Machado-Joseph Disease / Spinocerebellar Ataxia Type 3

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1. Introduction

Spinocerebellar Ataxia type 3 (SCA3) or Machado-Joseph disease (MJD) is one of the most common polyglutamine (polyQ) diseases, which comprise a group of inherited neurodegenerative conditions characterized by the pathological expansion of CAG trinucleotide repeats in the translated regions of unrelated genes. The expansion of a (CAG) tract in the coding region of the causative gene MJD1, translates into an expanded polyglutamine tract that confers a toxic gain of function to the ataxin-3 protein. The mutant protein form has 55-84 consecutive glutamines, in contrast to the normal ataxin-3, which carries 10-51 glutamines.

MJD is a fatal disease of the central nervous system (CNS) and a dominant neurodegenerative disorder of adult onset, characterized by a wide range of clinical symptoms, including gait and limb ataxia, peripheral neuropathy, bulging eyes, ophthalmoplegia, postural instability, dystonia, amyotrophy, dysarthria, nystagmus, lingual fasciculation’s, facial myokymia and, in some cases, parkinsonism. The expression of mutant ataxin-3 is widespread, although neurodegeneration in MJD has been described in particular brain regions such as the cerebellum, brainstem, substantia nigra, pontine nuclei and striatum. A hallmark of the disease is the presence of neuronal intranuclear inclusions of mutant ataxin-3. The genetic basis of MJD is well described, however, the molecular basis is still poorly understood and controversial. Several pathogenesis mechanisms have been proposed for MJD (as well for other polyQ diseases), which could be explored as potential therapeutic approaches to MJD. Decreasing the expression of mutant ataxin-3 through gene silencing has been shown to be one of the most promising therapeutic approaches to MJD. However, several others are presently under investigation, such as the inhibition of protein cleavage, and the induction of autophagy, as well as strategies based on neuroprotection or regulation of transcriptional dysfunction. The main aim of this chapter is to review the current knowledge about MJD/SCA3, including a short review of clinical and neuropathological aspects of MJD and a particular focus on the pathogenesis and potential therapeutic strategies for the disease.
2. Machado-Joseph disease

Machado-Joseph disease (MJD) or spinocerebellar ataxia type 3 (SCA3) is the most common autosomal subtype of ataxia worldwide (Coutinho and Andrade, 1978; Rosenberg, 1992; Ranum et al., 1995; Schols et al., 2004). It is caused by the unstable expansion of a CAG repeat in the MJD1 gene, which translates into a polyglutamine tract within the ataxin-3 protein (Takiyama et al., 1993; Kawaguchi et al., 1994). This neurodegenerative disorder of adult onset was named after Antone Joseph and William Machado, of Portuguese Azorean origin, who migrated to USA. MJD was subsequently identified in Brazil, Japan, China, Australia and many other countries. In the islands of the Azores, namely São Miguel and Flores, MJD reaches the highest prevalence (1:140 in the small island of Flores) reported worldwide (Sudarsky and Coutinho, 1995).

3. Clinical and physiological features

MJD is characterized primarily by cerebellar ataxia and pyramidal signs variably associated with a dystonic-rigid extrapyramidal syndrome or peripheral amyotrophy (Lima and Coutinho, 1980; D’Abreu et al., 2010). The clinical hallmark of MJD is progressive ataxia, a dysfunction of motor coordination that can affect gaze, speech, gait, and balance (Taroni and DiDonato, 2004). Other clinical manifestations include external progressive ophthalmoplegia, dystonia, intention fasciculation-like movements of facial and lingual muscles, as well as bulging eyes. Progressive ataxia, hyperreflexia, nystagmus, and dysarthria may occur early in the disease (Lima and Coutinho, 1980; Sudarsky and Coutinho, 1995).

| MJD type | Age of onset | Prevalence | Symptoms |
|----------|--------------|------------|----------|
| I        | 5-30 years   |            | Limb and gait ataxia, severe dystonia, pyramidal signs, progressive external ophthalmoplegia. Fast progression of symptoms |
| II       | ≈ 36 years   | The most common | Ataxia, pyramidal deficits and progressive external ophthalmoplegia |
| III      | ≈ 50 years   | The second most common | Limb and gait ataxia, with marked pyramidal signs. The progressive external ophthalmoplegia can or not manifest. This type has a moderate progression and can evolve to one of the other types |
| IV       | 38-47 years  | In patients with the fewest CAG-repeats expansion | Slow progressive parkinsonism, responsive to the L-DOPA treatment, fasciculations and peripheral neuropathy |
| V        |              | Marked spastic paraplegia with or without cerebellar ataxia. This type is usually mis-diagnosed as hereditary spastic paraplegia (HSP) |

Table 1. Classification of MJD according to symptoms, prevalence and age of onset.

Recent clinical data has demonstrated increased incidence of non-motor symptoms, which include cognitive and psychiatric disturbances, olfactory dysfunction, and sleep disorders (Rub et al., 2008). Levodopa-responsive parkinsonism symptoms resembling Parkinson’s disease were also reported (Gwinn-Hardy et al., 2001). MJD patients present attention and
executive dysfunctions, and mildly depressed mood (Klinke et al., 2010). Based on clinical manifestations, MJD was divided into four sub phenotypes (Riess et al., 2008), which in some cases during the progression of the disease can evolve from one type to the other (Fowler, 1984). Recently, an additional MJD type (V) has been proposed based in a homozygous 33-years old patient of Portuguese/Brazilian descent (Lysenko et al., 2010) (Table 1).

4. Neuropathological features

The neuropathological alterations of MJD in the brain consist of widespread neuronal degeneration affecting multiple neuronal systems and not confined to the cerebellum, brain stem, and basal ganglia (Rub et al., 2008). The neuropathology involves cerebellar systems (particularly dentate nucleus and pontine neurons), substantia nigra, and cranial nerve motor nuclei, with relative preservation of cerebellar cortex, particularly Purkinje cells and inferior olive (Sudarsky and Coutinho, 1995; Durr et al., 1996; Yamada et al., 2008). However in some cases, loss of granule and Purkinje cells was found in the cerebellum, mainly in the vermis (Munoz et al., 2002). A marked degeneration of Clarke’s column nuclei and vestibular and pontine nuclei is observed (Durr et al., 1996). Marked neuronal loss is also observed in the anterior horn of the spinal cord, and motor nuclei of the brainstem (Rub et al., 2008). Involvement of cerebellar cortex, autonomic ganglia and striatum were also confirmed in MJD (Yamada et al., 2001; Paulson et al., 1997b; Alves et al., 2008b). Recent data based on neuroimaging techniques (magnetic resonance imaging – MRI, and quantitative 3-D volumetry) confirmed a severe atrophy in MJD patients in the whole brainstem (midbrain, pons, and medulla), whole cerebellum, cerebellar hemispheres and cerebellar vermis, putamen and caudate nuclei (Schulz et al., 2010). Significant correlation of both brainstem and cerebellar atrophy with CAG repeat length, age, disease duration and degree of disability has also been recently reported (Camargos et al., 2011). Furthermore, an inverse relationship has been found in MJD patients between posture, gait and limb kinetic sub score (assessed by the Scale for Assessment and Rating Ataxia) and the brainstem and cerebellar hemispheric volumes (Jacobi et al., 2011).

