Human Molecular Genetics, 2007, Vol. 16, Review Issue 2 ***R115–R123***
doi:10.1093/hmg/ddm213

Polyglutamine diseases: emerging concepts in pathogenesis and therapy

Jieya Shao[1,2] and Marc I. Diamond[1,2,*]

[1]Department of Neurology and [2]Department of Cellular and Molecular Pharmacology, UCSF, San Francisco, CA 94143, USA

Received June 22, 2007; Revised June 22, 2007; Accepted July 27, 2007

Polyglutamine diseases are a family of neurodegenerative conditions that each derive from a CAG triplet repeat expansion in a specific gene. This produces a pathogenic protein that contains a critically expanded tract of glutamines. These prototypical protein misfolding disorders include Huntington disease, spinobulbar muscular atrophy, dentatorubral-pallidoluysian atrophy and several spinocerebellar ataxias. This article reviews the emerging concepts in pathogenesis and therapy. Key ideas include the role of proteolytic cleavage, the importance of conformational change in the pathogenic proteins, the role of protein aggregation and the importance of transcriptional and metabolic disturbances. The relative role of functional perturbation in a target protein induced by a polyglutamine expansion is also discussed. Therapeutic strategies include counteracting cellular perturbations and direct targeting of polyglutamine protein expression, cleavage or conformation.

OVERVIEW (INTRODUCTION)

The first CAG triplet repeat disease was described in 1991: a mutation in the androgen receptor (AR) gene that causes the progressive motor neuron disease spinal bulbar muscular atrophy (SBMA) (1). Eight other related diseases have now been described; all derive from a CAG codon expansion past a specific threshold (Table 1). CAG encodes glutamine, and thus affected proteins have elongated glutamine tracts (2). These prototypical disorders of protein folding are collectively termed 'polyglutamine' diseases, and include SBMA, Huntington disease (HD), several spinocerebellar ataxias (SCAs) and dentatorubral-pallidoluysian atrophy (DRPLA) (2). Each, with the exception of SCA6 (which forms cytoplasmic aggregates that stain negative for ubiquitin) (3), features the accumulation of the mutant protein in large intranuclear inclusions (4). Initially, it was proposed that these large inclusions were the proximal cause of neurodegeneration. However, in many cases, the appearance of intranuclear inclusions has been dissociated from the pathogenic process (5–8). A more nuanced interpretation that distinguishes protein aggregation (the self-association of peptides) from inclusion bodies (macromolecular structures formed by the cell) is thus warranted (9,10). The general genetic and pathogenic features of these diseases have been reviewed extensively in the past (2,4,11,12). This review will focus on emerging areas of research, emphasizing where mechanistic knowledge might impact treatment (see Fig. 1 for pathogenesis and Fig. 2 for therapeutic strategies).

PATHOGENESIS

Proteolytic cleavage

Several polyglutamine diseases, such as HD, SBMA and SCA3, appear clearly linked to proteolytic cleavage that liberates toxic polyglutamine-containing fragments (10,13–20). In others, such as SCA1, no evidence has been found for proteolysis. Recently full-length mouse models of HD were created with mutations of a caspase-6 cleavage site in the huntingtin (Htt) protein. The pathogenic phenotype was attenuated in these animals (21). However, it remains possible that multiple cleavage events could produce a variety of toxic fragments in humans (22). Further work will thus be required to determine whether or not a single protease is responsible to initiate pathogenesis in HD and other polyglutamine diseases.

Conformational change

An expanded polyglutamine protein is aggregation-prone *in vitro* (23), and the expanded polyglutamine tract within a

*To whom correspondence should be addressed at: GH-S572B, 600 16th Street, San Francisco, CA 94143, USA. Tel: +1 4155143646; Fax: +1 4155144112; Email: marc.diamond@ucsf.edu

Table 1. Polyglutamine diseases: emerginig concepts in pathogenesis and therapy

Disease	Protein	Repeat	Normal repeat length	Pathogenic repeat length	Inclusions	Brain regions most affected
Typical polyglutamine diseases (gain of function)						
HD	Huntingtin	CAG	6–34	36–121	Nucleus and cytoplasm	Striatum, cerebral cortex
SBMA	Androgen receptor	CAG	9–36	38–62	Nucleus and cytoplasm	Anterior horn and bulbar neurons, dorsal root ganglia
DRPLA	Atrophin 1	CAG	7–34	49–88	Nucleus	Cerebellum, cerebral cortex, basal ganglia, Luys body
SCA1	Ataxin 1	CAG	6–39	40–82	Nucleus	Cerebellar Purkinje cells, dentate nucleus, brainstem
SCA2	Ataxin 2	CAG	15–24	32–200	Nucleus	Cerebellar Purkinje cells, brain stem, frontotemporal lobes
SCA3	Ataxin 3	CAG	13–36	61–84	Nucleus	Cerebellar dentate neurons, basal ganglia, brain stem, spinal cord
SCA7	Ataxin 7	CAG	4–35	37–306	Nucleus	Cerebellum, brain stem, macula, visual cortex
SCA17	TATA box binding protein	CAG	25–42	47–63	Nucleus	Cerebelllar Purkinje cells, inferior olive
Atypical polyglutamine disease (mimicked by missense mutation)						
SCA6	α1a voltage-dependent calcium channel subunit	CAG	4–20	20–29	Cytoplasm	Cerebellar Purkinje cells, dentate nucleus, inferior olive
Atypical polyglutamine disease (reverse transcription of CTG repeats)						
SCA8	Unknown	CTG	16–34	>74	Nucleus	Cerebellar Purkinje cells, granule cells, inferior olive

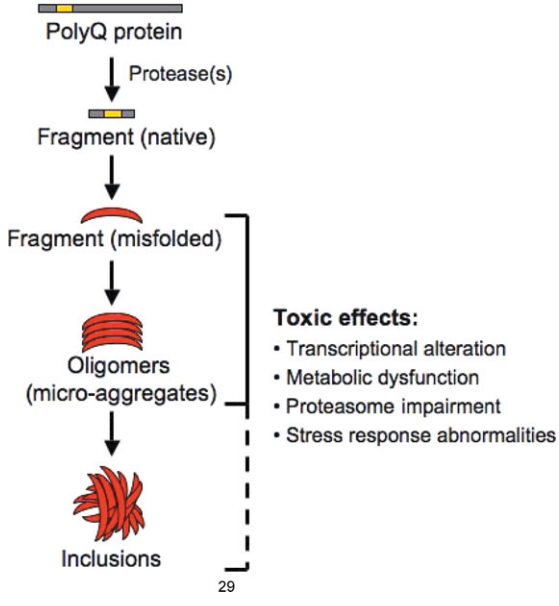

Figure 1. Pathogenesis of polyglutamine diseases. Many, but not all, polyglutamine diseases appear to be initiated by proteolytic cleavage to generate a toxic fragment. The expanded polyglutamine tract allows transition into a distinct conformation that may cause toxicity in several ways. The peptide may exert toxicity as a monomer or it may self-associate to form toxic oligomers. The oligomers can assemble into larger aggregated species and ultimately are deposited in macromolecular intracellular inclusions. The principal toxic effects of the aberrantly folded protein may include alterations in transcription, metabolism or impairment of the proteasome or stress response pathways.

target protein facilitates transition to a novel, toxic conformation (24,25). This aggregation-prone conformation is not an inevitable consequence of the expanded polyglutamine tract, however, and aggregation-prone conformers may form specifically in certain cell contexts (26). For example, two discernable forms of an expanded AR peptide, but not the unexpanded form, have been detected in cell extracts and appear to have distinct potential for aggregation and toxicity (27). Similarly, a conformational change in expanded Htt peptide was found to precede its subsequent aggregation *in vitro* (24). Recent experiments demonstrate that two distinct conformational states result from fusion of an expanded polyglutamine tract to thioredoxin (25). In this case, an α-helical state predominates initially after protein purification. After several days *in vitro*, this protein shifts to a β-sheet-rich conformation that is much more prone to aggregation, and which causes cellular toxicity upon microinjection into cultured cells. Intriguingly, a polyglutamine-binding peptide (QBP1) prevents the toxic conformational transition (25). Taken together, these data indicate that an expanded polyglutamine tract facilitates a crucial conformational transition, which can be influenced by numerous factors, including the protein context of the repeats and intracellular protein interactions.

