr and Zoghbi, 2007).

An important subject of HD research is how the ubiquitously expressed mHtt protein elicits degeneration in certain regions of the brain, and in certain subsets of cells, while sparing others. This facet of HD is not unique to this particular neurodegenerative disease—Parkinson's disease is at least in part due to the death of dopaminergic neurons of the substantia nigra, Alzheimer's disease (AD) sees robust neuronal loss in the hippocampus and entorhinal cortex, and amyotrophic lateral sclerosis is caused by the death of motor neurons. While selective vulnerability of specific neuronal populations in these age-dependent neurodegenerative diseases is common, HD is a particularly attractive "model disorder" for research on mechanisms involved in selective neurodegeneration due to its monogenetic etiology and a relatively large population of gene carriers and manifested patients for longitudinal clinical studies (Ross and Tabrizi, 2011). Moreover, HD is one of nine polyglutamine disorders having distinct neuropathology and clinical features, together constituting an attractive group of disorders to study how distinct disease-specific molecular features beyond the polyglutamine repeat expansion (e.g. protein domains and interacting proteins) are critical to determine the differences in these diseases, including the selective patterns of neurodegeneration. This review will cover recent advances in imaging studies that have expanded our knowledge on vulnerable neuronal populations in HD, the use of genetic animal models to identify critical novel mechanisms underlying selective vulnerability, and the implications of these studies have on therapeutic development.

An updated view of selective neuronal vulnerability in HD

Early neuropathological studies of postmortem HD patient brains provided the initial understanding of the selective patterns of regional brain atrophy and neuronal loss in HD. However, postmortem brains typically represent the end-stage of a prolonged disease course, and may not reveal spatial and temporal neurodegenerative processes, with this information likely to be relevant to clinical progression and intervention for HD. Such a dynamic view of HD neurodegeneration has been revealed by the recent application of advanced neuroimaging to cohorts of HD gene carriers and early diagnosed patients. These latter studies also provide us an updated view of selective neuronal vulnerability at different clinical stages of HD.

Neuropathological studies of HD postmortem brains

Early studies of HD postmortem tissue showed gross decreases in brain weight, with severe degeneration of cortex and the basal ganglia (Mattsson et al., 1974). Brain weight loss of approximately 20% in the cortex and 60% in the basal ganglia were commonly found, with the worst degeneration being found in the striatum (Lange et al., 1976). The finding of degenerating neurons and decreased neuronal density, especially in these brain regions, was matched by concomitant increases in astrocytosis (Lange et al., 1976; Averback, 1980; Vonsattel et al., 1985; Roos et al., 1986). Further research focusing on degeneration within the striatum determined that the vast majority of cells lost in this region were medium-sized spiny neurons (MSNs) that are GABAergic projection neurons making up roughly 95% of the striatal neuronal population (Kita and Kitai, 1988), with relative sparing of the remaining diverse population of striatal interneurons (Vonsattel et al., 1985; Ferrante et al., 1985; 1987). Interestingly, within MSN subpopulations, there was found to be an early and disproportionate loss of Enkephalin-positive MSNs that project to the external segment of the Globus Pallidus externa (GPe; indirect pathway MSNs) compared to Substance P positive MSNs that project to the globus pallidus interna (GPi; direct pathway MSNs; Ferrante et al., 1985; Reiner et al., 1988; Albin et al., 1990; 1992). Similar studies focusing on degeneration in HD cortex found that cortical pyramidal neurons (CPNs), particularly those of the deeper layers V and VI, also degenerated, but to a lesser extent compared to the striatum (Cudkowicz and Kowall, 1990; Hedreen et al., 1991). These neuronal losses in the cortex and striatum alone were not sufficient to explain the gross brain weight loss in HD, however, suggesting degeneration of neuropil (i.e. axons, dendrites and synapses) and shrinkage of neuronal cell bodies in additional to the overt cell loss. Indeed, white matter loss, such as 30% reduction in the area of the corpus callosum, has been described in postmortem HD brains (Mann et al., 1993). Finally, more recent HD pathological studies also suggest additional brain regions, such as thalamus, hypothalamus, and amygdala, may also be affected in HD (Mann et al., 1993; Petersén and Björkqvist, 2006). Although selective pathology is apparent in the majority of adult onset HD cases, juvenile HD cases (with the age of onset less than 20 years old) often have more severe symptoms and broader neuropathology (Vonsattel and DiFiglia, 1998).

Neuroimaging of brain morphology and function in premanifest HD gene carriers and HD patients

The application of *in vivo* imaging technologies such as MRI

and PET to the study of HD, with increasingly sophisticated tools developed in the past decade to analyze such data, has lead to a comprehensive and dynamic view of brain morphological and functional changes in manifest HD patients and pre-manifest gene carriers. Such studies allow more precise correlations between brain region morphometric and functional changes with the onset and progression of clinical symptoms of HD (Rosas et al., 2004). Early structural imaging studies largely recapitulated prior postmortem findings, with significant volume reductions found in the cortex, basal ganglia, thalamus, and white matter tracts (Bydder et al., 1982; Jernigan et al., 1991; Savoiardo et al., 1991; Harris et al., 1992; Sharma et al., 1996). Several important new insights have been gained from these studies: First, the onset of both cortical and striatal atrophy occurs many years prior to the onset of motor symptoms in HD (Rosas et al., 2003; Aylward et al., 2004). Second, there is a previously unappreciated, highly significant correlation between the cortical regional atrophy and total functional capacity (TFC), which is a major clinical readout for HD (Rosas et al., 2008). Finally, using diffusion tensor imaging (DTI), several groups have reported early and progressive loss of cortical axon bundles (i.e. white matter in the corpus callosum or corticofugal axons in the internal capsule) in pre-symptomatic and early stage HD, with such axonal loss being correlated with severity of motor and cognitive symptoms (Reading et al., 2005; Rosas et al., 2006; Klöppel et al., 2008). These studies strongly suggest that early cortical and striatal involvement may contribute to the pathogenesis of clinical symptoms of HD.