5. The MJD1 gene

MJD is associated with an unstable expansion of a CAG tract in the coding region of the MJD1 gene localized on chromosome 14q32.1 (Takiyama et al., 1993; Kawaguchi et al., 1994). MJD1 encodes ataxin-3, a polyubiquitin-binding protein whose physiological function has been linked to ubiquitin-mediated proteolysis (Burnett et al., 2003; Donaldson et al., 2003; Doss-Pepe et al., 2003; Scheel et al., 2003; Chai et al., 2004; Durcan et al., 2011). The mutation results in an expanded polyglutamine tract at the C-terminus of ataxin-3 (Kawaguchi et al., 1994; Durr et al., 1996). The CAG repeats in the MJD1 gene range from 10 to 51 in the normal population and from 55 to 87 in MJD patients (Cummings and Zoghbi, 2000; Maciel et al., 2001; Gu et al., 2004; Padiath et al., 2005). This high threshold of pathogenicity is a special characteristic of this disorder, since in most other polyglutamine disorders trinucleotide repeats over 36 to 40 become pathogenic. There is an inverse correlation between the age of onset and the number of CAG repeats, as is the case for other polyglutamine disorders (Maciel et al., 1995; Maruyama et al., 1995; Globas et al., 2008).
6. The ataxin-3 protein

Ataxin-3 is a modular protein with an overall molecular weight of 42 kDa, containing a conserved N-terminal Josephin domain (Masino et al., 2003; Scheel et al., 2003; Albrecht et al., 2004), followed by two ubiquitin-interaction motif (UIM) domains and the polyglutamine repeat region (Figure 1). Alternative splicing of the MJD1 gene has been shown to result in the production of different isoforms of ataxin-3 varying at the C-terminal portion of the protein (Goto et al., 1997), one of these containing a third UIM domain after the polyglutamine region (Ichikawa et al., 2001). Fifty-six alternative splicing variants of the ataxin-3 mRNA were recently identified, from which 50 had not been previously described, and 26 were only found in MJD patients (Bettencourt et al., 2010). Alternative splicing of ataxin-3 sequences distinct from the trinucleotide repeat may alter the properties of the encoded polyglutamine disease protein and thereby perhaps contribute to selective neurotoxicity (Harris et al., 2010). The protein is expressed in various tissues, suggesting that it plays an important role in eukaryotic cells (see Matos et al., 2011 for an extensive revision of putative ataxin-3 functions).

Fig. 1. Structure of the ataxin-3 protein. Ataxin-3 is mainly composed of a highly conserved N-terminal domain (Josephin), encoding a predicted ubiquitin-specific protease with the catalytic triad of amino acids (Cys14, His119, and Asn136), a nuclear export signal (NES), followed by a flexible C-terminal tail with 2 or 3 ubiquitin-interacting motifs (UIM), a nuclear localization signal (NLS) and the polyglutamine stretch (Q(n)). Rad23 and VCP/p97, the two most frequently described interacting partners of ataxin-3, bind to the Josephin domain and the C-terminal region of the protein, respectively.

Regarding subcellular localization, ataxin-3 has been detected both in the nucleus and in the cytoplasm (Paulson et al., 1997a; Trottier et al., 1998; Ichikawa et al., 2001). A putative nuclear localization signal (NLS) has been identified upstream the polyglutamine repeat region at position 282 (Taft et al., 1998; Albrecht et al., 2004), and shown to have a weak nuclear import activity (Antony et al., 2009). Furthermore, two nuclear export signals (NES) with significant activity were identified in ataxin-3: NES 77 (177-Y99) and NES 141 (E141-E258) (Antony et al., 2009). Ataxin-3 its actively imported to and exported from the cell nucleus, and this nuclear export activity could also be dependent on a motif localized at is N-terminal region (Rodrigues et al., 2007; Macedo-Ribeiro et al., 2009), which is coherent with the hypothesis of the presence of a nuclear export signal (NES 174) following the Josephin domain (Albrecht et al., 2004).
Although the precise cellular role of ataxin-3 and how it is altered upon polyglutamine expansion is presently unknown, ataxin-3 was shown to be a polyubiquitin-binding protein (Donaldson et al., 2003; Doss-Pepe et al., 2003), interacting via the first two UIM domains with K48-linked tetraubiquitin chains (Burnett et al., 2003; Chai et al., 2004). Several lines of evidence suggest that ataxin-3 plays a major role in the ubiquitin proteasomal system, by interacting with ubiquitin and an ubiquitin-like protein called NEDD8 (Ferro et al., 2007). Ataxin-3 was reported to bind and hydrolyze polyubiquitin chains in vitro (Burnett et al., 2003). Recently, it was shown that ataxin-3 deubiquitinates parkin directly (Durcan et al., 2011). The same study argued that compared with wild-type ataxin-3, MJD-linked polyQ-expanded mutant ataxin-3 is more active, possibly owing to its greater efficiency at DUB K27- and K29-linked Ub conjugates on parkin. Ataxin-3 has been also shown to be involved in the regulation of the proteasome by interacting with various substrates (Wang et al., 2006, 2007; Rodrigues et al., 2009). Ataxin-3 deubiquitinating activity is thought to contribute to proteasomal degradation of ubiquitinated proteins by removing the poly-ubiquitin chains from substrates prior to digestion (Boeddrich et al., 2006; Winborn et al., 2008; Todi et al., 2009; Scaglione et al., 2011). Ubiquitination and deubiquitination enzymes help to control neuronal fate determination, axonal path finding and synaptic communication and plasticity (see Todi and Paulson, 2011 for a review). Altogether, these data imply that ataxin-3 modulates ubiquitin-dependent mechanisms, having an active role in the ubiquitin-proteasome pathway.

7. Nuclear inclusions

In MJD, mutant ataxin-3 aggregates into intranuclear inclusions (NIIs) with many affected neurons exhibiting more than one inclusion body, both in and outside areas affected by neurodegeneration (Paulson et al., 1997b; Schimdt et al., 1998; Rub et al., 2006a, b). Aggregates are also found in the cytoplasm of neurons in several affected areas (Hayashi et al., 2003), and in axons within fiber tracts (corpus callosum, the nigrostriatal tract, the olivocerebellar fiber, and others) known to undergo neurodegeneration in MJD (Seidel et al., 2010). The presence of these NIIs is a hallmark of neurodegeneration in the brains of MJD patients (Figure 2A), and to all the CAG repeat diseases except for the spinocerebellar ataxia type 6 (SCA6) (Paulson, 1999; Schols et al., 2004; Soong and Paulson, 2007). NIIs are eosinophilic round structures and vary in size from 0.7 to 3.7 μm. Ultrastructurally, NIIs are non-membrane bound, heterogeneous in composition, and contain a mix of granular and filamentous structures. Both normal and expanded ataxin-3, and ubiquitin are components of NIIs of affected neurons in MJD patients (Paulson et al., 1997a), as well as other proteins, including heat shock proteins (HSPs) and transcription factors (Hayashi et al., 2003; Perez et al., 1998; Yamada et al., 2001). Ataxin-2, the protein that upon polyglutamine expansion causes spinocerebellar ataxia type 2 – SCA2, and the TATA box binding protein (TBP) were also found in NIIs of the pontine neurons of MJD patients (Uchihara et al., 2001).

The NIIs in MJD are distributed in many neurons covering a wide range of central and peripheral nervous system regions, including the cerebral cortex (Figure 2B), thalamus and autonomic ganglia (Schilling et al., 1999). The exact role of NIIs in neuronal cell death of MJD patients remains unclear and controversial (Bates, 2003; Michalik and Broeckhoven, 2003; Yamada et al., 2008). However, as NIIs are present in degenerated as well as spared brain regions in advanced MJD patients, NIIs are not thought to be directly pathogenic in
affected nerve cells (Rub et al., 2006b). In the other polyglutamine disorders the cytotoxicity of NIIs is also controversial. Several studies raised the possibility that NII formation may be a cellular reaction to reduce the toxic effect of mutant proteins (Klement et al., 1998; Saudou et al., 1998; Cummings et al., 1999). On the other hand, other studies revealed that the presence of transcription factors in NIIs (Yamada et al., 2001; Shimohata et al., 2000a,b), may induce secondarily transcriptional abnormalities in cell nuclei, resulting in slowly progressive neuronal degeneration.

Fig. 2. **Intranuclear inclusions in the striatum of Machado Joseph disease patients.** (A) Fluorescence analysis shows ataxin-3 reaction intranuclear inclusions (green) in the neurons of the striatum of postmortem brain samples of MJD patients (white arrows). (B) Fluorescence microscopy analysis shows ataxin-3 intranuclear inclusions (green) in neurons of the cortex of postmortem brain samples of MJD patients (white arrows). Scale bar: 40µm.
8. Pathogenesis

The genetic basis of MJD is well described, however, the molecular basis is still poorly understood and controversial. It is widely accepted that polyglutamine diseases may share pathogenic mechanisms. In this section several pathogenic mechanisms that could be implicated in MJD are reviewed (Figure 3).