Transcription

Interactions of expanded polyglutamine proteins with specific transcription factors may perturb gene expression, and thus initiate neurodegeneration. Such interactions could involve sequestration of a target protein by polyglutamine protein monomers, or recruitment into aggregates. Many aberrant interactions between expanded polyglutamine proteins and transcriptional factors/co-factors have been described [e.g. CREB-binding protein (CBP), p300/CBP-associated factor (p/CAF), p53, Sp1, TAFII130, PQBP-1] (28). For example, CBP has been found in nuclear inclusions formed by several polyglutamine-expanded proteins including Htt (29), AR (30), ataxin-1 (31) and atrophin-1 (29) in animal disease models or human brains. This results in its depletion from normal nuclear locations and disruption of its regulation of target genes. In contrast, Sp1 directly associates with soluble Htt in a polyglutamine-dependent fashion, and this interaction represses Sp1 transcriptional activity (32,33). In its soluble form, polyglutamine expanded Htt is also reduced in its cytoplasmic interaction with the repressor element-1 transcription factor/neuron restrictive silencer factor (REST/NRSF). This

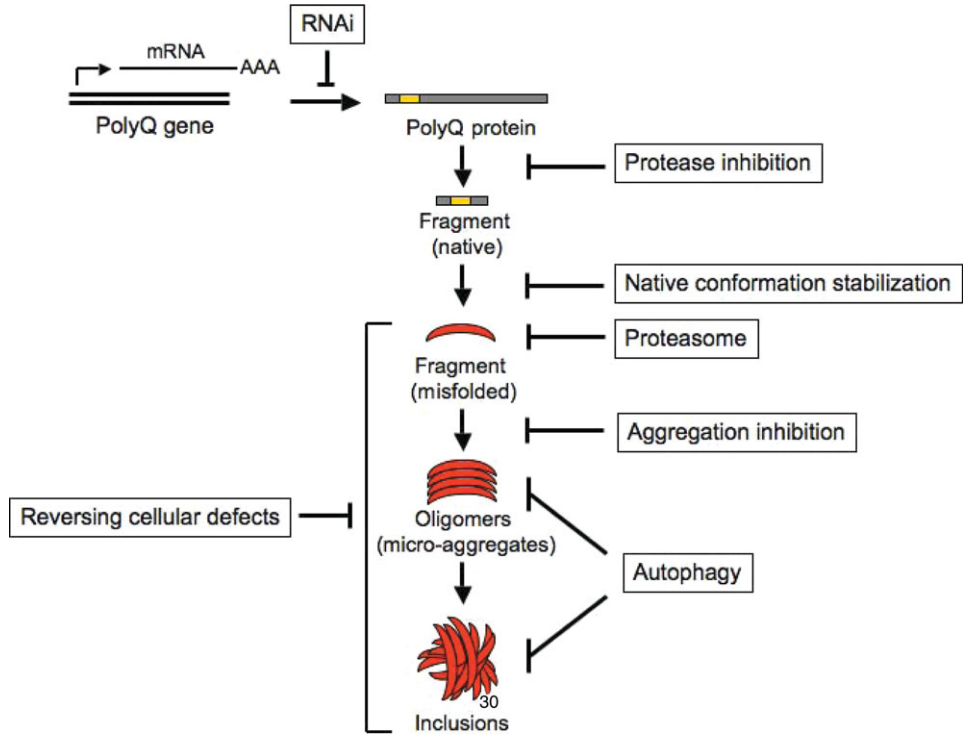

Figure 2. Therapeutic strategies. Therapeutic strategies fall into two categories based on whether they specifically target the polyglutamine protein (right side) or whether they counteract cellular defects induced by the toxic species (left side). In the first category, RNAi could be used to inhibit polyglutamine protein expression; protease inhibitors could be used to block generation of a toxic fragment; normal cellular interactions, peptides or small molecules could be used to help stabilize the polyglutamine protein in a non-toxic form; methods to increase degradation via activation of proteasome or autophagy pathways could reduce protein levels; inhibition of self-association could block formation of toxic aggregates. In the second category, pharmacological intervention could be used to reverse transcriptional and metabolic abnormalities.

leads to nuclear enrichment of REST/NRSF, its enhanced binding to the neuron restrictive silencer element, and transcriptional repression of the gene encoding brain-derived neurotrophic factor (BDNF) (34). Recent work also suggests that soluble mutant Htt selectively represses the transcription of PGC-1α, a regulator of essential mitochondrial genes, via interfering with the CREB/TAF4-dependent transcriptional pathway (35). Likewise, a pathological interaction of expanded ataxin-1 with a transcriptional repressor capicua may produce transcriptional alterations in SCA1 (36).

Most polyglutamine interactions with transcription factors cannot yet explain cell specificity, whereas studies of ataxin-7 have revealed how transcriptional repression might possibly lead to a neuron-specific pathology. Ataxin-7 is a subunit of the TFTC/STAGA transcriptional complex (37,38) and interacts with the photoreceptor-specific transcriptional activator CRX (39). Ataxin-7 thus recruits TFTC/STAGA to promoters of retina-specific genes. Polyglutamine expanded ataxin-7 suppresses the activities of both CRX and the acetyltransferase component of the TFTC/STAGA complex, and thus inhibits the expression of genes vital for retinal function (38,39). Although a different study in a knock-in mouse model argued against a primary role of CRX (40), these findings still provide a possible explanation of how specific retinal degeneration might occur in SCA7. In general terms, the transcription repression model predicts that polyglutamine protein interaction with transcription factors necessary for the survival of specific groups of neurons leads to selective neuronal loss. Most of the factors known to interact with expanded proteins such as Htt, AR and ataxin-1 are ubiquitously expressed, however, so a simple titration model cannot explain all aspects of pathology.

Metabolism and mitochondrial dysfunction

HD patients exhibit well-described metabolic defects (41,42), characterized by weight loss despite adequate calorie intake (43). This has been linked to mitochondrial dysfunction (reviewed in 44–46). Indeed, defects in striatal glucose metabolism occur in gene carriers, years prior to the onset of motor symptoms (47,48). Htt protein might influence mitochondrial function in several ways. Recent studies have described increased mitochondrial depolarization and early calcium defects in HD patients, and in a transgenic mouse model (49,50). This could be due to a direct binding of Htt to mitochondria (50,51) or an indirect effect via transcriptional repression of PGC-1α, a transcriptional co-activator that regulates mitochondrial biogenesis and respiration (35,52). It remains to be determined whether mitochondrial deficits are specific to HD (as predicted by Htt repression of PGC-1α) or whether they are a feature of polyglutamine diseases in general.

Proteotoxic stress

The pathogenic polyglutamine length threshold that causes human disease closely matches that which predisposes

polyglutamine proteins to aggregate *in vitro* (23). Protein misfolding thus appears to play a key role in pathogenesis. Indeed, protein quality control has now been linked to several human neurodegenerative diseases (reviewed in 53–55). The brain seems uniquely susceptible to protein misfolding, as most of the major neurodegenerative diseases are associated with large intracellular inclusions. Moreover, it seems likely that protein quality control mechanisms in humans diminish with age, as most neurodegenerative protein misfolding disorders are age-dependent (56,57). Autophagy, a process whereby the cell can degrade aggregated proteins, has been implicated in resistance to polyglutamine pathology in cells, *Drosophila* and mice (58–60). Its importance has been further demonstrated by findings that loss of autophagy induces neurodegeneration in mice associated with accumulation of misfolded proteins (61,62). Likewise, proteasome malfunction has been implicated in polyglutamine pathogenesis. In cultured cells, large intracellular inclusions formed by Htt and cystic fibrosis transmembrane conductance regulatory protein are associated with proteasome impairment (63). This may indicate that proteasome blockage underlies impairment. Problems might also arise from an inability of proteasome to fully digest soluble expanded polyglutamine proteins and the generation of polyglutamine fragments (64,65). Additionally, aggregated proteins may sequester important quality control machinery (e.g. chaperones), compromising the ability of the cell to mount an appropriate stress response (66). In *Caenorhabditis elegans*, it is observed that polyglutamine aggregates can destabilize in *trans*-diverse metastable proteins that contain temperature-sensitive mutations (67).

Aggregation versus inclusion formation

Although the link between polyglutamine length, aggregation potential and toxicity is inescapable, it is crucial to discriminate the pathogenic significance of large macromolecular inclusions versus small aggregates or oligomers. Multiple studies have now dissociated large inclusions from toxicity *in vivo* (6,8) and *in vitro* (5,7). This is very consistent with the idea that such inclusions represent an end-stage of the adaptive cellular response to large quantities of misfolded protein. However, polyglutamine proteins *in vitro* clearly form small aggregates, or oligomers (23,24,68–70), and very small Htt aggregates not visible by conventional immunohistology have been detected by a polyglutamine probe in HD brain (71). Recently soluble polyglutamine oligomers were detected for the first time in a mouse model of SBMA. These oligomers were comprised of N-terminal fragments of AR. They appeared several weeks prior to symptom onset, well before any detectable inclusions, and disappeared rapidly with castration, which halts disease progression (10). Taken together, these studies are consistent with emerging reports for a variety of neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, in which the importance of protein oligomerization in pathogenesis has been emphasized (reviewed in 72,73). In summary, misfolded protein (especially small soluble oligomers) may directly interfere with critical cellular events, challenge the cell's ability to prevent more widespread misfolding, and compromise its ability to keep up with protein degradation.