There are several concerted clinical research efforts to assess longitudinal behavioral changes in pre-manifest HD gene carriers and HD patients, and to correlate these changes with brain structural and functional alterations by neuroimaging. Such studies aim to identify brain regions relevant to the onset and progression of disease symptoms, and to identify useful biomarkers for testing therapeutic intervention. The Neurobiological Predictors of HD (PREDICT-HD) study is a large, multi-center collaborative project that aims to quantify phenotypes relating to HD progression (Paulsen et al., 2006). Subjects in the large cohort, consisting of $>$ 700 HD mutation carriers and approximately 200 control non-carriers, are longitudinally monitored for motor, cognitive, and neuroimaging measures up to decades before the estimated time of disease diagnosis. A similar multi-center longitudinal study, although shorter in duration and smaller in scale, is the TRACK-HD project (Tabrizi et al., 2009). This study enrolled approximately 120 age- and gender-matched subjects from each of three groups: non-HD controls, pre-manifest HD gene carriers, and clinically diagnosed early HD patients. A key difference between the design of the PREDICT-HD and TRACK-HD studies is that those in TRACK-HD were followed for only two years in an effort to identify relatively short-term, yet sensitive outcome measures that could be useful for future clinical trials. The PREDICT-HD and TRACK-HD studies confirmed and extended previous smaller-scale imaging studies by demonstrating unequivocally that subtle motor and cognitive deficits can predate the clinical diagnosis of HD, sometimes by more than ten years (Biglan et al., 2009; Duff et al., 2010). Some of these measures appear to be useful in the prediction of time to disease diagnosis, including motor examination scores, striatal volume, word-list learning, odor identification, and others (Paulsen et al., 2008; Tabrizi et al., 2009; 2012). These studies validated that striatal volume appears to be the best predictor of onset of clinical symptoms, but in addition cortical gray matter and cerebral white matter all correlate with time to disease diagnosis, suggesting that circuitry dysfunction preceding clinical onset may be at the root of early clinical manifestations in HD (Paulsen et al., 2010; van den Bogaard et al., 2011a, 2011b; Dumas et al., 2012). Together, current imaging studies suggest that the progressive cortical and striatal degenerative changes, as well as cortical axonal changes, are likely the brain substrates for clinical disease and may provide biomarkers for disease intervention.

In summary, both neuropathological and neuroimaging studies paint a picture of progressive pathological changes in the HD brain that involve early and more limited disease in certain brain regions, including the posterior cortex and posterior putamen, long before the onset of clinical symptoms, relatively robust neurodegeneration in these regions by the time of disease diagnosis, and disease progression associated with more widespread neuronal and axonal degeneration involving multiple brain regions until end stage. These human studies provide a new spatiotemporal perspective on selective disease pathogenesis in HD. They also pose a challenge in understanding how the causal mHtt gene elicits the dynamic disease process; a question likely needing to be resolved using genetic animal models of HD.

Cellular mechanisms in the pathogenesis of selective neurodegeneration in HD

There are clearly complex, yet fundamental biological processes underlying selective vulnerability in HD pathogenesis. Mutant Htt is broadly expressed, yet degeneration is relatively restricted not just to the CNS, but to particular neuronal populations. To devise effective strategies to treat HD, the field needs to determine what makes these neurons vulnerable to mHtt. Such studies of the cellular basis of neuropathology require genetically engineered HD animal models that express mHtt and exhibit pathological features of the disease. The HD field is richly endowed with a variety of transgenic mouse models of HD which reproduce aspects of HD phenotypes (e.g. behavioral impairment, neuronal dysfunction and brain atrophy), yet none show the frank movement disorder and overt striatal neuronal loss seen in HD patients (Vonsattel, 2008; Crook and Housman, 2011; Yang and Gray, 2011). HD mouse models can be grouped into

three major classes. The first group of models expresses toxic polyglutamine (polyQ) fragments of mHtt that are normally generated by proteolysis and accumulate in HD brains as aggregates. The fragment models of HD (e.g. *R6/2* and *N171-82Q*) often exhibit early onset behavioral impairment and rapid, often lethal disease course, clearly demonstrating that mHtt fragments are more neurotoxic than intact full-length mHtt (Mangiarini et al., 1996; Schilling et al., 1999). Additionally, fragment models tend to exhibit more global brain atrophy, suggesting that they may model more severe forms of HD, such as juvenile HD, and that additional mHtt protein context may be necessary for more selective disease pathogenesis in HD. The next two groups of mHtt mice express full-length mHtt. Knock-in models (e.g. CAG140 and Q150) express expanded polyQ repeats from the endogenous murine Htt locus, hence preserving the chromosomal and genomic context of Htt. The Q150 knock-in model uses the full context of the murine genomic background (Woodman et al., 2007), while CAG140 mice carry a chimeric mHtt, with human Htt exon 1 and murine Htt beyond the first exon (Menalled et al., 2003). The second major class of full-length mHtt mouse models is the human genomic transgene mouse models (i.e. YAC128 and BACHD), which express full-length mHtt from the human genomic context on YAC or BAC transgenes (Slow et al., 2003; Gray et al., 2008). Both types of full-length models (knock-in and transgenic) appear to exhibit slowly progressive motor, psychiatric-like, and cognitive behavioral deficits, with human genomic transgene models such as BACHD showing earlier and more robust phenotypes (Menalled et al., 2009). Moreover, unlike the fragment models, the full-length mHtt mouse models appear to exhibit some of the HD-like selective neuropathology including cortical and striatal atrophy, with relative sparing of the cerebellum (Slow et al., 2003; Gray et al., 2008; Yang and Gray, 2011). Hence, full-length mHtt mouse models appear more ideal to study slowly the progressive, selective neuropathogenic processes mimicking HD, while fragment models are informative to understanding the role of mHtt fragments in disease pathogenesis in different cell types.

A two-step reductionist approach to unravel the cellular pathogenic logic in Huntington's disease

At the cellular level, there are two major models that could account for the selective degeneration of deep-layer CPNs and striatal MSNs in HD. The first model is the cell-autonomy model, which suggests that mHtt exerts its toxicity solely within the vulnerable neurons to cause their disease, with expression of mHtt outside these neurons not playing a role in the dysfunction and degeneration. The second model is the cell-cell interaction model, which implies that the dysfunction or degeneration of the striatal or cortical neurons in HD may require mHtt expression in other cell types, with pathological cell-cell interaction a critical part of the disease process. While these pathological cell-cell interactions certainly could occur within a cellular population, the current state of mouse genetics allow us to more readily address such a question at the level of interactions between distinct neuronal populations. As mouse genetic technology advances (e.g. applications of single neuron genetic manipulations), it should become more feasible to directly address questions of non-cell-autonomous pathogenesis within defined cellular populations (e.g. whether an MSN can exert toxic effects on a neighboring MSN). For this review, we will remain focused on pathological interactions between defined cell populations, for example, altered glutamatergic output from CPNs exerting toxic effects on MSNs. The concepts of cell-autonomous and non-cell-autonomous pathogenesis, however, are not mutually exclusive, since it is plausible that mHtt could elicit both cell-autonomous toxicity and mediate pathological cell-cell interactions to confer synergistic vulnerability to susceptible neurons, a model we refer to as the "two-hit model." Demonstrating which of these cellular pathogenic mechanisms are critical to selective disease pathogenesis is a major goal in HD research.