![Mechanisms of pathogenesis in Machado-Joseph disease](https://www.intechopen.com)

**Fig. 3.** Mechanisms of pathogenesis in Machado-Joseph disease. Several events and mechanisms could contribute to pathogenesis in MJD and other polyglutamine diseases. The presence of mutant ataxin-3 with an expanded tract in the cellular environment, triggers several events that lead to neurodegeneration in selective areas of the brain. For the neuronal cytotoxicity and dysfunction several mechanisms related to the toxicity of the expanded polyglutamine stretch are important such as the oligomerization and aggregation, the formation of toxic fragments or posttranslational modifications. Furthermore, the normal function of ataxin-3 in the cell could contribute to the impairment of UPS in MJD, and thus contribute to a dysfunction in cellular quality-control mechanisms. Other mechanisms could also be important to MJD pathogenesis, such as dysregulation of transcription, mitochondrial dysfunction, aberrant protein-protein interactions, calcium homeostasis dysregulation and axonal transport disruption.
8.1 Toxicity of the polyglutamine stretch

A common feature of polyglutamine diseases is the deposition of insoluble intracellular ubiquitinated inclusions containing the misfolded disease protein (Paulson, 1999). These inclusions have long been suspected to be pathologic structures in polyglutamine diseases (Ross, 1997; Martindale et al., 1998; Yamada et al., 2000). Although this correlation is controversial and unclear (Bates, 2003; Michalik and Broeckhoven, 2003; Yamada et al., 2008), the NIIs could physically impair axonal transport or nuclear function (Morfini et al., 2005). Furthermore, the NIIs recruit other proteins, transcription factors and proteasome subunits (Chai et al., 1999a,b), underlying misfolding events that may be critical to pathogenesis (Paulson, 1999; Goti et al., 2004; Jana and Nukina, 2004; Taylor et al., 2002).

Polyglutamine monomers of ataxin-3 acquire β-strand conformations that have been shown to be cytotoxic in cultured cells (Nagai et al., 2007), assembling into oligomers (Bevivino and Loll, 2001; Takahashi et al., 2008), both of ataxin-3 as well as other polyglutamine monomers (Stott et al., 1995; Lathrop et al., 1998; Tanaka et al., 2001; Thakur and Wetzel, 2002), and can also simultaneously dissociate into monomers (Schaffar et al., 2004). Thus, it seems that β-stranded polyglutamine monomers are important for pathogenesis in MJD and other polyglutamine diseases, however its contribution to neurotoxicity is still controversial.

In several neurodegenerative disorders, including Alzheimer’s disease, Parkinson’s disease, prion diseases, and polyglutamine diseases, including MJD, oligomers of causative proteins have been proposed to be the most toxic structures (Walsh et al., 2002; Kayed et al., 2004) and candidates for a pathogenic intermolecular structure. Polyglutamine oligomers, in particular, have been shown to induce greater toxicity than polyglutamine monomers or inclusion bodies in differentiated neurons (Takahashi et al., 2008). This and other findings support the hypothesis that polyglutamine oligomers may have a crucial role in cytotoxicity (Poirier et al., 2002; Sanchez et al., 2003; Kayed et al., 2003; Ross and Poirier, 2005; Behrends et al., 2006).

The proteolytic cleavage of mutant protein may produce smaller toxic fragments containing an expanded polyglutamine tract, in this way facilitating the entry of cytoplasmic polyglutamine proteins into the nucleus. These toxic cleavage fragments upon release undergo the conformational change required for aggregation formation (Wanker, 2000; Ross et al., 2003). The misfolded expanded fragments may interact with full-length ataxin-3, possibly inducing a misfolding event in the polyQ tract of ataxin-3, which facilitates its stable incorporation into the fibrillar aggregates (Ikeda et al., 1996; Haacke et al., 2006). The proteolytic fragment has been proposed to be a product of caspase enzymes (Wellington et al., 1998; Berke et al., 2004), of autolytic cleavage (Mauri et al., 2006) or of calpains (Haacke et al., 2007). This toxic fragments hypothesis was also proposed for other polyglutamines diseases (Walsh et al., 2005), namely Huntington disease (Goldberg et al., 1996; Schilling et al., 2006) and spinocerebellar ataxia type 7 (SCA7) (Young et al., 2007; Takahashi-Fujigasaki et al., 2011). The mutant ataxin-3 mj11a putative-cleavage fragment was identified in permanent clones of a transfected cell line (Yamamoto et al., 2001), transgenic mice and MJD patient’s brains (Goti et al., 2004). Nevertheless, some controversy remains as other studies failed to identify the proteolytic fragments of ataxin-3 (Cemal et al., 2002; Berke et al., 2004; Chou et al., 2006). Recently, it was reported that the presence of a 259 N-terminal ataxin-3 fragment (without the polyglutamine stretch) was sufficient to induce MJD neurological phenotype in mice (Hubener et al., 2011).
The toxicity of causative gene products in MJD and other polyglutamine diseases has been proposed to be influenced not only by the polyglutamine stretch but also by the post-translational modification of amino acid residues outside the polyglutamine stretch, including phosphorylation (Fei et al., 2007; Tao et al., 2008; Mueller et al., 2009), acetylation (Li et al., 2002; Evert et al., 2006; Chou et al., 2011), ubiquitination (Matsumoto et al., 2004; Jana et al., 2005; de Pril et al., 2007), and sumoylation (Ueda et al., 2002; Shen et al., 2005). These modifications might result in aberrant interactions with other proteins or modification of the properties of causative proteins, including the stability or tendency to form toxic structures.

8.2 Protein interactions

The importance of expanded polyglutamine protein in disease progression is important, however, the toxicity of expanded polyglutamine protein does not fully explain the selective neuronal degeneration in MJD and in other polyglutamine diseases. Mutant ataxin-3 is widely expressed in the brain (Paulson et al., 1997a), even in areas with no significant neuronal degeneration. Thus, the normal function of ataxin-3 or interactions with other proteins in each neuronal subpopulation might explain its selective toxicity (Takahashi et al., 2010). Normal ataxin-3 is found in nuclear inclusions of different polyglutamine diseases, particularly in spinocerebellar ataxia type 1 – SCA1, SCA2, Dentatorubral-pallidolysian atrophy, (Uchihara et al., 2001) and in neuronal intranuclear hyaline inclusion disease (Takahashi et al., 2001). It is also found in Marfansco bodies under stressful conditions and aging in human and non-human primates brains (Fujigasaki et al., 2000; Fujigasaki et al., 2001; Kettner et al., 2002).

Ataxin-3 recruitment to inclusions raises the possibility that normal ataxin-3 and ubiquitin-mediated pathways may be involved in cellular reactions against stress and misfolded proteins (Fujigasaki et al., 2001). In a Drosophila model normal ataxin-3 suppressed the neurotoxicity of mutant ataxin-3 by an ubiquitin-mediated mechanis in association with the proteasome (Warrick et al., 2005). However in a MJD lentiviral rat model the overexpression of normal ataxin-3 did not mitigate the mutant ataxin-3 induced neurodegeneration and even aggravated inclusion generation (Alves et al., 2010).

Several studies have revealed the importance of protein-protein interactions in understanding the normal function of the disease-causing protein (Steffan et al., 2001; Yoshida et al., 2002; Chen et al., 2004; Goehler et al., 2004; Ravikumar et al., 2004; Kaytor et al., 2005; Tsuda et al., 2005). Recently, the normal activity of ataxin-2 was shown to be important to MJD neurodegeneration, suggesting that toxicity of one polyglutamine disease protein could be modulated by the normal activity of another (Lessing and Bonini, 2008). The protein-protein interaction and alteration of the activity of causative proteins was also reported for other neurodegenerative disorders and is therefore an important subject of research (Lim et al., 2006; Zoghbi and Orr, 2009; Elden et al., 2010).