Alteration of normal protein function

Polyglutamine diseases are dominantly inherited, with an abnormal, new toxic activity of polyglutamine-expanded proteins being principally responsible for pathogenesis. Recent studies suggest that in some cases this dominant effect might in part derive from perturbation of normal polyglutamine protein function. For example, Htt inactivation in mice leads to progressive neurodegeneration (74), its function is essential for neurogenesis and postnatal development (74–77), and overexpression of wild-type Htt in transgenic mice can rescue mutant Htt toxicity (78). This may be due to the ability of Htt to promote BDNF production and transport, and its anti-apoptotic activity, which might be impaired by polyglutamine expansion (reviewed in 79). In the case of SCA1, it has now been proposed that polyglutamine expansion within ataxin-1 interferes with its modulation of the transcriptional repressor capicua in a regulatory complex (36). Duplication of an ataxin-1-like gene competes mutant ataxin-1 away from the capicua complex and suppresses SCA1 neuropathology in mice (80). These data imply that pathogenesis of SCA1 might result in part from perturbation of the normal function of ataxin-1 as a result of polyglutamine expansion. Ataxin-3 is a polyubiquitin-binding protein with ubiquitin protease activity (81,82). Patients homozygous for mutant alleles have earlier age-of-onset and more severe phenotypes than heterozygous patients. This could be explained either by loss of function or gain of toxic activity (83). Recent studies in flies demonstrate that normal ataxin-3 suppresses neurodegeneration caused by mutant ataxin-3, and this suppression depends on its ubiquitin-binding activity and protease activities (84). This implies (at least in this *Drosophila* model) that part of the neurodegenerative phenotype might derive from loss of ataxin-3 function.

It must be emphasized, however, that multiple knockout models of polyglutamine proteins have been created, and none mimics the disease phenotype (75,77,85,86). Nor, except in the atypical case of SCA6 (87), do point mutations in the target protein replicate the polyglutamine disease. In humans, loss-of-function mutations in AR cause testicular feminization, which does not feature any motor neuron disease (88). Humans with genomic deletion of genes encoding Htt (89) and ataxin-1 (90) also do not develop HD or ataxia, nor do knockout mice lacking ataxin-1 or Htt (75,77,85,86). Furthermore, mutant Htt can rescue the knockout phenotype (76,78). Finally, homozygous HD patients have similar disease severity and age-of-onset compared with heterozygote patients, effectively ruling out loss of function as the principal mechanism in this disease (91).

Dual mechanisms

There is currently little evidence that classical polyglutamine diseases are mediated primarily by non-coding RNA abnormalities. However, recently a fascinating pathogenic mechanism for SCA8 has been described, in which reverse strand transcription of a CTG repeat produces polyglutamine peptides that can be detected in the inclusions of transgenic mouse and patient material. It remains possible that reverse strand transcription could play a more widespread role in human

disease (92), and SCA8 could thus be the first example of a new subclass of polyglutamine diseases.

THERAPEUTIC STRATEGIES

Therapeutic strategies for polyglutamine diseases may be divided into two categories: (i) reversal of cellular defects and (ii) targeting the expression, processing or conformation of the pathogenic protein (Fig. 2).

Reversing cellular defects

Transcription. Polyglutamine pathogenesis (particularly HD) has been conceived as a problem of transcriptional regulation, whereby mutant proteins disrupt the activity of key factors, many of which possess acetyltransferase activity. Indeed, HDAC inhibitors such as suberoylanilide hydroxamic acid, sodium butyrate, and phenylbutyrate, which are purported to increase gene expression, have shown efficacy in various disease models (93–98), and phenylbutyrate is in clinical trial. Although the neuroprotective effects of HDAC inhibitors are intriguing, and they may function by correcting transcriptional defects, they might also increase acetylation of other non-histone proteins [e.g. tubulin (99) and Hsp90 (100)], and upregulate levels of heat shock proteins (e.g.Hsp70) (101,102), ameliorating polyglutamine toxicity via transcription-independent mechanisms. These myriad effects are reflected in the fact that HDAC inhibitors are also effective in mouse models of other diseases, including amyotrophic lateral sclerosis (103), and immune-mediated demyelination (104). Their chronic use in humans, at least in current forms, is likely to be limited by their fairly high toxicity. Moreover, since the specific acetyltransferase targets that mediate the effects of these compounds are not known, it will be very hard to optimize them to reduce toxicity. Further studies of their molecular mechanism, and development of more selective HDAC inhibitors, might ultimately provide better therapies.

Cellular metabolism. Various compounds that improve energy metabolism or possess antioxidant activities have been tested and have proven effective in mouse models (e.g. creatine and coenzyme Q10) (105), a finding consistent with the link between mitochondrial defects and HD pathogenesis. Clinical trials with these drugs in HD patients, however, have not shown significant benefits (106–109). Recently, the transcriptional regulator of mitochondrial biogenesis and respiration, PGC-1α, has been proposed as a target of mutant Htt (35,52). PGC-1α over-expression prevents striatal atrophy in transgenic HD mice (35) and protects neuronal culture from oxidative stress-mediated death (110). Treatments that elevate PGC-1α activity might thus prove beneficial.

Targeting polyglutamine proteins

Gene therapy. The most straightforward approach to therapy may be to selectively reduce expression of the expanded allele. The use of small interfering RNAs to selectively knockdown gene expression has now been validated in mouse models of polyglutamine disease (111,112). Indeed, for diseases with relatively localized pathology (e.g. retina in SCA7), it is quite feasible to consider such an approach. However, more widespread CNS pathology (e.g. cortical and striatal neurons in HD) will present a greater challenge. Long-term safety is uncertain, but ongoing trials of viral-mediated gene therapy in humans should relieve concerns. Another challenge will be to create an allele-specific sequence that only targets the mutant gene, particularly for those diseases where the normal gene is vital (e.g. HD and SCA3). Nonetheless, if such therapies are tolerated, they will clearly hold great promise.

Proteolysis. Several studies have implicated caspase activation in the pathogenesis of polyglutamine diseases, due to their cleavage of the polyglutamine proteins and induction of apoptosis (113–115). Indeed, the modest activity of minocycline (a putative apoptosis inhibitor) in a mouse model of HD (116) has inspired an ongoing clinical trial. The more general role of caspase activation in the neurodegenerative process is still being elucidated. However, if specific proteases are found to cleave polyglutamine proteins to generate toxic fragments, then it may be possible to create protease inhibitors that will be of benefit.

Protein clearance. Stimulating cellular degradation pathways that preferentially target misfolded disease proteins may be beneficial. Emerging evidence implicates autophagy as a protective mechanism in polyglutamine disease (reviewed in 117). The mTOR inhibitor rapamycin, which stimulates autophagy, has been beneficial in cell, *Drosophila* and mouse disease models (58–60) and may be a potential drug candidate. Additionally, recent high throughput chemical screens have identified compounds that selectively stimulate clearance of Htt (118) and AR proteins (119), although the underlying mechanisms are poorly understood. Activation of cellular protein clearance mechanisms might thus be a viable strategy.

Protein aggregation. Direct targeting of polyglutamine aggregation has been a focus of therapeutic development for several years. Pharmacological induction of molecular chaperones (e.g. Hsp70) that aid in protein refolding and degradation has been proposed (e.g. geldanamycin and geranylgeranylacetone) (120–122). However side effects associated with such strategies are likely to be limiting. Multiple attempts have been made to screen for small molecules that directly interfere with polyglutamine protein aggregation (123–128). However, despite promising data in cell-based assays and model organisms, few convincing results in mice have been described. One potential problem is that compounds designed to prevent formation of large aggregates may not stop the initial pathological misfolding of protein monomers, which will retain their capacity for pathogenesis, either as single molecules or as toxic oligomers.

Stabilizing native conformation. Because an expanded polyglutamine protein can exist in multiple conformations (24,25,27), it may be possible to influence the equilibrium between a toxic and non-toxic conformation by directly targeting the protein with interventions that stabilize the native conformer. (Indeed, rescue of polyglutamine toxicity by over-expression of various interacting proteins may occur by this mechanism.) This general idea was recently validated by the use of a polyglu-

tamine binding peptide (QBP1) to stabilize the native conformation of a thioredoxin/polyglutamine fusion protein. This prevents it from converting into an aggregation-prone β-sheet-rich confirmation (25,129,130). A similar approach has been adopted by the use of a bivalent Htt-binding peptide to suppress polyglutamine aggregation and toxicity in *Drosophila* (131), and antibody-based therapies may also be exploited in this manner (132–134). Delivery of peptides directly to the CNS remains a significant challenge and may require virus-based gene therapy. However, small molecules that have the potential to stabilize a non-toxic conformation of a polyglutamine protein (as opposed to those simply blocking aggregate formation) might ultimately achieve this goal.