Engineered mouse models with cell-type-specific and conditional expression of mHtt have played a large role in the determination of cell-autonomous vs. cell-cell interaction mechanisms involved in HD pathogenesis. Interpretation of results from such mice should take into consideration the context of mHtt protein (fragment vs. full-length) and the expression levels of mHtt within both the vulnerable neurons and different interacting cell types. Ideally, an animal model to study HD cell-cell interactions should preserve the genomic and protein contexts of intact human mHtt and should exhibit key features of the disease, from progressive behavioral impairment to selective neurodegenerative pathology. Such animal model systems would allow the dissection of selective pathogenesis in HD via a two-step reductionist approach (Fig. 1). The first step defining in which neuronal or non-neuronal cell types mHtt expression is necessary or sufficient to elicit critical HD phenotypes, and also whether these cells contribute to disease pathogenesis via cell-autonomous or cell-cell interaction mechanisms. Second, once the critical pathogenic cell types and their modes of action are defined, a further reductionist step will identify precise molecular mechanisms that underlie the genetically defined cellular or intercellular toxicity. Because of the monogenetic etiology and the availability of animal models recapitulating certain selective neuropathological features of the disease, HD appears to be an ideal model to use such a reductionist approach to unravel the cellular and molecular mechanisms in disease pathogenesis. In the past few years, significant progress has been made to demonstrate pathogenic roles of mHtt for several brain cell types in disease pathogenesis in HD mouse models.

Pathogenic roles of striatal medium spiny neurons in HD

Striatal MSNs bear the brunt of neurodegeneration in HD.

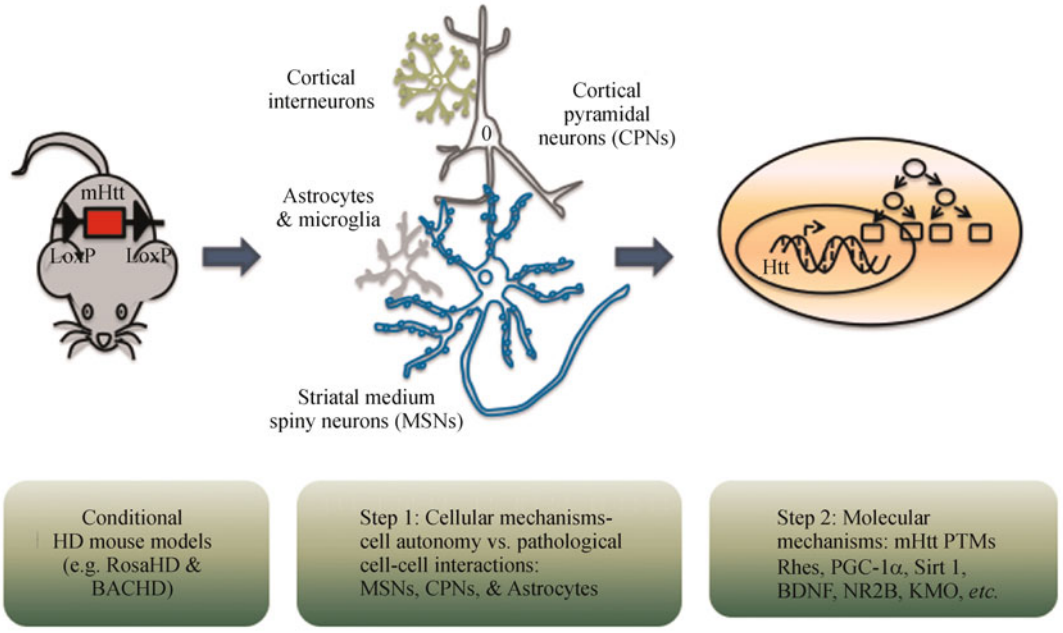

Figure 1 A two-step reductionist approach to dissect cellular and molecular pathogenic mechanisms in conditional HD mouse models. To elucidate how the ubiquitously expressed mHtt could elicit age-dependent, selective dysfunction and degeneration of specific neuronal types in the brain (e.g. MSNs and CPNs), a general stepwise reductionist approach can be used: First, models of HD are created in which the expression of mHtt or a toxic mHtt fragment can be regulated in specific genetically defined cell types by Cre recombinase. Examples of such models include RosaHD (Gu et al., 2005) in which mHtt-exon1 expression can be switched on in Cre-expressing cells, and BACHD in which full-length human mHtt expression can be genetically reduced in cell types expressing Cre (Gray et al., 2008; Gray and Yang, data not shown). In the first reductionist step, by systematically crossing such conditional HD models with mice expressing Cre in distinct cell types, one can address whether mHtt expression in these cell types are necessary or sufficient to elicit cell-autonomous disease or pathological cell-cell interactions. Using a further reductionist step, one can investigate the molecular mechanisms operating within the critical genetically defined cell types, with particular focus on the mechanisms that are consistent with their pathogenic roles in the disease as defined by the first reductionist step (e.g. cell-autonomy vs. pathological cell-cell interactions).

Although frank neurodegeneration has not been observed in HD mouse models, there is evidence of relatively striatal-selective disease in terms of striatal neuronal atrophy (Mangiarini et al., 1996), selective and early translocation of mHtt to the nucleus (Hodgson et al., 1999; Li et al., 2000), synaptic dysfunction (Levine et al., 1999; Zeron et al., 2002; Li et al., 2003; Milnerwood et al., 2006), and transcriptional dysregulation (Cha et al., 1999; Luthi-Carter et al., 2000). Such phenotypic readouts have been used to assess the contributions of cell-autonomous toxicity and pathological cell-cell interactions in HD striatal pathogenesis (Yang and Gray, 2011).

The first mouse model specifically created to address these questions is a conditional model, called RosaHD, which was designed to selectively switch on the expression of a mHtt-exon1 fragment in specific cell types in the brain (Gu et al., 2005; 2007). In this model, mHtt-exon1 with 103Q was targeted to the Rosa26 locus to drive ubiquitous expression. To confer conditional transgene expression, two loxP sites flanking a transcriptional STOP sequence were strategically placed in front of the mHtt-exon1 sequence so that this toxic mHtt fragment is expressed only in cell types that have expressed Cre recombinase. By crossing RosaHD mice with a pan-neuronal Cre mouse line (i.e. Nestin-Cre) or predominantly striatal-selective Cre mouse line (i.e. Dlx5/6-Cre, which also expresses in a population of cortical interneurons), one can assess whether cell-autonomous toxicity of mHtt-exon1 fragment in the striatal MSNs/cortical interneurons (using RosaHD/Dlx5/6-Cre double transgenic mice) is comparable to that found in the pan-neuronal model (RosaHD/Nestin-Cre). Surprisingly, although the pan-neuronal model shows motor impairment, striatal pathology including reactive gliosis, and EM evidence of neurodegeneration (Gu et al., 2005), the striatal MSN/cortical interneuron model did not exhibit evidence of motor dysfunction, striatal gliosis, or neuorodegenerative pathology (Gu et al., 2007). There is, however, some evidence that the striatal neurons in the latter model are not completely devoid of the disease, since they accumulate aggregated nuclear mHtt, and dissociated neurons show evidence of deficits in NMDA receptor currents (Gu et al., 2007). Overall, the study of the RosaHD model provides evidence that cell-autonomous toxicity elicited by a mHtt fragment is likely insufficient to elicit robust striatal pathogenesis, and pathological cell-cell interactions are likely to be required in HD striatal pathogenesis.