8.3 Dysregulation of transcription

Expanded polyglutamine proteins tend to accumulate in the nucleus, where the high concentration of solutes creates favorable conditions for interaction with transcriptional factors or cofactors (Yamada et al., 2000; Lim et al., 2008). Furthermore, many of the proteins
affected by polyglutamine expansion, such as ataxin-1 or ataxin-2 either interact or function as transcription factors (Fernandez-Funez et al., 2000; Lim et al., 2006; Lastres-Becker et al., 2008) suggesting that transcriptional dysregulation may be a central feature of the neurodegenerative mechanism in the polyglutamine disorders (Steffan et al., 2001; Nucifora et al., 2001; Minamiyama et al., 2004; La Spada et al., 2001; Hughes et al., 2001; Yamada et al., 2000; Lim et al., 2008; Godavarthi et al., 2009; Yamanaka et al., 2008, Riley and Orr, 2006). Accordingly, the transcription factor TBP and transcription co-factor CBP were shown to be incorporated into nuclear inclusions of polyglutamine-expanded ataxin-3 (McCormick et al., 2000). Thus, it is possible that mutant polyglutamine ataxin-3 causes transcriptional dysregulation and resulting neurotoxicity. Downregulation of mRNA levels of genes involved in glutamatergic signaling and signal transduction, but no neurological phenotype, were reported in a MJD transgenic mouse expressing ataxin-3 with 79 CAG repeats in brain regions affected in the disease. This suggests the involvement of transcriptional abnormality in initiating the pathological process of MJD, with expanded ataxin-3 disrupting the normal pattern of gene transcription and contributing to cerebellar dysfunction and ataxia (Chou et al., 2008).

8.4 Ubiquitin-proteasome system dysfunctions

Cells produce a large amount of misfolded proteins, thus protein degradation systems like the UPS or autophagy are crucial to maintain cellular function and viability. A dysfunction in the UPS leads to the accumulation of misfolded proteins, resulting in dysfunction and cell death in neurons. The normal function of ataxin-3 has been linked to protein surveillance pathways (Chai et al., 2004). Ataxin-3 acts as polyubiquitin-binding protein, recruiting poly-ubiquitinated substrates through a carboxy-terminal cluster of ubiquitin interaction motifs (Burnett et al., 2003; Raoul et al., 2005). A loss of mutant ataxin-3 function could affect the UPS and in that way enhance neuronal degeneration and death. Moreover, mutant ataxin-3 nuclear inclusions are ubiquitinated and contain proteasome components, suggesting that the UPS may be disrupted by expanded protein (Paulson et al., 1997b; Chai et al., 1999b).

8.5 Autophagy impairment

There are strong evidences that proteins with a mutant polyglutamine tract are inefficiently degraded by the UPS but could be degraded by macroautophagy, a mechanism with a crucial role in degradation of insoluble aggregate-prone proteins and essential for neuronal survival (Cuervo, 2004a, b; Williams et al., 2006). Recently, our group has shown that important autophagy proteins are sequestered by mutant ataxin-3 inclusions in an MJD lentiviral model and abnormally accumulate in MJD patient’s brain (Nascimento-Ferreira et al., 2011). As it happens with the UPS system a disruption in the autophagy system could enhance neurodegeneration and cell death induced by mutant ataxin-3. Accordingly, impairments in the autophagy pathway have been reported in other neurodegenerative diseases (Shibata et al., 2006, Pickford et al., 2008; Crews et al., 2010), as well as a decrease of activity with ageing (Cuervo, 2004b; Vellai, 2009).

8.6 Mitochondrial dysfunction

There is growing evidence that mitochondrial dysfunction may play important roles in neurodegeneration (Knott et al., 2008), and could be implicated in the pathogenesis of MJD.
(Yu et al., 2009) and other polyglutamine diseases (Browne et al., 1997; Panov et al., 2002; Cui et al., 2006). In addition, mitochondrial dysfunction has been implicated in ageing, which is a major risk factor of progressive neurodegenerative diseases. Oxidative stress is induced by reactive oxygen species (ROS) or free radicals, and increasing with age, and possibly diminished capacity to deal with oxidative stress may cause modification of cellular macromolecules and lead to cell damage.

8.7 Impairment of axonal transport

The function and survival of neurons demands continuous axonal transport of mRNA and proteins. Several studies suggest that axonal transport disturbance is an attractive hypothesis that could explain the vulnerability of neurons (Gunawardena et al., 2003; Szenbenyi et al., 2003; Caviston et al., 2007). However, currently there is no sufficient evidence to confirm this hypothesis in polyglutamine diseases. Recently, the presence of inclusions in axons was identified in several brain regions of MJD patients affected by neurodegeneration (Seidel et al., 2010). It was hypothesized that the presence of axonal inclusions could be detrimental to axonal transport mechanisms and thereby contribute to degeneration of nerve cells in MJD.

8.8 Dysregulation of intracellular Ca^{2+} homeostasis

Intracellular Ca^{2+} homeostasis is important for the function and survival of neurons, and it has become clear that cellular Ca^{2+} overload, or perturbation of intracellular Ca^{2+} compartmentalization, can cause cytotoxicity and trigger either apoptotic or necrotic cell death (Orrenius et al., 2003). Several studies proposed that deranged Ca^{2+} signaling might play an important role in Huntington’s disease (Tang et al., 2003; 2005; Bezprozvanny and Hayden, 2004; Wu et al., 2006). Abnormal Ca^{2+} homeostasis has been reported in mitochondria isolated from lymphoblasts from patients and from brains of the YAC72 HD mouse model (Hodgson et al., 1999; Panov et al., 2002). This Ca^{2+} role could also be important in other polyglutamine diseases, as it is generally assumed that many of these diseases share a common pathogenic mechanism (Cummings and Zoghbi, 2000; Gusella and MacDonald, 2000; Zoghbi and Orr, 2000; Gatchel and Zoghbi, 2005). Accordingly, recent evidence suggests that abnormal neuronal Ca^{2+} signaling might also contribute to pathogenesis in SCAs (Bezprozvanny, 2009; Kasumu and Bezprozvanny, 2010). In MJD, data also suggest that deranged neuronal Ca^{2+} signaling plays a significant role in pathology onset and progression (Chen et al., 2008). Mutant ataxin-3 has been shown to specifically bind to and activate an intracellular calcium channel, similar to huntingtin. Moreover, long-term feeding of MJD-transgenic mice with a Ca^{2+} stabilizer (dantrolene) alleviated age-dependent motor coordination deficits and prevented neuronal loss in pontine nuclei and substantia nigra regions (Chen et al., 2008).

9. Therapeutic strategies in MJD

Expansion of the polyglutamine tract of ataxin-3 initiates a cascade of events that include the accumulation of insoluble inclusions and culminates in degeneration of specific neurons. The strategies that can be used to treat MJD or other polyglutamine diseases can be grouped into five main approaches: i) reducing the levels of expanded proteins, ii) preventing mutant ataxin-3 cleavage, oligomerization and aggregation, iii) activating the
clearance mechanisms, iv) targeting a specific cellular mechanism and v) promoting neuroprotection (Figure 4).

**Fig. 4. Potential therapeutic strategies to Machado-Joseph disease.** Expansion of the polyglutamine tract of ataxin-3 initiates a cascade of events that culminates with the accumulation of insoluble inclusions and degenerations in selected neurons. The strategies that can be used to treat MJD or other polyglutamine diseases can be grouped into five approaches: i) reducing the levels of expanded proteins (using gene silencing by RNAi-based strategies), ii) preventing mutant ataxin-3 cleavage, oligomerization and aggregation (inhibiting proteolysis, using aggregation inhibitors or preventing the nuclear transport), iii) activation of the clearance mechanisms (upregulation of UPS and autophagy), iv) targeting a specific cellular mechanism (increase transcription, stabilize Ca\(^{2+}\) homeostasis or inhibit oxidative stress) and v) neuroprotection strategies (using drugs, proteins or factors to protect neurons).
9.1 RNA interference-based therapeutics

Although several approaches could be envisioned to treat MJD and other polyglutamine diseases, the most direct solution to counter these diseases’ pathogenesis is to reduce the expression of the mutant allele (Kim and Rossi, 2007). RNA interference (RNAi) is a powerful tool for selective knockdown of gene expression. Gene silencing by RNAi has been successfully used to downregulate the expression of mutant genes and rescue phenotype in various neurodegenerative diseases, including Huntington’s disease (Harper et al., 2005; Rodriguez-Lebron et al., 2005; DiFiglia et al., 2007, van Bilsen et al., 2008; Lombardi et al., 2009; Pfister et al., 2009), familial forms of amyotrophic lateral sclerosis (ALS) (Raoul et al., 2005; Ralph et al., 2005; Azzouz, 2006), SCA1 (Xia et al., 2004), and MJD (Miller et al., 2003; Alves et al., 2008a, 2010; Hu et al., 2009).