Polyglutamine protein aggregation potential can be regulated by interactions with cellular binding partners (135,136). Thus, it may be possible to stabilize the mutant proteins in a less toxic form indirectly via targeting these interactions. For example, phosphorylation of ataxin-1 at Ser-776 by Akt increases its affinity for 14-3-3 protein, which increases ataxin-1 steady-state level, and likewise its toxicity (137,138). An inhibitor of the Rho-associated protein kinase, a regulator of actin dynamics, reduces Htt aggregation and toxicity (127), and genetic modifiers of actin polymerization similarly affect polyglutamine aggregation (139), presumably based on (as yet undetermined) protein interactions. Ultimately, modulation of intracellular signaling pathways that regulate such interactions could form the basis of effective treatment.

Conflict of Interest statement. None declared.

FUNDING

The authors gratefully acknowledge funding from the Muscular Dystrophy Association (J.S.), the Taube Family Foundation Program in Huntington's Disease Research (M.I.D), and the Sandler Family Supporting Foundation (J.S., M.I.D.).

REFERENCES

1. La Spada, A.R., Wilson, E.M., Lubahn, D.B., Harding, A.E. and Fischbeck, K.H. (1991) Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. *Nature*, **352**, 77–79.
2. Zoghbi, H.Y. and Orr, H.T. (2000) Glutamine repeats and neurodegeneration. *Ann. Rev. Neurosci.*, **23**, 217–247.
3. Ishikawa, K., Fujigasaki, H., Saegusa, H., Ohwada, K., Fujita, T., Iwamoto, H., Komatsuzaki, Y., Toru, S., Toriyama, H., Watanabe, M. *et al.* (1999) Abundant expression and cytoplasmic aggregations of [alpha]1A voltage-dependent calcium channel protein associated with neurodegeneration in spinocerebellar ataxia type 6. *Hum. Mol. Genet.*, **8**, 1185–1193.
4. Cummings, C.J. and Zoghbi, H.Y. (2000) Trinucleotide repeats: mechanisms and pathophysiology. *Annu. Rev. Genomics Hum. Genet.*, **1**, 281–328.
5. Saudou, F., Finkbeiner, S., Devys, D. and Greenberg, M.E. (1998) Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. *Cell*, **95**, 55–66.
6. Klement, I.A., Skinner, P.J., Kaytor, M.D., Yi, H., Hersch, S.M., Clark, H.B., Zoghbi, H.Y. and Orr, H.T. (1998) Ataxin-1 nuclear localization and aggregation: role in polyglutamine-induced disease in SCA1 transgenic mice [see comments]. *Cell*, **95**, 41–53.
7. Arrasate, M., Mitra, S., Schweitzer, E.S., Segal, M.R. and Finkbeiner, S. (2004) Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. *Nature*, **431**, 805–810.
8. Slow, E.J., Graham, R.K., Osmand, A.P., Devon, R.S., Lu, G., Deng, Y., Pearson, J., Vaid, K., Bissada, N., Wetzel, R. *et al.* (2005) Absence of behavioral abnormalities and neurodegeneration *in vivo* despite widespread neuronal huntingtin inclusions. *Proc. Natl Acad. Sci. USA*, **102**, 11402–11407.
9. Taylor, J.P., Tanaka, F., Robitschek, J., Sandoval, C.M., Taye, A., Markovic-Plese, S. and Fischbeck, K.H. (2003) Aggresomes protect cells by enhancing the degradation of toxic polyglutamine-containing protein. *Hum. Mol. Genet.*, **12**, 749–757.
10. Li, M., Chevalier-Larsen, E.S., Merry, D.E. and Diamond, M.I. (2007) Soluble androgen receptor oligomers underlie pathology in a mouse model of spinobulbar muscular atrophy. *J. Biol. Chem.*, **282**, 3157–3164.
11. Gatchel, J.R. and Zoghbi, H.Y. (2005) Diseases of unstable repeat expansion: mechanisms and common principles. *Nat. Rev. Genet.*, **6**, 743–755.
12. Ross, C.A. (2002) Polyglutamine pathogenesis: emergence of unifying mechanisms for Huntington's disease and related disorders. *Neuron*, **35**, 819–822.
13. Wellington, C.L., Ellerby, L.M., Hackam, A.S., Margolis, R.L., Trifiro, M.A., Singaraja, R., McCutcheon, K., Salvesen, G.S., Propp, S.S., Bromm, M. *et al.* (1998) Caspase cleavage of gene products associated with triplet expansion disorders generates truncated fragments containing the polyglutamine tract. *J. Biol. Chem.*, **273**, 9158–9167.
14. Wellington, C.L., Ellerby, L.M., Gutekunst, C.A., Rogers, D., Warby, S., Graham, R.K., Loubser, O., van Raamsdonk, J., Singaraja, R., Yang, Y.Z. *et al.* (2002) Caspase cleavage of mutant huntingtin precedes neurodegeneration in Huntington's disease. *J. Neurosci.*, **22**, 7862–7872.
15. Sieradzan, K.A., Mechan, A.O., Jones, L., Wanker, E.E., Nukina, N. and Mann, D.M. (1999) Huntington's disease intranuclear inclusions contain truncated, ubiquitinated huntingtin protein. *Exp. Neurol.*, **156**, 92–99.
16. DiFiglia, M., Sapp, E., Chase, K.O., Davies, S.W., Bates, G.P., Vonsattel, J.P. and Aronin, N. (1997) Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. *Science*, **277**, 1990–1993.
17. Martindale, D., Hackam, A., Wieczorek, A., Ellerby, L., Wellington, C., McCutcheon, K., Singaraja, R., Kazemi-Esfarjani, P., Devon, R., Kim, S.U. *et al.* (1998) Length of huntingtin and its polyglutamine tract influences localization and frequency of intracellular aggregates. *Nat. Genet.*, **18**, 150–154.
18. Kim, Y.J., Yi, Y., Sapp, E., Wang, Y., Cuiffo, B., Kegel, K.B., Qin, Z.H., Aronin, N. and DiFiglia, M. (2001) Caspase 3-cleaved N-terminal fragments of wild-type and mutant huntingtin are present in normal and Huntington's disease brains, associate with membranes, and undergo calpain-dependent proteolysis. *Proc. Natl Acad. Sci. USA*, **98**, 12784–12789.
19. Li, M., Miwa, S., Kobayashi, Y., Merry, D.E., Yamamoto, M., Tanaka, F., Doyu, M., Hashizume, Y., Fischbeck, K.H. and Sobue, G. (1998) Nuclear inclusions of the androgen receptor protein in spinal and bulbar muscular atrophy. *Ann. Neurol.*, **44**, 249–254.
20. Paulson, H.L., Perez, M.K., Trottier, Y., Trojanowski, J.Q., Subramony, S.H., Das, S.S., Vig, P., Mandel, J.L., Fischbeck, K.H. and Pittman, R.N. (1997) Intranuclear inclusions of expanded polyglutamine protein in spinocerebellar ataxia type 3. *Neuron*, **19**, 333–344.
21. Graham, R.K., Deng, Y., Slow, E.J., Haigh, B., Bissada, N., Lu, G., Pearson, J., Shehadeh, J., Bertram, L., Murphy, Z. *et al.* (2006) Cleavage at the caspase-6 site is required for neuronal dysfunction and degeneration due to mutant huntingtin. *Cell*, **125**, 1179–1191.
22. Hoffner, G., Island, M.L. and Djian, P. (2005) Purification of neuronal inclusions of patients with Huntington's disease reveals a broad range of N-terminal fragments of expanded huntingtin and insoluble polymers. *J. Neurochem.*, **95**, 125–136.
23. Scherzinger, E., Lurz, R., Turmaine, M., Mangiarini, L., Hollenbach, B., Hasenbank, R., Bates, G.P., Davies, S.W., Lehrach, H. and Wanker, E.E. (1997) Huntingtin-encoded polyglutamine expansions form amyloid-like protein aggregates *in vitro* and *in vivo*. *Cell*, **90**, 549–558.
24. Schaffar, G., Breuer, P., Boteva, R., Behrends, C., Tzvetkov, N., Strippel, N., Sakahira, H., Siegers, K., Hayer-Hartl, M. and Hartl, F.U. (2004) Cellular toxicity of polyglutamine expansion proteins: mechanism of transcription factor deactivation. *Mol. Cell*, **15**, 95–105.
25. Nagai, Y., Inui, T., Popiel, H.A., Fujikake, N., Hasegawa, K., Urade, Y., Goto, Y., Naiki, H. and Toda, T. (2007) A toxic monomeric conformer of the polyglutamine protein. *Nat. Struct. Mol. Biol.*, **14**, 332–340.