A second model was developed to address the question of whether selective expression of a mHtt fragment in striatal MSNs, with very little expression elsewhere in the brain, could be sufficient to elicit cell-autonomous disease. Using the murine DARPP-32 promoter to drive expression of a mHtt N-terminal 171 amino acid fragment with 98Q repeats (DE5 mice), Ehrlich and colleagues showed that predominantly striatal-specific expression of a mHtt fragment is sufficient to elicit cell-autonomous mHtt aggregation, reactive gliosis, forebrain atrophy and age-dependent motor deficits (Brown et al., 2008). Importantly, compared to a prior model with pan-neuronal expression of a similar 171 amino acid mHtt fragment (PrP-N171-82Q), DE5 mice exhibit delayed-onset, less severe behavioral and neuropathological phenotypes, and lack of premature lethality, despite the longer polyglutamine repeat length and higher level of striatal mHtt expression in DE5 compared to N171 mice (Schilling et al., 1999; Brown et al., 2008). This latter comparison is consistent with a role for extra-striatal mHtt N171 fragments in determining the onset and severity of disease *in vivo*. An important insight gained from studying DE5 mice is that striatum-specific expression of the mHtt fragment appears to be sufficient to induce transcriptional dysregulation that is similar both to models with ubiquitous expression of mHtt fragment and to HD (Thomas et al., 2011). A similar conclusion was made in a striatal primary neuron model expressing a mHtt 171 amino acid fragment (Runne et al., 2008). Together, these studies suggest cell-autonomous expression of certain toxic mHtt fragments may be sufficient to induce HD-like striatal transcription changes and certain disease phenotypes (e.g. motor deficits), but that the full severity of striatal disease elicited by the pan-neuronal expression of toxic fragments likely involves the contribution of extra-striatal mHtt expression. Thus, studies with mHtt fragment mice so far suggest that the "two-hit" model is likely to underlie striatal pathogenesis in HD.

Pathogenic roles of cortical pyramidal neurons (CPNs) in HD

CPNs are glutamatergic excitatory projection neurons that comprise about 80% of the neurons in the cortex, with the remainder of cortical neurons being a variety of GABAergic interneurons. CPNs send long-distance projections to other CPNs as well as diverse subcortical structures including the striatum, thalamus, brain stem and spinal cord. In HD, CPNs are affected in multiple ways, including atrophy (de la Monte et al., 1988), degeneration in the deep cortical layers (Cudkowicz and Kowall, 1990; Macdonald and Halliday, 2002), and axonal abnormalities (DiFiglia et al., 1997; Rosas et al., 2006, 2010). Intriguingly, CPNs appear to express higher levels of mHtt compared to MSNs (DiFiglia et al., 1995; Fusco et al., 1999; Reiner et al., 2003), and preferentially accumulate mHtt nuclear inclusions (NIs) and neuropil aggregates (DiFiglia et al., 1997; Gutekunst et al., 1999). The precise role of CPNs in HD pathogenesis remains poorly defined, and there are competing ideas regarding whether the cortical pathology could be a primary pathogenic event in HD, or if it could be secondary to the massive striatal degeneration.

To test whether mHtt in CPNs could critically contribute to cortical disease or elicit pathological cell-cell interactions to impact striatal pathogenesis in HD, our laboratory crossed RosaHD mice with Emx1-Cre mice, switching on the expression of mHtt-exon1 in predominantly forebrain glutamatergic neurons in the cortex and hippocampus, while driving very little expression in striatal MSNs (Iwasato et al., 2000; Gorski et al., 2002; Gu et al., 2005). Interestingly, the cortical model (RosaHD/Emx1-Cre double transgenic mice) exhibits age-dependent and cortex-selective mHtt aggregation, but in contrast to the cortical pathology observed in the pan-neuronal model, RosaHD/Emx1-Cre mice have no evidence of motor deficits, cortical gliosis or neurodegeneration (Gu et al., 2005). This suggests that pathological cell-cell interactions are likely to be critical to cortical pathogenesis in this model. However, similar to our striatal study, CPNs in the cortical model exhibit some mild degenerative changes under electron microscope, suggesting mHtt-exon1 can elicit some mild cell-autonomous toxicity. Although the precise cell types that can provide pathological interaction with CPNs remain to be defined, a clue from our study is the demonstration of abnormal interneuron-mediated inhibitory input onto CPNs in the pan-neuronal model but not in the cortical model (Gu et al., 2005). Interestingly, such deficits in cortical inhibitory inputs onto CPNs were replicated as an age-dependent phenotype in the BACHD model which expresses full-length mHtt (Spampanato et al., 2008), further supporting a role for pathological interneuron-CPN interactions in HD cortical pathogenesis. In summary, evidence thus far supports the two-hit model in HD cortical pathogenesis, and suggests that cortical interneurons may play a role in the disease pathogenesis.

Pathogenic roles of astrocytes in HD

Astrocytes are a major glial cell population in the brain and play an essential role in neuronal metabolism of cholesterol (Pfrieger and Ungerer, 2011) and glucose (Brown and Ransom, 2007), and in maintaining normal synaptic transmission (Fiacco and McCarthy, 2004), including removal of glutamate from the synaptic cleft (Bezzi et al., 2004). Moreover, astrocytes are active participants in neuroinflammatory responses in a variety of disease conditions including neurodegeneration, which may itself have both beneficial as well as harmful consequences in the brain (Glass et al., 2010). In HD, reactive astrocytosis, marked by increased GFAP expression, is a consistent finding in the striatum and cortex of postmortem HD brains (Myers et al., 1991) and a subset of HD mouse models (Heng et al., 2008). Huntingtin is normally expressed in astrocytes (Liévens et al., 2001; Faideau et al.,