However, a major problem of gene silencing may be the lack of discrimination between normal and mutant forms of the causative protein. In some diseases partial silencing of normal protein could be tolerated; for example, in HD transgenic animal models silencing of mutant huntingtin and 75% of endogenous protein led to behavioral enhancement (Boudreau et al., 2009). However, it has been reported that in cellular MJD models absence of wild-type ataxin-3 leads to cytoskeletal disorganization and increased cell death (Rodrigues et al., 2010). This would suggest that for some polyglutamine disorders it might be prudent to preserve the wild-type protein, as prolonged full knockdown of normal protein function could be harmful. This would demand specific targeting of the mutant allele for RNAi.

It was first demonstrated in cell models that RNAi species could be engineered to specifically silence the causative genes while preserving the wild-type, which differed in a single nucleotide (Miller et al., 2003). More recently, our group showed both in vitro and in a rat model of MJD that lentiviral-mediated silencing of the mutant human ataxin-3 was efficient and selective, allowing preservation of wild-type ataxin-3 (Alves et al., 2008a).

Specific silencing has also been later reported to SNPs targeting ataxin-7 in SCA7 (Scholefield et al., 2009) and huntingtin in Huntington’s disease (Zhang et al., 2009; Hu et al., 2009). This allele-specific silencing of ataxin-3 significantly decreased the severity of the neuropathological abnormalities associated with the disease by targeting a single nucleotide polymorphism (SNPs) that is present in more than 70% of the patients with MJD (Stevanin et al., 1995; Gaspar et al., 1996). These data support the therapeutic potential of RNAi for MJD. However, this therapy would benefit ~70% of MJD patients at best. Whether silencing not discriminating between wild type and mutant alleles would be safe and effective was recently investigated, by either overexpressing or silencing wild-type ataxin-3 in a rat model of MJD. It was shown that (i) overexpression of wild-type ataxin-3 did not protect against MJD pathology, (ii) knockdown of wild-type ataxin-3 did not aggravate MJD pathology and that (iii) non-allele-specific silencing of ataxin-3 strongly reduced neuropathology in a rat model of MJD. These findings indicate that therapeutic strategies involving non-allele-specific silencing to treat MJD patients may also be safe and effective (Alves et al., 2010).

9.2 Preventing the cleavage of ataxin-3

In MJD, it was proposed that production of a cleavage fragment of mutant ataxin-3 contributes to neurotoxicity (Ikeda et al., 1996; Goti et al., 2004; Colomer-Gould, 2005;
Haacke et al., 2006). Thus, blocking the proteases involved in ataxin-3 cleavage and decreasing the concentration of the cleavage fragment below a critical level in the brain could be an effective strategy for MJD treatment. This approach has been used for other neurodegenerative diseases, including Alzheimer (Citron, 2004) and Huntington’s diseases (Ona et al., 1999; Gafni et al., 2004) and therefore could also be a therapeutic strategy for MJD (Tarlac and Storey, 2003). Nevertheless, the natures of the protease and of the cleavage fragment still need investigation.

9.3 Acceleration of the degradation of misfolded proteins

The acceleration of the proteolysis mechanisms (UPS and autophagy machinery) could promote mutant ataxin-3 degradation and probably prevent or delay the MJD progression. Overexpression of chaperones has been shown to aid in the handling of misfolded or aggregated polyglutamine-expanded ataxin-3 and suppress polyglutamine aggregation with a parallel decrease in toxicity (Chai et al., 1999b). Thus the induction of such molecular chaperones can be envisaged as a strategy for therapy of polyglutamine diseases (Nagai et al., 2010; Robertson et al., 2010). Accordingly, the use of chemical chaperones such as the organic solvent dimethyl sulfoxide – DMSO, cellular osmolytes glycerol, trimethylamine N-oxide – TMAO, and ectoine reduce aggregate formation and cytotoxicity induced by truncated expanded ataxin-3 (Yoshida et al., 2002), alters subcellular localization of inclusions and reduces apoptotic cell death induced by mutant ataxin-3 (Furusho et al., 2005).

It was also shown that overexpression of UPS-related factors or proteins (e.g. E64 or CHIP) increase ubiquitination and degradation rate and decrease aggregation and cell death (Matsumoto et al., 2004; Jana et al., 2005; Miller et al., 2005). Therefore, overexpression of these proteins could be a molecular approach for therapy of MJD. It was shown that CRAG (guanosine triphosphatase) acts as an activator of promylocytic leukaemia protein-associated ubiquitin ligase and leads to the degradation of polyQ through the ubiquitin-proteasome pathway (Qin et al., 2006). Because the expression levels of CRAG decrease in the adult brain (Qin et al., 2006), it was suggested that a reduced level of CRAG could underlie the onset of polyglutamine diseases. In fact, lentiviral-mediated overexpression of CRAG in Purkinje cells of a transgenic mice model extensively cleared polyQ aggregates and re-activated dendritic differentiation, resulting in a striking rescue from ataxia (Torashima et al., 2008). It was also suggested that the activity of normal ataxin-3 could provide a therapeutic approach to MJD, enhancing the cellular pathways in which it participates (Warrick et al., 2005). However, in a lentiviral-based rat model for MJD as well as in double-transgenic mice, the overexpression of normal ataxin-3 did not decrease the pathological abnormalities induced by mutant ataxin-3 (Alves et al., 2010; Hübener et al., 2010).

Another possible therapeutic approach to MJD and to other polyglutamine diseases could be the up-regulation of autophagy, leading to a selective clearance of the mutant protein. Rapamycin, an activator of the autophagy pathway alleviated neurodegeneration in Drosophila and in a transgenic mouse model of HD. However, this drug failed to prolong life span in a mouse model (Ravikumar et al., 2004). In MJD, it was recently shown that the administration of a rapamycin ester improves motor coordination in a transgenic model of MJD (Menzies et al., 2010). The rapamycin ester reduced the number of aggregates in the
brains of transgenic mice and decreased the levels of cytosolic soluble mutant ataxin-3, while endogenous wild-type protein levels remained unaffected.

Recently, our group showed that lentiviral-mediated overexpression of beclin-1, a crucial protein in early and late steps of autophagy, led to a stimulation of autophagic flux, mutant ataxin-3 clearance and overall neuroprotective effects in neuronal cultures and in a lentiviral-based rat model of MJD (Nascimento-Ferreira et al., 2011). The same study found an abnormal expression of endogenous autophagy markers, accumulation of autophagosomes and decreased levels of beclin in the brain of MJD patients. Overall, these data suggest that up-regulation of UPS or autophagy can be a therapeutic option for MJD and for other polyglutamine diseases.

9.4 Inhibition of nuclear transport

It has been shown that ataxin-3 translocates to the nucleus, and that the polyglutamine expansion is not essential for this transport (Tait et al., 1998). The resulting presence of ataxin-3 in the nucleus has been shown to drastically aggravate the pathology in Machado-Joseph disease (Bichelmeier et al., 2007). Therefore, inhibition of nuclear transport may slow the disease progression, and might be sufficient to ameliorate the disease symptoms, and thus could be explored as therapeutic approach for MJD (Breuer et al., 2010).