26. Diamond, M.I., Robinson, M.R. and Yamamoto, K.R. (2000) Regulation of expanded polyglutamine protein aggregation and nuclear localization by the glucocorticoid receptor. *Proc. Natl Acad. Sci. USA*, **97**, 657–661.
27. Welch, W.J. and Diamond, M.I. (2001) Glucocorticoid modulation of androgen receptor nuclear aggregation and cellular toxicity is associated with distinct forms of soluble expanded polyglutamine protein. *Hum. Mol. Genet.*, **10**, 3063–3074.
28. Okazawa, H. (2003) Polyglutamine diseases: a transcription disorder? *Cell. Mol. Life Sci.*, **60**, 1427–1439.
29. Nucifora, F.C., Jr, Sasaki, M., Peters, M.F., Huang, H., Cooper, J.K., Yamada, M., Takahashi, H., Tsuji, S., Troncoso, J., Dawson, V.L. *et al.* (2001) Interference by huntingtin and atrophin-1 with CBP-mediated transcription leading to cellular toxicity. *Science*, **291**, 2423–2428.
30. McCampbell, A., Taylor, J.P., Taye, A.A., Robitschek, J., Li, M., Walcott, J., Merry, D., Chai, Y., Paulson, H., Sobue, G. *et al.* (2000) CREB-binding protein sequestration by expanded polyglutamine. *Hum. Mol. Genet.*, **9**, 2197–2202.
31. Stenoien, D.L., Mielke, M. and Mancini, M.A. (2002) Intranuclear ataxin1 inclusions contain both fast- and slow-exchanging components. *Nat. Cell Biol.*, **4**, 806–810.
32. Li, S.H., Cheng, A.L., Zhou, H., Lam, S., Rao, M., Li, H. and Li, X.J. (2002) Interaction of Huntington disease protein with transcriptional activator sp1. *Mol. Cell. Biol.*, **22**, 1277–1287.
33. Dunah, A.W., Jeong, H., Griffin, A., Kim, Y.M., Standaert, D.G., Hersch, S.M., Mouradian, M.M., Young, A.B., Tanese, N. and Krainc, D. (2002) Sp1 and TAFII130 transcriptional activity disrupted in early Huntington's disease. *Science*, **296**, 2238–2243.
34. Zuccato, C., Tartari, M., Crotti, A., Goffredo, D., Valenza, M., Conti, L., Cataudella, T., Leavitt, B.R., Hayden, M.R., Timmusk, T. *et al.* (2003) Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes. *Nat. Genet.*, **35**, 76–83.
35. Cui, L., Jeong, H., Borovecki, F., Parkhurst, C.N., Tanese, N. and Krainc, D. (2006) Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. *Cell*, **127**, 59–69.
36. Lam, Y.C., Bowman, A.B., Jafar-Nejad, P., Lim, J., Richman, R., Fryer, J.D., Hyun, E.D., Duvick, L.A., Orr, H.T., Botas, J. *et al.* (2006) ATAXIN-1 interacts with the repressor Capicua in its native complex to cause SCA1 neuropathology. *Cell*, **127**, 1335–1347.
37. Helmlinger, D., Hardy, S., Sasorith, S., Klein, F., Robert, F., Weber, C., Miguet, L., Potier, N., Van-Dorsselaer, A., Wurtz, J.M. *et al.* (2004) Ataxin-7 is a subunit of GCN5 histone acetyltransferase-containing complexes. *Hum. Mol. Genet.*, **13**, 1257–1265.
38. Palhan, V.B., Chen, S., Peng, G.H., Tjernberg, A., Gamper, A.M., Fan, Y., Chait, B.T., La Spada, A.R. and Roeder, R.G. (2005) Polyglutamine-expanded ataxin-7 inhibits STAGA histone acetyltransferase activity to produce retinal degeneration. *Proc. Natl Acad. Sci. USA*, **102**, 8472–8477.
39. La Spada, A.R., Fu, Y.H., Sopher, B.L., Libby, R.T., Wang, X., Li, L.Y., Einum, D.D., Huang, J., Possin, D.E., Smith, A.C. *et al.* (2001) Polyglutamine-expanded ataxin-7 antagonizes CRX function and induces cone-rod dystrophy in a mouse model of SCA7. *Neuron*, **31**, 913–927.
40. Yoo, S.Y., Pennesi, M.E., Weeber, E.J., Xu, B., Atkinson, R., Chen, S., Armstrong, D.L., Wu, S.M., Sweatt, J.D. and Zoghbi, H.Y. (2003) SCA7 knockin mice model human SCA7 and reveal gradual accumulation of mutant ataxin-7 in neurons and abnormalities in short-term plasticity. *Neuron*, **37**, 383–401.
41. Leenders, K.L., Frackowiak, R.S., Quinn, N. and Marsden, C.D. (1986) Brain energy metabolism and dopaminergic function in Huntington's disease measured *in vivo* using positron emission tomography. *Mov. Disord.*, **1**, 69–77.
42. Jenkins, B.G., Koroshetz, W.J., Beal, M.F. and Rosen, B.R. (1993) Evidence for impairment of energy metabolism *in vivo* in Huntington's disease using localized 1H NMR spectroscopy. *Neurology*, **43**, 2689–2695.
43. Djousse, L., Knowlton, B., Cupples, L.A., Marder, K., Shoulson, I. and Myers, R.H. (2002) Weight loss in early stage of Huntington's disease. *Neurology*, **59**, 1325–1330.
44. Lin, M.T. and Beal, M.F. (2006) Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature*, **443**, 787–795.
45. Browne, S.E. and Beal, M.F. (2006) Oxidative damage in Huntington's disease pathogenesis. *Antioxid. Redox Signal.*, **8**, 2061–2073.
46. Browne, S.E. and Beal, M.F. (2004) The energetics of Huntington's disease. *Neurochem. Res.*, **29**, 531–546.
47. Grafton, S.T., Mazziotta, J.C., Pahl, J.J., St George-Hyslop, P., Haines, J.L., Gusella, J., Hoffman, J.M., Baxter, L.R. and Phelps, M.E. (1992) Serial changes of cerebral glucose metabolism and caudate size in persons at risk for Huntington's disease. *Arch. Neurol.*, **49**, 1161–1167.
48. Antonini, A., Leenders, K.L., Spiegel, R., Meier, D., Vontobel, P., Weigell-Weber, M., Sanchez-Pernaute, R., de Yebenez, J.G., Boesiger, P., Weindl, A. *et al.* (1996) Striatal glucose metabolism and dopamine D2 receptor binding in asymptomatic gene carriers and patients with Huntington's disease. *Brain*, **119**, 2085–2095.
49. Sawa, A., Wiegand, G.W., Cooper, J., Margolis, R.L., Sharp, A.H., Lawler, J.F., Jr., Greenamyre, J.T., Snyder, S.H. and Ross, C.A. (1999) Increased apoptosis of Huntington disease lymphoblasts associated with repeat length-dependent mitochondrial depolarization. *Nat. Med.*, **5**, 1194–1198.
50. Panov, A.V., Gutekunst, C.A., Leavitt, B.R., Hayden, M.R., Burke, J.R., Strittmatter, W.J. and Greenamyre, J.T. (2002) Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. *Nat. Neurosci.*, **5**, 731–736.
51. Yu, Z.X., Li, S.H., Evans, J., Pillarisetti, A., Li, H. and Li, X.J. (2003) Mutant huntingtin causes context-dependent neurodegeneration in mice with Huntington's disease. *J. Neurosci.*, **23**, 2193–2202.
52. Weydt, P., Pineda, V.V., Torrence, A.E., Libby, R.T., Satterfield, T.F., Lazarowski, E.R., Gilbert, M.L., Morton, G.J., Bammler, T.K., Strand, A.D. *et al.* (2006) Thermoregulatory and metabolic defects in Huntington's disease transgenic mice implicate PGC-1alpha in Huntington's disease neurodegeneration. *Cell Metab.*, **4**, 349–362.
53. Muchowski, P.J. and Wacker, J.L. (2005) Modulation of neurodegeneration by molecular chaperones. *Nat. Rev. Neurosci.*, **6**, 11–22.
54. Rubinsztein, D.C., Gestwicki, J.E., Murphy, L.O. and Klionsky, D.J. (2007) Potential therapeutic applications of autophagy. *Nat. Rev. Drug Discov.*, **6**, 304–312.
55. Ross, C.A. and Pickart, C.M. (2004) The ubiquitin-proteasome pathway in Parkinson's disease and other neurodegenerative diseases. *Trends Cell Biol.*, **14**, 703–711.
56. Zhou, H., Cao, F., Wang, Z., Yu, Z.X., Nguyen, H.P., Evans, J., Li, S.H. and Li, X.J. (2003) Huntingtin forms toxic NH2-terminal fragment complexes that are promoted by the age-dependent decrease in proteasome activity. *J. Cell Biol.*, **163**, 109–118.
57. Soti, C. and Csermely, P. (2002) Chaperones and aging: role in neurodegeneration and in other civilizational diseases. *Neurochem. Int.*, **41**, 383–389.
58. Ravikumar, B., Duden, R. and Rubinsztein, D.C. (2002) Aggregate-prone proteins with polyglutamine and polyalanine expansions are degraded by autophagy. *Hum. Mol. Genet.*, **11**, 1107–1117.
59. Ravikumar, B., Vacher, C., Berger, Z., Davies, J.E., Luo, S., Oroz, L.G., Scaravilli, F., Easton, D.F., Duden, R., O'Kane, C.J. *et al.* (2004) Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. *Nat. Genet.*, **36**, 585–595.
60. Berger, Z., Ravikumar, B., Menzies, F.M., Oroz, L.G., Underwood, B.R., Pangalos, M.N., Schmitt, I., Wullner, U., Evert, B.O., O'Kane, C.J. *et al.* (2006) Rapamycin alleviates toxicity of different aggregate-prone proteins. *Hum. Mol. Genet.*, **15**, 433–442.
61. Hara, T., Nakamura, K., Matsui, M., Yamamoto, A., Nakahara, Y., Suzuki-Migishima, R., Yokoyama, M., Mishima, K., Saito, I., Okano, H. *et al.* (2006) Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. *Nature*, **441**, 885–889.
62. Komatsu, M., Waguri, S., Chiba, T., Murata, S., Iwata, J., Tanida, I., Ueno, T., Koike, M., Uchiyama, Y., Kominami, E. *et al.* (2006) Loss of autophagy in the central nervous system causes neurodegeneration in mice. *Nature*, **441**, 880–884.
63. Bence, N.F., Sampat, R.M. and Kopito, R.R. (2001) Impairment of the ubiquitin-proteasome system by protein aggregation. *Science*, **292**, 1552–1555.
64. Venkatraman, P., Wetzel, R., Tanaka, M., Nukina, N. and Goldberg, A.L. (2004) Eukaryotic proteasomes cannot digest polyglutamine sequences and release them during degradation of polyglutamine-containing proteins. *Mol. Cell*, **14**, 95–104.
65. Holmberg, C.I., Staniszewski, K.E., Mensah, K.N., Matouschek, A. and Morimoto, R.I. (2004) Inefficient degradation of truncated polyglutamine proteins by the proteasome. *EMBO J.*, **23**, 4307–4318.