2010), and a variety of glial cell pathology and functional alterations have been described in HD mouse models. This includes formation of nuclear mHtt inclusions (Shin et al., 2005), altered cholesterol metabolism (Valenza et al., 2010), reduced glutamate transport capacity (Liévens et al., 2001; Shin et al., 2005), and reduction of neurotrophic factors and chemokines (Chou et al., 2008; Wang et al., 2012). These findings suggest that astrocyte dysfunction could contribute to aspects of disease phenotypes in HD. To directly test this hypothesis, Shihua Li, Xiao-Jiang Li and colleagues created transgenic mice using the GFAP promoter to drive the expression of the N171 mHtt fragment with either 160Q or 23Q specifically in astrocytes (Bradford et al., 2009). Three independent lines of mice expressing the mHtt fragment in astrocytes develop age-dependent neurological phenotypes, including motor impairment in the rotarod test, bodyweight loss, and reduced survival, while mice expressing the wildtype fragment do not. Consistent with a pathogenic role for astrocytes in neuronal excitotoxicity, the astrocyte selective mHtt mice showed reduced expression of astrocyte-specific glutamate transporter, GLT-1 (*aka* Slc1a2 or Eaat2), which is normally involved in the removal of extracellular glutamate. The authors showed that the underlying pathogenic mechanism is the cell-autonomous effect of mHtt fragments impeding the Sp1-mediated transcription of GLT-1 in astrocytes (Bradford et al., 2009), a finding that confirmed earlier studies suggesting such a mechanism in the R6/2 fragment model (Liévens et al., 2001; Behrens et al., 2002; Shin et al., 2005). Interestingly, the same group recently developed a GFAP promoter driven mHtt N171 fragment model with 98Q (Bradford et al., 2010). Unlike the astrocyte-specific N171-160Q mice, the new model did not exhibit significant disease symptoms, but the mHtt fragment conferred increased susceptibility to glutamate-induced seizures. Importantly, crossing this model with the pan-neuronal N171-82Q model resulted in double transgenic mice with worsening neuropathology and earlier death, underscoring the important role of pathological astrocyte-neuronal interactions in HD mouse models. Consistent with this hypothesis, normalizing GLT-1 transcription via administration of ceftriaxone (a β-lactam antibiotic), resulted in improvement of several disease phenotypes in a fragment model of HD (Miller et al., 2008). Thus, targeting astrocytic mHtt to normalize glia-neuronal interactions could prove to be a valuable avenue for HD therapy.

Despite the progress summarized above, the study of cellular pathogenic mechanisms in HD is still in its infancy. It should not be surprising that additional cell types beyond those in the striatum and cortex could contribute to certain disease phenotypes. One example of such is a study shows that mHtt expression in the hypothalamus is both necessary and sufficient to elicit certain metabolic deficits in HD mouse models (Hult et al., 2011). Among many research agendas in this area, a pressing one is to use mouse models with more accurate construct validity (e.g. expressing full-length mHtt from its own promoter) to define the role of individual cell types in disease pathogenesis. Moreover, it would be important to identify the sources of cell types that exert pathological cell-cell influence critical to cortical and striatal pathogenesis in HD. Ideally, if one can define the minimal group of cell types in which mHtt expression is responsible for the core disease process in HD, it would offer critical insight to reduce or prevent the disease. The latter scenario is particularly relevant to the ongoing development of mHtt-lowering therapy, which aims to use either RNA interference or antisense oligonucleotides (ASOs) to reduce mHtt expression in the HD brain (Harper et al., 2005; DiFiglia et al., 2007; McBride et al., 2008; Kordasiewicz et al., 2012). Since such therapeutics cannot cross the blood brain barrier, and current delivery strategies for Htt lowering therapy can often reach limited brain regions and cell types, the precise understanding of when and where mHtt expression is critical to disease pathogenesis will be necessary to select optimal therapeutic agents and delivery strategies in clinical trials for HD (Lu and Yang, 2012).

Selected molecular mechanisms implicated in cortical and striatal pathogenesis in HD

There are numerous molecular mechanisms linked to mHtt toxicity in cellular and animal models of HD. It is beyond the scope of this review to enumerate all the molecules that have been implicated in the disease, and they can be found in several recent reviews (e.g. Zuccato et al., 2010; Ross and Tabrizi, 2011). Instead, we will focus on a selected subset of molecular mechanisms that have been implicated in the pathogenesis of cortical or striatal neurodegeneration in HD, by either cell-autonomous mechanisms or pathological cell-cell interactions. Importantly, many of these selected genes have already been validated as genetic modifiers of disease pathogenesis in HD mouse models or shown to be able to be pharmacologically targeted by small molecules to ameliorate disease phenotypes. They should be viewed as examples, rather than a comprehensive catalog of potential genes that could contribute to cortical and striatal pathogenesis in HD.

Molecular mechanisms directly impinging on the mutant Huntingtin protein

Post-translational modification of mutant huntingtin

In HD, as well as other polyglutamine disorders, post translational modifications (PTMs) of protein domains beyond the polyglutamine stretch have been shown to play a major role in disease modification in animal models (reviewed by Orr and Zoghbi, 2007; Ehrnhoefer et al., 2011). In HD, several types of PTM have been shown to modify molecular properties such as aggregation or alter toxicity of mHtt fragments in cellular or invertebrate models. For example, palmitoylation of mHtt at cysteine 214, mediated

by Hip14, has been shown to reduce mHtt inclusion formation, and reduction of Hip14 exacerbates mHtt toxicity in neuronal cells (Yanai et al., 2006). Another well-characterized Htt PTM is phosphorylation of mHtt at serine 421, mediated by Akt, which is neuroprotective in cellular models and reduces mHtt inclusion formation (Humbert et al., 2002; Warby et al., 2009; Metzler et al., 2010). Interestingly, reduction of S421 phosphorylation is observed in the YAC128 model of HD, suggesting polyglutamine expansion may interfere with this potentially neuroprotective mechanism in HD. Finally, mHtt exon1, particularly the first 17 amino acid domain (N17), has been shown to undergo multiple PTMs, including SUMOylation, ubiquitination, acetylation and phosphorylation (Steffan et al., 2004; Aiken et al., 2009; Thompson et al., 2009). Importantly, these PTMs exert strong effects on subcellular distribution, aggregation, and toxicity of mHtt in cells and fly models of HD (Steffan et al., 2004; Aiken et al., 2009).

Relevant to the pathogenesis of selective neurodegeneration in HD, there are two mHtt PTMs have been demonstrated for their pathogenic relevance in mouse models of HD. The first such PTM is acetylation of huntingtin at lysine 444, which is can target mHtt for autophagic degradation in the lysosome (Jeong et al., 2009). Importantly, lentivirus-mediated expression of a toxic mHtt fragment resistant to such acetylation (by mutating lysine 444 to arginine) enhances striatal toxicity. Since this acetylation event can be fostered by CBP and inhibited by Hdac1, this study suggests pharmacological inhibition of Hdac1 could be one way to boost this novel molecular pathway for selective mHtt clearance.