9.5 Prevention of protein misfolding, oligomerization and aggregation

Protein misfolding, oligomerization, and formation of insoluble inclusions represent a common physiological response to pathogenic proteins. Thus, different research groups have developed high-throughput screening assays aiming at the discovery of molecules with selective binding affinities for polyglutamine expanded proteins, with the ability to modulate their pathogenic properties and potential therapeutic applications (Desai et al., 2006; Lansbury and Lashuel, 2006). Several compounds have been identified as potential inhibitors of polyglutamine aggregation (Heiser et al., 2000, 2002; Apostol et al., 2003; Sánchez et al., 2003; Tanaka et al., 2005; Wolfgang et al., 2005; Herbst and Wancker, 2006). The prevention of aggregation and oligomerization by polyglutamine disease can also be promoted by modulation of molecular chaperones (Nagai et al., 2010; Roberston et al., 2010). The Hsp90 inhibitor geldanamycin suppresses aggregation of polyQ-expanded mutant huntingtin through induction of endogenous molecular chaperones (Sittler et al., 2001). In MJD Drosophila models, it was shown that the administration of a less toxic derivative of geldanamycin suppresses polyQ-induced neurodegeneration through the induction of multiple endogenous molecular chaperones (Fujikake et al., 2008).

Another therapeutic approach involves the use of small peptides or molecules with the ability to modulate protein folding, stabilize proteins in their native conformation, and prevent or inhibit aggregation (Tanaka et al., 2005). Several compounds proved to be suitable in preventing polyglutamine proteins aggregation, mainly for Huntington Disease (Table 2). In a screening of 16,000 compounds a small molecule (IC_{50}) that inhibits polyglutamine aggregation in HD neurons and suppresses neurodegeneration in vivo was found (Zhang et al., 2005). In a MJD Drosophila model a tandem repeat of the polyglutamine binding peptide QBP1, which preferentially binds to polyglutamine stretches, has been shown to decrease aggregate formation and rescue survival (Nagai et al., 2003). More
recently a high-content chemical and RNAi screening in a Drosophila primary neuronal culture of HD model identified several compounds that suppress mutant huntingtin aggregate formation (Schulte et al., 2011).

| Compound                                      | Disease tested | Study                      |
|-----------------------------------------------|----------------|----------------------------|
| Geldanamycin                                  | Huntington Disease | Sittler et al., 2001       |
| 17-(allylamino)-17-demethoxygeldanamycin (17AAG) | Machado-Joseph Disease | Fujikake et al., 2008      |
| Congo red                                     | Huntington Disease | Frid et al., 2007          |
| C2-8                                          | Huntington Disease | Chopra et al., 2007        |
| Trehalose                                     | Huntington Disease | Tanaka et al., 2005        |
| GW5074                                        | Huntington Disease | Schulte et al., 2011       |
| Juglone                                       | Huntington Disease | Schulte et al., 2011       |
| Radicicol                                     | Huntington Disease | Schulte et al., 2011       |
| Rapamycin                                     | Huntington Disease | Schulte et al., 2011       |
| Rapamycin ester                               | Machado-Joseph Disease | Menzies et al., 2010      |
| Camptothecin                                  | Huntington Disease | Schulte et al., 2011       |
| Etoposide                                     | Huntington Disease | Schulte et al., 2011       |
| Ouabain                                       | Huntington Disease | Schulte et al., 2011       |
| Proscillaridin A                              | Huntington Disease | Schulte et al., 2011       |
| Ethacrynic acid                               | Huntington Disease | Schulte et al., 2011       |
| IC_{50}                                        | Huntington Disease | Zhang et al., 2005         |

Table 2. Compounds that have shown to prevent or inhibit polyglutamine proteins aggregation.

### 9.6 Targeting transcriptional dysfunction

Polyglutamine-expanded ataxin-3 (as other polyglutamine expanded proteins) has been shown to repress transcription. Ataxin-3 acts through distinct mechanisms involving both the polyglutamine-containing C-terminus and the N-terminus of ataxin-3 (Li et al., 2002). Transcriptional dysregulation has been suggested to play a central role in neurodegenerative mechanisms of the polyglutamine disorders (Chou et al., 2008). The overexpression of transcription factors that interact with polyglutamine diseases reduces the cytotoxicity of mutant proteins (Dunah et al., 2002; Taylor et al., 2003). Moreover, it was shown that the use of several reagents that increase transcription reduce the toxicity of expanded polyglutamine (Steffan et al., 2001; Ferrante et al., 2003, 2004; Hockly et al., 2003; Gardian et al., 2005; Shimohata et al., 2005). Recently, it was shown that regulation of transcriptional activity through an inhibition of histone hypoacetylation (Chou et al., 2011) might be a promising therapeutic intervention for MJD. Histone acetylation, which is controlled by histone acetyltransferase and histone deacetylase (HDAC), plays an important role in regulating transcriptional activity (Kurdistani et al., 2004). The H3 and H4 histones were hypoacetylated in the cerebellum of MJD transgenic mice, which displayed transcription downregulation and ataxic symptoms. Daily administration of a HDAC inhibitor (sodium butyrate) reversed histone hypoacetylation and transcriptional downregulation in the cerebellum of the MJD transgenic mice, delaying the onset of ataxic symptoms, ameliorated the neurological phenotype and improved the survival rate of the mice (Chou et al., 2011).
9.7 Targeting the calcium homeostasis

It has been shown that deranged calcium signaling might play an important role in MJD pathology (Chen et al., 2008). The same study found that feeding a MJD transgenic mice with dantrolene, a clinically relevant stabilizer of intracellular Ca\textsuperscript{2+} signaling, improved motor performance and prevented neuronal cell loss in pontine nuclei and \textit{substantia nigra} regions. Therefore, calcium-signaling stabilizers such as dantrolene may be considered as potential therapeutic drugs for the treatment of MJD patients.

9.8 Targeting mitochondrial dysfunctions

Several studies have shown that administration of antioxidants ameliorates motor deficits and prolongs survival in transgenic mouse model of HD (Ferrante et al., 2002). Moreover, drugs that improve transcriptional regulation of genes necessary for energy metabolism also improve HD motor phenotype (Hathorn et al., 2011). In MJD, evidences point to a role of mitochondrial dysfunction in MJD pathogenesis (Yu et al., 2009). Decreased mitochondrial DNA copy numbers were found in mutant cells stably transfected with ataxin-3 with 78 CAG repeats and in MJD patients, compared to normal controls. Furthermore, mitochondrial DNA depletion was higher in MJD patients compared with that in normal individuals. Overall, mutant ataxin-3 may influence the activity of enzymatic components to remove O\textsubscript{2} and H\textsubscript{2}O\textsubscript{2} efficiently and promote mitochondrial DNA damage or depletion, which leads to dysfunction of mitochondria (Yu et al., 2009). Therefore, therapies targeting mitochondrial dysfunction in MJD should be further investigated.

9.9 Neuroprotection

The possibility of administration of drugs or molecules with neuroprotective properties in neurodegenerative diseases has also been explored. Many research groups have investigated the use of neurotrophic factors for therapy of polyglutamine disorders over the last decade (Bensadoun et al., 2000; de Almeida et al., 2001; Zala et al., 2004; Xie et al., 2010). In HD the BDNF supply to striatal neurons is compromised. Therefore delivery of this factor has been investigated as a replacement therapy for the missing factor (Zuccato et al., 2001). BDNF replacement was later shown to enhance the motor phenotype (Canals et al., 2004), and BDNF overexpression prevented loss and atrophy of striatal neurons and motor dysfunction (Xie et al., 2010), both in in HD transgenic mice.

Studies in mouse models of Alzheimer’s and Parkinson’s diseases found that caffeine could alleviate pathological signs and behavior deficits in these neurodegenerative disease paradigms, by antagonizing A2A adenosine receptors (Arendash and Cao, 2010; Prediger, 2010; reviewed in Cunha and Agostinho, 2010). Moreover, administration of caffeine and other stimulants in orexin/ataxin-3 transgenic narcoleptic mice induced an increase in motor activity but the effects on neuropathology remain to be investigated (Okuro et al., 2010) and should be further investigated in MJD models.

Several evidences suggest that neuroprotective compounds could be also explored as a therapeutic strategy in MJD and the drug ability of some of these compounds may contribute to earlier access of patients to much needed disease-modifying therapies.
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11. References

Albrecht M, Golatta M, Wullner U, Lengauer T (2004) Structural and functional analysis of ataxin-2 and ataxin-3. Eur J Biochem 271:3155-3170.