66. Cowan, K.J., Diamond, M.I. and Welch, W.J. (2003) Polyglutamine protein aggregation and toxicity are linked to the cellular stress response. *Hum. Mol. Genet.*, **12**, 1377–1391.
67. Gidalevitz, T., Ben-Zvi, A., Ho, K.H., Brignull, H.R. and Morimoto, R.I. (2006) Progressive disruption of cellular protein folding in models of polyglutamine diseases. *Science*, **311**, 1471–1474.
68. Poirier, M.A., Li, H., Macosko, J., Cai, S., Amzel, M. and Ross, C.A. (2002) Huntingtin spheroids and protofibrils as precursors in polyglutamine fibrilization. *J. Biol. Chem.*, **277**, 41032–41037.
69. Wacker, J.L., Zareie, M.H., Fong, H., Sarikaya, M. and Muchowski, P.J. (2004) Hsp70 and Hsp40 attenuate formation of spherical and annular polyglutamine oligomers by partitioning monomer. *Nat. Struct. Mol. Biol.*, **11**, 1215–1222.
70. Kayed, R., Head, E., Thompson, J.L., McIntire, T.M., Milton, S.C., Cotman, C.W. and Glabe, C.G. (2003) Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. *Science*, **300**, 486–489.
71. Osmand, A.P., Berthelier, V. and Wetzel, R. (2006) Imaging polyglutamine deposits in brain tissue. *Methods Enzymol.*, **412**, 106–122.
72. Ross, C.A. and Poirier, M.A. (2004) Protein aggregation and neurodegenerative disease. *Nat. Med.*, **10** (suppl), S10–S17.
73. Haass, C. and Selkoe, D.J. (2007) Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. *Nat. Rev. Mol. Cell Biol.*, **8**, 101–112.
74. Dragatsis, I., Levine, M.S. and Zeitlin, S. (2000) Inactivation of Hdh in the brain and testis results in progressive neurodegeneration and sterility in mice. *Nat. Genet.*, **26**, 300–306.
75. Duyao, M.P., Auerbach, A.B., Ryan, A., Persichetti, F., Barnes, G.T., McNeil, S.M., Ge, P., Vonsattel, J.P., Gusella, J.F., Joyner, A.L. *et al.* (1995) Inactivation of the mouse Huntington's disease gene homolog Hdh. *Science*, **269**, 407–410.
76. White, J.K., Auerbach, W., Duyao, M.P., Vonsattel, J.P., Gusella, J.F., Joyner, A.L. and MacDonald, M.E. (1997) Huntingtin is required for neurogenesis and is not impaired by the Huntington's disease CAG expansion. *Nat. Genet.*, **17**, 404–410.
77. Zeitlin, S., Liu, J.P., Chapman, D.L., Papaioannou, V.E. and Efstratiadis, A. (1995) Increased apoptosis and early embryonic lethality in mice nullizygous for the Huntington's disease gene homologue. *Nat. Genet.*, **11**, 155–163.
78. Leavitt, B.R., Guttman, J.A., Hodgson, J.G., Kimel, G.H., Singaraja, R., Vogl, A.W. and Hayden, M.R. (2001) Wild-type huntingtin reduces the cellular toxicity of mutant huntingtin *in vivo*. *Am. J. Hum. Genet.*, **68**, 313–324.
79. Cattaneo, E., Zuccato, C. and Tartari, M. (2005) Normal huntingtin function: an alternative approach to Huntington's disease. *Nat. Rev. Neurosci.*, **6**, 919–930.
80. Bowman, A.B., Lam, Y.C., Jafar-Nejad, P., Chen, H.K., Richman, R., Samaco, R.C., Fryer, J.D., Kahle, J.J., Orr, H.T. and Zoghbi, H.Y. (2007) Duplication of Atxn1l suppresses SCA1 neuropathology by decreasing incorporation of polyglutamine-expanded ataxin-1 into native complexes. *Nat. Genet.*, **39**, 373–379.
81. Burnett, B., Li, F. and Pittman, R.N. (2003) The polyglutamine neurodegenerative protein ataxin-3 binds polyubiquitylated proteins and has ubiquitin protease activity. *Hum. Mol. Genet.*, **12**, 3195–3205.
82. Chai, Y., Berke, S.S., Cohen, R.E. and Paulson, H.L. (2004) Poly-ubiquitin binding by the polyglutamine disease protein ataxin-3 links its normal function to protein surveillance pathways. *J. Biol. Chem.*, **279**, 3605–3611.
83. Lerer, I., Merims, D., Abeliovich, D., Zlotogora, J. and Gadoth, N. (1996) Machado–Joseph disease: correlation between the clinical features, the CAG repeat length and homozygosity for the mutation. *Eur. J. Hum. Genet.*, **4**, 3–7.
84. Warrick, J.M., Morabito, L.M., Bilen, J., Gordesky-Gold, B., Faust, L.Z., Paulson, H.L. and Bonini, N.M. (2005) Ataxin-3 suppresses polyglutamine neurodegeneration in *Drosophila* by a ubiquitin-associated mechanism. *Mol. Cell*, **18**, 37–48.
85. Nasir, J., Floresco, S.B., O'Kusky, J.R., Diewert, V.M., Richman, J.M., Zeisler, J., Borowski, A., Marth, J.D., Phillips, A.G. and Hayden, M.R. (1995) Targeted disruption of the Huntington's disease gene results in embryonic lethality and behavioral and morphological changes in heterozygotes. *Cell*, **81**, 811–823.
86. Matilla, A., Roberson, E.D., Banfi, S., Morales, J., Armstrong, D.L., Burright, E.N., Orr, H.T., Sweatt, J.D., Zoghbi, H.Y. and Matzuk, M.M. (1998) Mice lacking ataxin-1 display learning deficits and decreased hippocampal paired-pulse facilitation. *J. Neurosci.*, **18**, 5508–5516.
87. Ophoff, R.A., Terwindt, G.M., Vergouwe, M.N., van Eijk, R., Oefner, P.J., Hoffman, S.M., Lamerdin, J.E., Mohrenweiser, H.W., Bulman, D.E., Ferrari, M. *et al.* (1996) Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. *Cell*, **87**, 543–552.
88. Pinsky, L., Trifiro, M., Kaufman, M., Beitel, L.K., Mhatre, A., Kazemi-Esfarjani, P., Sabbaghian, N., Lumbroso, R., Alvarado, C., Vasiliou, M. *et al.* (1992) Androgen resistance due to mutation of the androgen receptor. *Clin. Invest. Med.*, **15**, 456–472.
89. Ambrose, H.J., Byrd, P.J., McConville, C.M., Cooper, P.R., Stankovic, T., Riley, J.H., Shiloh, Y., McNamara, J.O., Fukao, T. and Taylor, A.M. (1994) A physical map across chromosome 11q22-q23 containing the major locus for ataxia telangiectasia. *Genomics*, **21**, 612–619.
90. Davies, A.F., Mirza, G., Sekhon, G., Turnpenny, P., Leroy, F., Speleman, F., Law, C., van Regemorter, N., Vamos, E., Flinter, F. *et al.* (1999) Delineation of two distinct 6p deletion syndromes. *Hum. Genet.*, **104**, 64–72.
91. Wexler, N.S., Young, A.B., Tanzi, R.E., Travers, H., Starosta-Rubinstein, S., Penney, J.B., Snodgrass, S.R., Shoulson, I., Gomez, F., Ramos Arroyo, M.A. *et al.* (1987) Homozygotes for Huntington's disease. *Nature*, **326**, 194–197.
92. Moseley, M.L., Zu, T., Ikeda, Y., Gao, W., Mosemiller, A.K., Daughters, R.S., Chen, G., Weatherspoon, M.R., Clark, H.B., Ebner, T.J. *et al.* (2006) Bidirectional expression of CUG and CAG expansion transcripts and intranuclear polyglutamine inclusions in spinocerebellar ataxia type 8. *Nat. Genet.*, **38**, 758–769.
93. Minamiyama, M., Katsuno, M., Adachi, H., Waza, M., Sang, C., Kobayashi, Y., Tanaka, F., Doyu, M., Inukai, A. and Sobue, G. (2004) Sodium butyrate ameliorates phenotypic expression in a transgenic mouse model of spinal and bulbar muscular atrophy. *Hum. Mol. Genet.*, **13**, 1183–1192.
94. Hockly, E., Richon, V.M., Woodman, B., Smith, D.L., Zhou, X., Rosa, E., Sathasivam, K., Ghazi-Noori, S., Mahal, A., Lowden, P.A. *et al.* (2003) Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. *Proc. Natl Acad. Sci. USA*, **100**, 2041–2046.
95. Ferrante, R.J., Kubilus, J.K., Lee, J., Ryu, H., Beesen, A., Zucker, B., Smith, K., Kowall, N.W., Ratan, R.R., Luthi-Carter, R. *et al.* (2003) Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington's disease mice. *J. Neurosci.*, **23**, 9418–9427.
96. Gardian, G., Browne, S.E., Choi, D.K., Klivenyi, P., Gregorio, J., Kubilus, J.K., Ryu, H., Langley, B., Ratan, R.R., Ferrante, R.J. *et al.* (2005) Neuroprotective effects of phenylbutyrate in the N171-82Q transgenic mouse model of Huntington's disease. *J. Biol. Chem.*, **280**, 556–563.
97. Ying, M., Xu, R., Wu, X., Zhu, H., Zhuang, Y., Han, M. and Xu, T. (2006) Sodium butyrate ameliorates histone hypoacetylation and neurodegenerative phenotypes in a mouse model for DRPLA. *J. Biol. Chem.*, **281**, 12580–12586.
98. Steffan, J.S., Bodai, L., Pallos, J., Poelman, M., McCampbell, A., Apostol, B.L., Kazantsev, A., Schmidt, E., Zhu, Y.Z., Greenwald, M. *et al.* (2001) Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in *Drosophila*. *Nature*, **413**, 739–743.
99. Hubbert, C., Guardiola, A., Shao, R., Kawaguchi, Y., Ito, A., Nixon, A., Yoshida, M., Wang, X.F. and Yao, T.P. (2002) HDAC6 is a microtubule-associated deacetylase. *Nature*, **417**, 455–458.
100. Kovacs, J.J., Murphy, P.J., Gaillard, S., Zhao, X., Wu, J.T., Nicchitta, C.V., Yoshida, M., Toft, D.O., Pratt, W.B. and Yao, T.P. (2005) HDAC6 regulates Hsp90 acetylation and chaperone-dependent activation of glucocorticoid receptor. *Mol. Cell*, **18**, 601–607.
101. Ren, M., Leng, Y., Jeong, M., Leeds, P.R. and Chuang, D.M. (2004) Valproic acid reduces brain damage induced by transient focal cerebral ischemia in rats: potential roles of histone deacetylase inhibition and heat shock protein induction. *J. Neurochem.*, **89**, 1358–1367.
102. Zhao, Y., Sun, H., Lu, J., Li, X., Chen, X., Tao, D., Huang, W. and Huang, B. (2005) Lifespan extension and elevated hsp gene expression in *Drosophila* caused by histone deacetylase inhibitors. *J. Exp. Biol.*, **208**, 697–705.