The only Htt PTMs that have been shown to modify full-length mHtt induced disease pathogenesis are the phosphorylation of serines 13 and 16 within the N17 domain (Gu et al., 2009). These two residues have been shown to be phosphorylated in cells by IKK and CK2, which in turn changing the subcellular localization and aggregation of mHtt (Thompson et al., 2009; Atwal et al., 2011). To investigate the pathogenic significance of such phosphorylation events *in vivo*, our laboratory developed BAC transgenic mice expressing full-length mHtt with 97Q, but with serines 13 and 16 mutated to either aspartate to mimic phosphorylation (SD mutants) or alanine to prevent phosphorylation (SA mutants; Gu et al., 2009). Surprisingly, SD but not SA mutations completely abolish fl-mhtt induced behavioral deficits and selective cortical and striatal atrophy (a measure of neurodegeneration in this model). Importantly, both the *in vivo* mouse model as well as *in vitro* studies showed SD mutations inhibit mHtt aggregation and prevent amyloid fibril formation. These findings suggest that S13 and S16 phosphorylation could act as a molecular switch to slow or prevent HD pathogenesis *in vivo*. The precise mechanisms that can be targeted to foster neuroprotective phosphorylation of mHtt at S13 and S16 are still being investigated (Greiner and Yang, 2011), but a recent study surprisingly demonstrated that the neuroprotective function of GM1 in HD mice is likely mediated by boosting S13 and S16 phosphorylation of full-length mHtt (Di Pardo et al., 2012). Undoubtedly, further mechanistic and preclinical studies are needed to fully explore the potential of mHtt PTMs as therapeutic targets to reduce mHtt-mediated selective neuropathogenesis in HD.

Proteolysis of mHtt by caspase 6 to generate toxic mHtt fragments

A rich history of literature in the HD field points to a pathogenic role of mHtt proteolysis in HD (Wellington et al., 2003; Ross and Tabrizi, 2011). Such proteolytic events can be mediated by caspases, calpains, and matrix metalloproteinases, resulting in the generation of small, but more toxic N-terminal mHtt fragments that accumulate in HD brains (Lunkes et al., 2002; DiFiglia et al., 1997; Ratovitski et al., 2009; Miller et al., 2010). Among multiple mHtt proteolytic cleavage events, considerable interest has been focused on the cleavage of mHtt by caspase-6 to generate a 586 amino acid fragment, and YAC transgenic mice expressing full-length mHtt with a caspase-6 cleavage resistant mutation completely abolish the disease symptoms including striatal neurodegeneration (Graham et al., 2006). Consistent with the pathogenicity of this mHtt fragment, cleavage of mHtt at this site has been shown shown in the striatum and cortex of HD patients and HD mice, with the appearance of these fragments inversely correlated with CAG repeat size and age of onset (Graham et al., 2010). Moreover, transgenic overexpression of a mHtt caspase-6 fragment elicits relatively severe neurological and pathological deficits in mice (Tebbenkamp et al., 2011; Waldron-Roby et al., 2012). However, these studies also showed that the aggregated mHtt in these mice may consist of smaller, further cleaved mHtt fragments. A recent genetic study crossing capase-6 null mice with the BACHD model revealed a somewhat complex picture, and although deletion of caspase-6 could partially improve BACHD phenotypes (i.e. motor deficits but not forebrain atrophy), the benefit is likely due to increased mHtt clearance, and intriguingly a mHtt fragment consistent with the 586 amino acid caspase-6 fragment of mHtt can still be detected in these mice (Gafni et al., 2012). The latter finding suggests that additional proteases could contribute to the generation of the specific mHtt fragment, and hence further studies are needed to explore mechanisms for the generation of the mHtt 586 amino acid fragment and to test whether small molecules blocking the generation of such fragments could be overall beneficial in genetic mouse models of HD.

Molecular targets implicated in cell-autonomous toxicity in striatal MSNs

Rhes is a striatal-specific gene mediating mHtt SUMOylation and modifying its toxicity in cellular models of HD

A promising candidate that may contribute to the cell-autonomous susceptibility of striatal MSNs to toxic insults in

HD is the small guanine nucleotide binding factor Rhes (Ras homolog enriched in striatum; Harrison, 2012). Rhes has been found to bind to mHtt preferentially over wild-type Htt and can enhance mHtt toxicity in mammalian cells by selectively enhancing SUMOylation and disaggregation of mutant but not wild-type Htt (Subramaniam et al., 2009). Interestingly, Rhes has also been found to be a physiological binder and activator of mTor activity in the striatum, and it is postulated that preferential binding of Rhes by mHtt could reduce its ability to activate mTor in the striatum, which in turn may lead to reduced protein translation (Subramaniam and Snyder, 2011). The latter mechanism, if validated in genetic models of HD, could account for the striking selective striatal atrophy observed in HD.

PGC1α is a transcriptional mediator of mitochondrial dysfunction in HD

Mitochondrial energetics are consistently found to be altered in HD patients and mouse models, leading to decreased Ca^{2+} buffering, metabolic disruption, and enhanced susceptibility to excitotoxicity (Browne and Beal, 2004; Bezprozvanny and Hayden, 2004; Damiano et al., 2010; Kim et al., 2010). The peroxisome proliferator-activated receptor γ co-activator 1 alpha (Ppargc1a, or PGC1α) is a transcriptional co-activator with roles in mitochondrial biogenesis and function (Wu et al., 1999; Lin et al., 2005). An initial link between PGC1α and striatal-selective neurodegeneration was established when PGC1α null mice showed hyperactivity and spongiform lesions that were particularly prominent in the striatum (Lin et al., 2004). Subsequently, two groups independently showed the pathogenic role of PGC1α in mitochondrial dysfunction and neurodegeneration in HD (Cui et al., 2006; McGill and Beal, 2006; Weydt et al., 2006). Krainc and colleagues showed that mHtt can occupy the PGC1α promoter, leading to downregulation of its expression in HD mice and patients. Importantly, crossing PGC1α knockout mice with a murine mHtt knock-in model (CAG140) leads to worsening motor deficits and striatal atrophy, while lentivirus-mediated overexpression of PGC1α in a mHtt-exon1 fragment model of HD (R6/2) reduces atrophy of striatal neurons (Cui et al., 2006). The study by La Spada and colleagues (Weydt et al., 2006) showed that HD mice and patients exhibit mitochondrial dysfunction and reduced expression of PGC1α target genes, which in turn may help to explain the profound thermoregulatory and metabolic defects in HD transgenic mice. This study also suggests that overexpression of PGC1α in striatal neurons from HD mice can confer protection against a mitochondrial toxin, 3-nitropropionic acid. Adding more credence to this line of inquiry is a recent study by La Spada's group that used an inducible PGC1α transgenic mouse line crossed to the N171-82Q model of HD to show that increased PGC1α expression could rescue motor and neurodegenerative phenotypes (Tsunemi et al., 2012). Strikingly, the HD mice with PGC1α overexpression showed virtual elimination of mHtt aggregates, which appears to be dependent on both the ubiquitin proteasome pathway and autophagy pathway. A key mechanistic finding in the new study is that PGC1α can reduce proteotoxicity and oxidative stress in HD cells via transcriptional activation of TFEB, which in turn augments autophagosome/lysosome-mediated clearance of misfolded mHtt protein. Human genetic studies have further supported a role for PGC1α in HD pathogenesis, with two SNP variants of PGC1α exerting opposing modifying influences on the age of onset in HD (Che et al., 2011), although a follow-up study of one of these SNPs in particular (rs7665116) has since downplayed its role (Ramos et al., 2012). Moreover, dysregulation of PGC1α-mediated gene expression is also a prominent pathological molecular signature in Parkinson's disease (Zheng et al., 2010), suggesting PGC1α as a potential therapeutic target for multiple age-dependent neurodegenerative disorders. Finally, one attractive aspect of studying PGC1α as a therapeutic target for HD and related neurodegenerative disorders is the availability of small molecules that can activate this pathway. A recent preclinical study of one pan activator of the PPAR pathway, bezafibrate, showed behavioral, pathological and survival benefits in the R6/2 fragment model of HD (Johri et al., 2012). Since bezafibrate has been used safely in humans for more than 20 years to treat hyperlipidemia, it may provide a suitable agent for further clinical studies to test the therapeutic efficacy of activation of PPAR/PGC1α transcriptional pathway in HD.