Alves S, Nascimento-Ferreira I, Auregan G, Hassig R, Dufour N, Brouillet E, Pedroso de Lima MC, Hantraye P, Pereira de Almeida L, Deglon N (2008a) Allele-specific RNA silencing of mutant ataxin-3 mediates neuroprotection in a rat model of Machado-Joseph disease. PLoS One 3:e3341.

Alves S, Regulier E, Nascimento-Ferreira I, Hassig R, Dufour N, Koeppen A, Carvalho AL, Simoes S, de Lima MC, Brouillet E, Gould VC, Deglon N, de Almeida LP (2008b) Striatal and nigral pathology in a lentiviral rat model of Machado-Joseph disease. Hum Mol Genet 17:2071-2083.

Alves S, Nascimento-Ferreira I, Dufour N, Hassig R, Auregan G, Nobrega C, Brouillet E, Hantraye P, Pedroso de Lima MC, Deglon N, de Almeida LP (2010) Silencing ataxin-3 mitigates degeneration in a rat model of Machado-Joseph disease: no role for wild-type ataxin-3? Hum Mol Genet 19:2380-2394.

Antony PM, Mantele S, Mollenkopf P, Boy J, Kehlenbach RH, Riess O, Schmidt T (2009) Identification and functional dissection of localization signals within ataxin-3. Neurobiol Dis 36:280-292.

Apostol BL, Kazantsev A, Raffioni S, Illes K, Pallos J, Bodai L, Slepko N, Bear JE, Gertler FB, Hersch S, Housman DE, Marsh JL, Thompson LM (2003) A cell-based assay for aggregation inhibitors as therapeutics of polyglutamine-repeat disease and validation in Drosophila. Proc Natl Acad Sci U S A 100:5950-5955.

Arendash GW, Cao C (2010) Caffeine and coffee as therapeutics against Alzheimer’s disease. J Alzheimers Dis 20 Suppl 1:S117-126.

Azzouz M (2006) Gene Therapy for ALS: progress and prospects. Biochim Biophys Acta 1762:1122-1127.

Bates G (2003) Huntingtin aggregation and toxicity in Huntington’s disease. Lancet 361:1642-1644.

Behrends C, Langer CA, Boteva R, Bottcher UM, Stemp MJ, Schaffar G, Rao BV, Giese A, Kretzschmar H, Siegers K, Hartl FU (2006) Chaperonin TRiC promotes the assembly of polyQ expansion proteins into nontoxic oligomers. Mol Cell 23:887-897.

Bensadoun JC, Deglon N, Tseng JL, Ridet JL, Zurn AD, Aebischer P (2000) Lentiviral vectors as a gene delivery system in the mouse midbrain: cellular and behavioral improvements in a 6-OHDA model of Parkinson’s disease using GDNF. Exp Neurol 164:15-24.
Berke SJ, Schmied FA, Brunt ER, Ellerby LM, Paulson HL (2004) Caspase-mediated proteolysis of the polyglutamine disease protein ataxin-3. J Neurochem 89:908-918.

Bettencourt C, Santos C, Montiel R, Costa Mdo C, Cruz-Morales P, Santos LR, Simoes N, Kay T, Vasconcelos J, Maciel P, Lima M (2010) Increased transcript diversity: novel splicing variants of Machado-Joseph disease gene (ATXN3). Neurogenetics 11:193-202.

Bevivino AE, Loll PJ (2001) An expanded glutamine repeat destabilizes native ataxin-3 structure and mediates formation of parallel beta -fibrils. Proc Natl Acad Sci U S A 98:11955-11960.

Bezprozvanny I (2009) Calcium signaling and neurodegenerative diseases. Trends Mol Med 15:89-100.

Bezprozvanny I, Hayden MR (2004) Deranged neuronal calcium signaling and Huntington disease. Biochem Biophys Res Commun 322:1310-1317.

Boeddrich A, Gaumer S, Haacke A, Tzvetkov N, Albrecht M, Evert BO, Muller EC, Lurz R, Breuer P, Schugardt N, Plassmann S, Xu K, Warrick JM, Suopanki J, Wullner U, Frank R, Hartl UF, Bonini NM, Wanker EE (2006) An arginine/lysine-rich motif is crucial for VCP/p97-mediated modulation of ataxin-3 fibrillogenesis. Embo J 25:1547-1558.

Boudreau RL, McBride JL, Martins I, Shen S, Xing Y, Carter BJ, Davidson BL (2009) Nonallele-specific silencing of mutant and wild-type huntingtin demonstrates therapeutic efficacy in Huntington's disease mice. Mol Ther 17:1053-1063.

Breuer P, Haacke A, Evert BO, Wullner U (2010) Nuclear aggregation of polyglutamine-expanded ataxin-3: fragments escape the cytoplasmic quality control. J Biol Chem 285:6532-6537.

Browne SE, Bowling AC, MacGarvey U, Baik MJ, Berger SC, Muqit MM, Bird ED, Beal MF (1997) Oxidative damage and metabolic dysfunction in Huntington's disease: selective vulnerability of the basal ganglia. Ann Neurol 41:646-653.

Burnett B, Li F, Pittman RN (2003) The polyglutamine neurodegenerative protein ataxin-3 binds polyubiquitylated proteins and has ubiquitin protease activity. Hum Mol Genet 12:3195-3205.

Camargos ST, Marques W, Jr., dos Santos AC (2011) Brain stem and cerebellum volumetric analysis of Machado Joseph disease patients. Arq Neuropsiquiatr 69:292-296.

Canals JM, Pineda JR, Torres-Peraza JF, Bosch M, Martin-Ibanez R, Munoz MT, Mengod G, Ernfors P, Alberch J (2004) Brain-derived neurotrophic factor regulates the onset and severity of motor dysfunction associated with enkephalinergic neuronal degeneration in Huntington's disease. J Neurosci 24:7727-7739.

Caviston JP, Ross JL, Antony SM, Tokito M, Holzbaur EL (2007) Huntingtin facilitates dynein/dynactin-mediated vesicle transport. Proc Natl Acad Sci U S A 104:10045-10050.

Cemal CK, Carroll CJ, Lawrence L, Lowrie MB, Ruddle P, Al-Mahdawi S, King RH, Pook MA, Huxley C, Chamberlain S (2002) YAC transgenic mice carrying pathological alleles of the MJD1 locus exhibit a mild and slowly progressive cerebellar deficit. Hum Mol Genet 11:1075-1094.
Chai Y, Berke SS, Cohen RE, Paulson HL (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.

Chai Y, Koppenhafer SL, Bonini NM, Paulson HL (1999a) Analysis of the role of heat shock protein (Hsp) molecular chaperones in polyglutamine disease. J Neurosci 19:10338-10347.

Chai Y, Koppenhafer SL, Shoesmith SJ, Perez MK, Paulson HL (1999b) Evidence for proteasome involvement in polyglutamine disease: localization to nuclear inclusions in SCA3/MJD and suppression of polyglutamine aggregation in vitro. Hum Mol Genet 8:673-682.

Chen S, Peng GH, Wang X, Smith AC, Grote SK, Sopher BL, La Spada AR (2004) Interference of Crx-dependent transcription by ataxin-7 involves interaction between the glutamine regions and requires the ataxin-7 carboxy-terminal region for nuclear localization. Hum Mol Genet 13:53-67.

Chen X, Tang TS, Tu H, Nelson O, Pook M, Hammer R, Nukina N, Bezprozvanny I (2008) Deranged calcium signaling and neurodegeneration in spinocerebellar ataxia type 3. J Neurosci 28:12713-12724.

Chopra V, Fox JH, Lieberman G, Dorsey K, Matson W, Waldmeier P, Housman DE, Kazantsiev A, Young AB, Hersch S (2007) A small-molecule therapeutic lead for Huntington's disease: preclinical pharmacology and efficacy of C2-8 in the R6/2 transgenic mouse. Proc Natl Acad Sci U S A 104:16685-16689.