103. Petri, S., Kiaei, M., Kipiani, K., Chen, J., Calingasan, N.Y., Crow, J.P. and Beal, M.F. (2006) Additive neuroprotective effects of a histone deacetylase inhibitor and a catalytic antioxidant in a transgenic mouse model of amyotrophic lateral sclerosis. *Neurobiol. Dis.*, **22**, 40–49.
104. Camelo, S., Iglesias, A.H., Hwang, D., Due, B., Ryu, H., Smith, K., Gray, S.G., Imitola, J., Duran, G., Assaf, B. *et al.* (2005) Transcriptional therapy with the histone deacetylase inhibitor trichostatin A ameliorates experimental autoimmune encephalomyelitis. *J. Neuroimmunol.*, **164**, 10–21.
105. Beal, M.F. and Ferrante, R.J. (2004) Experimental therapeutics in transgenic mouse models of Huntington's disease. *Nat. Rev. Neurosci.*, **5**, 373–384.
106. Verbessem, P., Lemiere, J., Eijnde, B.O., Swinnen, S., Vanhees, L., Van Leemputte, M., Hespel, P. and Dom, R. (2003) Creatine supplementation in Huntington's disease: a placebo-controlled pilot trial. *Neurology*, **61**, 925–930.
107. Tabrizi, S.J., Blamire, A.M., Manners, D.N., Rajagopalan, B., Styles, P., Schapira, A.H. and Warner, T.T. (2005) High-dose creatine therapy for Huntington disease: a 2-year clinical and MRS study. *Neurology*, **64**, 1655–1656.
108. Tabrizi, S.J., Blamire, A.M., Manners, D.N., Rajagopalan, B., Styles, P., Schapira, A.H. and Warner, T.T. (2003) Creatine therapy for Huntington's disease: clinical and MRS findings in a 1-year pilot study. *Neurology*, **61**, 141–142.
109. (2001) A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. *Neurology*, **57**, 397–404.
110. St-Pierre, J., Drori, S., Uldry, M., Silvaggi, J.M., Rhee, J., Jager, S., Handschin, C., Zheng, K., Lin, J., Yang, W. *et al.* (2006) Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. *Cell*, **127**, 397–408.
111. Xia, H., Mao, Q., Eliason, S.L., Harper, S.Q., Martins, I.H., Orr, H.T., Paulson, H.L., Yang, L., Kotin, R.M. and Davidson, B.L. (2004) RNAi suppresses polyglutamine-induced neurodegeneration in a model of spinocerebellar ataxia. *Nat. Med.*, **10**, 816–820.
112. Harper, S.Q., Staber, P.D., He, X., Eliason, S.L., Martins, I.H., Mao, Q., Yang, L., Kotin, R.M., Paulson, H.L. and Davidson, B.L. (2005) RNA interference improves motor and neuropathological abnormalities in a Huntington's disease mouse model. *Proc. Natl Acad. Sci. USA*, **102**, 5820–5825.
113. Wellington, C.L. and Hayden, M.R. (2000) Caspases and neurodegeneration: on the cutting edge of new therapeutic approaches. *Clin. Genet.*, **57**, 1–10.
114. Tarlac, V. and Storey, E. (2003) Role of proteolysis in polyglutamine disorders. *J. Neurosci. Res.*, **74**, 406–416.
115. Di Prospero, N.A. and Fischbeck, K.H. (2005) Therapeutics development for triplet repeat expansion diseases. *Nat. Rev. Genet.*, **6**, 756–765.
116. Chen, M., Ona, V.O., Li, M., Ferrante, R.J., Fink, K.B., Zhu, S., Bian, J., Guo, L., Farrell, L.A., Hersch, S.M. *et al.* (2000) Minocycline inhibits caspase-1 and caspase-3 expression and delays mortality in a transgenic mouse model of Huntington disease. *Nat. Med.*, **6**, 797–801.
117. Rubinsztein, D.C. (2006) The roles of intracellular protein-degradation pathways in neurodegeneration. *Nature*, **443**, 780–786.
118. Coufal, M., Maxwell, M.M., Russel, D.E., Amore, A.M., Altmann, S.M., Hollingsworth, Z.R., Young, A.B., Housman, D.E. and Kazantsev, A.G. (2007) Discovery of a novel small-molecule targeting selective clearance of mutant huntingtin fragments. *J. Biomol. Screen.*, **12**, 351–360.
119. Yang, Z., Chang, Y.J., Yu, I.C., Yeh, S., Wu, C.C., Miyamoto, H., Merry, D.E., Sobue, G., Chen, L.M., Chang, S.S. *et al.* (2007) ASC-J9 ameliorates spinal and bulbar muscular atrophy phenotype via degradation of androgen receptor. *Nat. Med.*, **13**, 348–353.
120. Sittler, A., Lurz, R., Lueder, G., Priller, J., Lehrach, H., Hayer-Hartl, M.K., Hartl, F.U. and Wanker, E.E. (2001) Geldanamycin activates a heat shock response and inhibits huntingtin aggregation in a cell culture model of Huntington's disease. *Hum. Mol. Genet.*, **10**, 1307–1315.
121. Hay, D.G., Sathasivam, K., Tobaben, S., Stahl, B., Marber, M., Mestril, R., Mahal, A., Smith, D.L., Woodman, B. and Bates, G.P. (2004) Progressive decrease in chaperone protein levels in a mouse model of Huntington's disease and induction of stress proteins as a therapeutic approach. *Hum. Mol. Genet.*, **13**, 1389–1405.
122. Katsuno, M., Sang, C., Adachi, H., Minamiyama, M., Waza, M., Tanaka, F., Doyu, M. and Sobue, G. (2005) Pharmacological induction of heat-shock proteins alleviates polyglutamine-mediated motor neuron disease. *Proc. Natl Acad. Sci. USA*, **102**, 16801–16806.