Sirt1-TORC1 (CRTC1)-CREB pathway in striatal pathogenesis in HD

Another molecular pathway with strong evidence for contributing to selective striatal pathogenesis in HD is the Sirt1-TORC1 (CRTC1)-CREB pathway. CREB is a stimulus-induced transcription factor known to respond to diverse stimuli (e.g. neuronal activity, hormones, and growth factors) to activate transcription (Shaywitz and Greenberg, 1999). In the striatum, CREB promotes neuronal survival, and deletion of Creb1 and its paralog Crem in the CNS leads to progressive striatal neurodegeneration reminiscent of HD (Mantamadiotis et al., 2002). There is ample evidence suggesting that there is dysregulated CREB signaling in HD striatum, with mouse genetic evidence that reduced CREB signaling in an HD mouse model worsens striatal pathology (Choi et al., 2009). Although there are multiple potential mechanisms through which CREB transcription could be altered in HD striatum (e.g. PGC1α, CBP, or abnormal dopamine receptor function), a novel genetically validated mechanism is interference of the Sirt1-TORC1 pathway.

Sirt1 belongs to a family of NAD-dependent deacetylases, called sirtuins, which have been shown to play a critical role in regulating metabolism and healthspan (i.e. the period of life free of serious diseases; Houtkooper et al., 2012). Emerging studies have showed that Sirt1 may have an important role in the suppression of pathogenesis of multiple neurodegenera-

tive disorders (Donmez, 2012). In HD, activation of the Sirt1 homolog (Sir2.1) in *C. elegans* was first implicated in suppressing mHtt fragment toxicity (Parker et al., 2005), but evidence in *Drosophila* models appears somewhat complex and inhibition of sirtuins appears neuroprotective (Burnett et al., 2011). Two independent studies, using multiple fragment and full-length HD mouse models, have found a consistent role for Sirt1 gene dosage in HD phenotypes, with genetic ablation of Sirt1 exacerbating motor and neurodegenerative phenotypes, while elevated Sirt1 levels ameliorated disease pathogenesis (Jeong et al., 2012; Jiang et al., 2012). Jeong et al. proposed that the mechanism of this rescue is dependent on Sirt1 deacetylation of TORC1, leading to enhanced TORC1 phosphorylation and nuclear translocation, with the latter event resulting in potent co-activation of CREB-mediated transcription (Jeong et al., 2012). Moreover, since Sirt1 can deacetylate PGC1α to transmit metabolic signals to modulate mitochondria biogenesis (Guarente, 2007), it is also a possibility that Sirt1 could reduce mHtt toxicity via the regulation of other known targets that are also relevant to HD, such as PGC1α or P53 (Jeong et al., 2012; Jiang et al., 2012). Finally, since TORC1 is both a potent mediator of activity-dependent neuronal transcription and neuronal plasticity (Kovács et al., 2007; Li et al., 2009), it would be interesting to investigate whether dysregulation of this pathway could contribute to cognitive and psychiatric-like deficits in HD mice. Together, genetic evidence so far supports the modulation of the Sirt1-TORC1-CREB pathway as a promising therapeutic strategy to reduce striatal neurodegeneration in HD.

Molecular targets implicated in pathological cortico-striatal interactions

BDNF as a cortex-derived neurotrophic factor implicated in HD striatal pathogenesis

BDNF is a neurotrophic factor expressed in cortex that is anterogradely transported in vesicles along corticostriatal axons to eventually be released in the striatum (Altar et al., 1997). Cortex-derived BDNF has been shown to be essential for the survival of adult striatal MSNs, and wild-type mice with cortical-specific deletion of BNDF show striatal transcriptional dysregulation reminiscent of that seen in HD mice and patients (Strand et al., 2007). Two separate mechanisms have demonstrated how mHtt may interfere with BDNF function in the cortical neurons. First, BDNF transcription can be stimulated by wild-type Htt via its ability to sequester the transcriptional repressor REST from binding the BDNF promoter. This function is impaired in mHtt, leading to transcriptional downregulation of BDNF in HD (Zuccato et al., 2001, 2003). Consistent with BDNF being a key target for mHtt toxicity, the Sirt1-TORC1-CREB pathway is also known to affect an alternative BDNF promoter distinct from the one regulated by REST (Jeong et al., 2012; Jiang et al., 2012). Interestingly, BDNF transcription is also impaired in a mouse model of Huntington's disease like-2 (HDL2), a disorder similar to HD both clinically and pathologically, but caused by a different CTG/CAG expansion mutation (Holmes et al., 2001; Wilburn et al., 2011). Thus, BNDF transcriptionopathy could be one of the overlapping pathogenic mechanisms that produce Huntington's-like phenotypes. The second mechanism by which mHtt may affect BDNF function is interference with its transport. Microtubule-dependent vesicular transport of BNDF depends on a complex containing Htt, Hap1 and the $P150^{glued}$ subunit of dynactin. Polyglutamine expansion in full-length Htt impairs this transport process, resulting in reduced BDNF release (Gauthier et al., 2004). Together, these two mechanisms lead to reduced release of pro-survival BDNF in the striatum, which is likely to be a mechanism of pathological cell-cell interaction leading to striatal neuronal toxicity in HD.

Consistent with this idea, BDNF gene dosage can bi-directionally regulate disease pathogenesis in HD mouse models. Reducing one allele of BDNF in a fragment model of HD worsens motor deficits, cortical and striatal atrophy, and HD-like transcriptionopathy (Canals et al., 2004). On the other hand, transgenic overexpression of BDNF in the forebrain rescues motor deficits, cortical and striatal neurodegeneration, and HD-like striatal gene dysregulation in the full-length YAC128 model of HD (Xie et al., 2010). BDNF remains a promising target that is being actively pursued for therapy. Strategies to upregulate striatal BDNF, including ampakine treatment (Simmons et al., 2009, 2011) or viral/cell-mediated delivery (Arregui et al., 2011), have shown positive effects on HD mouse models. Finally, a strategy of co-delivering BDNF and noggin also shows benefit in R6/2 model of HD, although the disease-suppression mechanism of this strategy is thought to be the induction of striatal neurogenesis (Cho et al., 2007).

NMDA receptor dysfunction implicated in HD striatal pathogenesis and therapy

Another form of pathological cortico-striatal interaction is in the form of neurotransmission. CPNs send massive glutamatergic projections to MSNs as part of the cortico-striato-thalamo-cortical circuitry that is crucial for motor control, procedural learning, and cognition (Graybiel, 2000). Abnormal glutamatergic excitotoxicity has been a longstanding hypothesis in HD pathogenesis, and recent electrophysiological studies of cortico-striatal synaptic transmission have supported a role for age-dependent pathological changes in excitatory neurotransmission in the striatum of HD mice (Raymond et al., 2011). Early synaptic dysfunction in HD mice manifests as dysregulated glutamate release and glutamate receptor function, and is followed by progressive disconnection between cortex and striatum (Milnerwood and Raymond, 2010). One gene implicated in MSN vulnerability to mHtt toxicity in HD models is the NMDA receptor subunit

NR2B (or GRIN2B), which was initially implicated in enhanced susceptibility of striatal MSNs to excitotoxicity in YAC128 mice (Zeron et al., 2002). Consistent with a role for NR2B in HD, both NR2A and NR2B allelic variants are associated with age of disease onset in a sex-specific manner (Arning et al., 2007). *In vivo* mouse genetic evidence also supports NR2B signaling being toxic, since transgenic overexpression of NR2B in a knockin mouse model of HD expressing full-length mHtt showed exacerbation of selective striatal neurodegeneration (Heng et al., 2009). Recent studies have begun to point at a more precise alteration of NMDA receptors in HD striatal neurons: a shift of NMDA receptor localization from the synapse to extrasynaptic sites in HD cell (Okamoto et al., 2009) and mouse models (Milnerwood et al., 2010). Since synaptic NMDA signaling is neuroprotective, and extrasynaptic NMDA is neurotoxic (Hardingham and Bading, 2003, 2010), it is not surprising that mHtt-induced NMDA receptor mis-localization could contribute to neuronal death in a primary neuron model of HD (Okamoto et al., 2009). From a therapeutic angle, though, pharmacological blockade of NR2B was not beneficial in one study using the R6/2 fragment model of HD (Tallaksen-Greene et al., 2010). A more promising approach may be to mitigate the extrasynatpic NMDA receptor signaling, as demonstrated by treatment with low-dose memantine, which reduced mHtt toxicity in cells and improved behavior and pathology in YAC128 mice (Okamoto et al., 2009; Milnerwood et al., 2010). Since memantine is an FDA-approved compound for treating cognitive impairment in AD, it constitutes a clinically-ready candidate to test whether modulating NMDA receptor function could confer therapeutic benefits and neuroprotection in HD.

Evidence for KMO in the blood as a target for treating neurodegeneration in HD

Kynurenine is a metabolic byproduct of tryptophan that can be further metabolized in the kynurenine pathway to generate neuroprotective kynurenic acid via kynurenine aminotransferases I or II pathways, or excitotoxic quinolinic acid via a Kynurenine 3-monooxygenase (KMO) dependent pathway (Kolodziej et al., 2011). Dysfunction of these pathways was implicated early in HD research (Schwarcz et al., 1977; Jauch et al., 1995), and quinolinic acid administration has been extensively used in rodents to create striatal lesions reminiscent of those in HD (Beal et al., 1986). The mechanistic link of this pathway to HD was initially made in a genome-wide screen for loss-of-function suppressors of mHtt fragment toxicity in a yeast model which identified the yeast homolog of KMO as a potent genetic suppressor (Giorgini et al., 2005). Subsequent studies have supported a role for this pathway, including elevated levels of the excitotoxin quinolinate in HD patients and mouse models (Guidetti et al., 2006). Further, genetic inhibition of this pathway prevents neurodegeneration in a fly model of HD (Campesan et al., 2011). Since the enzymes in the kynurenine pathway are present in microglia in the brain, it has been hypothesized that microglia, activated due to chronic neuroinflammation in HD, could release quinolinic acid, which in turn mediates striatal neurodegeneration in HD (Schwarcz et al., 2010). The therapeutic benefits of KMO inhibition were recently demonstrated in both HD and AD mice (Zwilling et al., 2011). Using a novel KMO inhibitor called JM6, Muchowski and colleagues showed that oral administration results in reduction of kynurenic acid and extracellular glutamate levels in the brain, leading to improvement of multiple behavioral and pathological phenotypes in HD and AD mice. Surprisingly, since JM6 does not cross the blood-brain-barrier, this result suggests that peripheral inhibition of KMO in the blood may reduce neuronal dysfunction and degeneration in the brain.

Conclusions

Selective neuronal vulnerability is a central, but still unresolved question for almost all age-dependent neurodegenerative disorders, including HD. In the past decade, tremendous advances have been made in the HD field to define dynamic patterns of neuronal dysfunction and neurodegeneration throughout the course of the disease, providing new insights into the brain substrates of HD symptoms and new biomarkers to track the disease. The precise mechanisms underlying selective neurodegeneration in HD have also been rigorously pursued using animal models that increasingly recapitulate genetic and phenotypic features of the disease. The “two-step reductionist” approach provides a conceptual framework to systematically address such questions using the conditional HD mouse models that are available to the field. Study of the cellular basis of selective HD pathogenesis has provided evidence that both cell-autonomous mHtt toxicity and pathological cell-cell interactions are likely to contribute to striatal and cortical neuronal vulnerability in HD, hence supporting a two-hit model in HD. These studies also suggest that non-neuronal cells, particularly astrocytes and possibly microglia, may also contribute to neuronal toxicity in HD. Finally, a number of candidate molecular targets have also emerged, with distinct rationales and levels of genetic proof, that they may be relevant to selective neuropathogenesis in HD. Importantly, a subset of these targets can also be engaged by small drug-like molecules or clinically-approved compounds, and some of these compounds have already shown benefit in pre-clinical models of HD. Thus, the unrelenting quest for the mechanisms underlying selective neurodegeneration in HD is likely to yield many novel candidate therapeutics that will soon be tested in the clinic.

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