123. Heiser, V., Scherzinger, E., Boeddrich, A., Nordhoff, E., Lurz, R., Schugardt, N., Lehrach, H. and Wanker, E.E. (2000) Inhibition of huntingtin fibrillogenesis by specific antibodies and small molecules: implications for Huntington's disease therapy. *Proc. Natl Acad. Sci. USA*, **97**, 6739–6744.
124. Heiser, V., Engemann, S., Brocker, W., Dunkel, I., Boeddrich, A., Waelter, S., Nordhoff, E., Lurz, R., Schugardt, N., Rautenberg, S. *et al.* (2002) Identification of benzothiazoles as potential polyglutamine aggregation inhibitors of Huntington's disease by using an automated filter retardation assay. *Proc. Natl Acad. Sci. USA*, **99** (Suppl. 4), 16400–16406.
125. Zhang, X., Smith, D.L., Meriin, A.B., Engemann, S., Russel, D.E., Roark, M., Washington, S.L., Maxwell, M.M., Marsh, J.L., Thompson, L.M. *et al.* (2005) A potent small molecule inhibits polyglutamine aggregation in Huntington's disease neurons and suppresses neurodegeneration *in vivo*. *Proc. Natl Acad. Sci. USA*, **102**, 892–897.
126. Desai, U.A., Pallos, J., Ma, A.A., Stockwell, B.R., Thompson, L.M., Marsh, J.L. and Diamond, M.I. (2006) Biologically active molecules that reduce polyglutamine aggregation and toxicity. *Hum. Mol. Genet.*, **15**, 2114–2124.
127. Pollitt, S.K., Pallos, J., Shao, J., Desai, U.A., Ma, A.A., Thompson, L.M., Marsh, J.L. and Diamond, M.I. (2003) A rapid cellular FRET assay of polyglutamine aggregation identifies a novel inhibitor. *Neuron*, **40**, 685–694.
128. Wang, J., Gines, S., MacDonald, M.E. and Gusella, J.F. (2005) Reversal of a full-length mutant huntingtin neuronal cell phenotype by chemical inhibitors of polyglutamine-mediated aggregation. *BMC Neurosci.*, **6**, 1.
129. Nagai, Y., Tucker, T., Ren, H., Kenan, D.J., Henderson, B.S., Keene, J.D., Strittmatter, W.J. and Burke, J.R. (2000) Inhibition of polyglutamine protein aggregation and cell death by novel peptides identified by phage display screening. *J. Biol. Chem.*, **275**, 10437–10442.
130. Nagai, Y., Fujikake, N., Ohno, K., Higashiyama, H., Popiel, H.A., Rahadian, J., Yamaguchi, M., Strittmatter, W.J., Burke, J.R. and Toda, T. (2003) Prevention of polyglutamine oligomerization and neurodegeneration by the peptide inhibitor QBP1 in *Drosophila*. *Hum. Mol. Genet.*, **12**, 1253–1259.
131. Kazantsev, A., Walker, H.A., Slepko, N., Bear, J.E., Preisinger, E., Steffan, J.S., Zhu, Y.Z., Gertler, F.B., Housman, D.E., Marsh, J.L. *et al.* (2002) A bivalent Huntingtin binding peptide suppresses polyglutamine aggregation and pathogenesis in *Drosophila*. *Nat. Genet.*, **30**, 367–376.
132. Wolfgang, W.J., Miller, T.W., Webster, J.M., Huston, J.S., Thompson, L.M., Marsh, J.L. and Messer, A. (2005) Suppression of Huntington's disease pathology in *Drosophila* by human single-chain Fv antibodies. *Proc. Natl Acad. Sci. USA*, **102**, 11563–11568.
133. Colby, D.W., Chu, Y., Cassady, J.P., Duennwald, M., Zazulak, H., Webster, J.M., Messer, A., Lindquist, S., Ingram, V.M. and Wittrup, K.D. (2004) Potent inhibition of huntingtin aggregation and cytotoxicity by a disulfide bond-free single-domain intracellular antibody. *Proc. Natl Acad. Sci. USA*, **101**, 17616–17621.
134. Khoshnan, A., Ko, J. and Patterson, P.H. (2002) Effects of intracellular expression of anti-huntingtin antibodies of various specificities on mutant huntingtin aggregation and toxicity. *Proc. Natl Acad. Sci. USA*, **99**, 1002–1007.
135. Sittler, A., Walter, S., Wedemeyer, N., Hasenbank, R., Scherzinger, E., Eickhoff, H., Bates, G.P., Lehrach, H. and Wanker, E.E. (1998) SH3GL3 associates with the Huntingtin exon 1 protein and promotes the formation of polygln-containing protein aggregates. *Mol. Cell*, **2**, 427–436.
136. Goehler, H., Lalowski, M., Stelzl, U., Waelter, S., Stroedicke, M., Worm, U., Droege, A., Lindenberg, K.S., Knoblich, M., Haenig, C. *et al.* (2004) A protein interaction network links GIT1, an enhancer of huntingtin aggregation, to Huntington's disease. *Mol. Cell*, **15**, 853–865.
137. Emamian, E.S., Kaytor, M.D., Duvick, L.A., Zu, T., Tousey, S.K., Zoghbi, H.Y., Clark, H.B. and Orr, H.T. (2003) Serine 776 of ataxin-1 is critical for polyglutamine-induced disease in SCA1 transgenic mice. *Neuron*, **38**, 375–387.
138. Chen, H.K., Fernandez-Funez, P., Acevedo, S.F., Lam, Y.C., Kaytor, M.D., Fernandez, M.H., Aitken, A., Skoulakis, E.M., Orr, H.T., Botas, J. *et al.* (2003) Interaction of Akt-phosphorylated ataxin-1 with 14-3-3 mediates neurodegeneration in spinocerebellar ataxia type 1. *Cell*, **113**, 457–468.
139. Meriin, A.B., Zhang, X., Alexandrov, I.M., Salnikova, A.B., Ter-Avanesian, M.D., Chernoff, Y.O. and Sherman, M.Y. (2007) Endocytosis machinery is involved in aggregation of proteins with expanded polyglutamine domains. *FASEB J.*, **21**, 1915–1925.