Chou AH, Chen SY, Yeh TH, Weng YH, Wang HL (2011) HDAC inhibitor sodium butyrate reverses transcriptional downregulation and ameliorates ataxic symptoms in a transgenic mouse model of SCA3. Neurobiol Dis 41:481-488.

Chou AH, Yeh TH, Kuo YL, Kao YC, Jou MJ, Hsu CY, Tsai SR, Kakizuka A, Wang HL (2006) Polyglutamine-expanded ataxin-3 activates mitochondrial apoptotic pathway by upregulating Bax and downregulating Bcl-xL. Neurobiol Dis 21:333-345.

Chou AH, Yeh TH, Ouyang P, Chen YL, Chen SY, Wang HL (2008) Polyglutamine-expanded ataxin-3 causes cerebellar dysfunction of SCA3 transgenic mice by inducing transcriptional dysregulation. Neurobiol Dis 31:89-101.

Citron M (2004) Strategies for disease modification in Alzheimer's disease. Nat Rev Neurosci 5:677-685.

Colomer Gould VF (2005) Mouse models of Machado-Joseph disease and other polyglutamine spinocerebellar ataxias. NeuroRx 2:480-483.

Coutinho P, Andrade C (1978) Autosomal dominant system degeneration in Portuguese families of the Azores Islands. A new genetic disorder involving cerebellar, pyramidal, extrapyramidal and spinal cord motor functions. Neurology 28:703-709.

Crews L, Spencer B, Desplats P, Patrick C, Paulino A, Rockenstein E, Hansen L, Adame A, Galasko D, Masliah E (2010) Selective molecular alterations in the autophagy pathway in patients with Lewy body disease and in models of alpha-synucleinopathy. PLoS One 5:e9313.

Cuervo AM (2004a) Autophagy: in sickness and in health. Trends Cell Biol 14:70-77.

Cuervo AM (2004b) Autophagy: many paths to the same end. Mol Cell Biochem 263:55-72.
Cui L, Jeong H, Borovecki F, Parkhurst CN, Tanese N, Krainc D (2006) Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. Cell 127:59-69.

Cummings CJ, Reinstein E, Sun Y, Antalffy B, Jiang Y, Ciechanover A, Orr HT, Beaudet AL, Zoghbi HY (1999) Mutation of the E6-AP ubiquitin ligase reduces nuclear inclusion frequency while accelerating polyglutamine-induced pathology in SCA1 mice. Neuron 24:879-892.

Cummings CJ, Zoghbi HY (2000) Trinucleotide repeats: mechanisms and pathophysiology. Annu Rev Genomics Hum Genet 1:281-328.

Cunha RA, Agostinho PM. (2010) Chronic caffeine consumption prevents memory disturbance in different animal models of memory decline. J Alzheimers Dis.;20 Suppl 1:S95-116.

de Almeida LP, Zala D, Aebischer P, Deglon N (2001) Neuroprotective effect of a CNTF-expressing lentiviral vector in the quinolinic acid rat model of Huntington's disease. Neurobiol Dis 8:433-446.

de Pril R, Fischer DF, Roos RA, van Leeuwen FW (2007) Ubiquitin-conjugating enzyme E2-25K increases aggregate formation and cell death in polyglutamine diseases. Mol Cell Neurosci 34:10-19.

Desai UA, Pallos J, Ma AA, Stockwell BR, Thompson LM, Marsh JL, Diamond MI (2006) Biologically active molecules that reduce polyglutamine aggregation and toxicity. Hum Mol Genet 15:2114-2124.

DiFiglia M, Sena-Esteves M, Chase K, Sapp E, Pfister E, Sass M, Yoder J, Reeves P, Pandey RK, Rajeev KG, Manoharan M, Sah DW, Zamore PD, Aronin N (2007) Therapeutic silencing of mutant huntingtin with siRNA attenuates striatal and cortical neuropathology and behavioral deficits. Proc Natl Acad Sci U S A 104:17204-17209.

Donaldson KM, Li W, Ching KA, Batalov S, Tsai CC, Joazeiro CA (2003) Ubiquitin-mediated sequestration of normal cellular proteins into polyglutamine aggregates. Proc Natl Acad Sci U S A 100:8892-8897.

Doss-Pepe EW, Stenroos ES, Johnson WG, Madura K (2003) Ataxin-3 interactions with rad23 and valosin-containing protein and its associations with ubiquitin chains and the proteasome are consistent with a role in ubiquitin-mediated proteolysis. Mol Cell Biol 23:6469-6483.

Dunah AW, Jeong H, Griffin A, Kim YM, Standaert DG, Hersch SM, Mouradian MM, Young AB, Tanese N, Krainc D (2002) Sp1 and TAFII130 transcriptional activity disrupted in early Huntington's disease. Science 296:2238-2243.

Durcan TM, Kontogiannea M, Thorarinsdottir T, Fallon L, Williams AJ, Djarmati A, Fantaneanu T, Paulson HL, Fon EA (2011) The Machado-Joseph disease-associated mutant form of ataxin-3 regulates parkin ubiquitination and stability. Hum Mol Genet 20:141-154.

Durr A, Stevanin G, Cancel G, Duyckaerts C, Abbas N, Didierjean O, Chneiweiss H, Benomar A, Lyon-Caen O, Julien J, Serdaru M, Penet C, Agid Y, Brice A (1996)
Spinocerebellar ataxia 3 and Machado-Joseph disease: clinical, molecular, and neuropathological features. Ann Neurol 39:490-499.

Elden AC, Kim HJ, Hart MP, Chen-Plotkin AS, Johnson BS, Fang X, Armakola M, Geser F, Greene R, Lu MM, Padmanabhan A, Clay-Falcone D, McCluskey L, Elman L, Juhr D, Gruber PJ, Rub U, Auburger G, Trojanowski JQ, Lee VM, Van Deerlin VM, Bonini NM, Gitler AD (2010) Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS. Nature 466:1069-1075.

Evert BO, Araujo J, Vieira-Saecker AM, de Vos RA, Harendza S, Klockgether T, Wullner U (2006) Ataxin-3 represses transcription via chromatin binding, interaction with histone deacetylase 3, and histone deacetylation. J Neurosci 26:11474-11486.

Fei E, Jia N, Zhang T, Ma X, Wang H, Liu C, Zhang W, Ding L, Nukina N, Wang G (2007) Phosphorylation of ataxin-3 by glycogen synthase kinase 3beta at serine 256 regulates the aggregation of ataxin-3. Biochem Biophys Res Commun 357:487-492.

Fernandez-Funez P, Nino-Rosales ML, de Gouyon B, She WC, Martinez P, Turiegan W, Benito J, Capovilla M, Skinner PJ, McCall A, Canal I, Orr HT, Zoghbi HY, Botas J (2000) Identification of genes that modify ataxin-1-induced neurodegeneration. Nature 408:101-106.

Ferrante RJ, Andreassen OA, Dedeoglu A, Ferrante KL, Jenkins BG, Hersch SM, Beal MF (2002) Therapeutic effects of coenzyme Q10 and remacemide in transgenic mouse models of Huntington's disease. J Neurosci 22:1592-1599.

Ferrante RJ, Kubilus JK, Lee J, Ryu H, Beesen A, Zucker B, Smith K, Kowall NW, Ratan RR, Luthi-Carter R, Hersch SM (2003) Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington's disease mice. J Neurosci 23:9418-9427.

Ferrante RJ, Ryu H, Kubilus JK, D'Mello S, Sugars KL, Lee J, Lu P, Smith K, Browne S, Beal MF, Kristal BS, Stavrovskaya IG, Hewett S, Rubinsztein DC, Langley B, Ratan RR (2004) Chemotherapy for the brain: the antitumor antibiotic mitramycin prolongs survival in a mouse model of Huntington's disease. J Neurosci 24:10335-10342.

Ferro A, Carvalho AL, Teixeira-Castro A, Almeida C, Tome RJ, Cortes L, Rodrigues AJ, Logarinho E, Sequeiros J, Macedo-Ribeiro S, Maciel P (2007) NEDD8: a new ataxin-3 interactor. Biochim Biophys Acta 1773:1619-1627.

Fowler HL (1984) Machado-Joseph-Azorean disease. A ten-year study. Arch Neurol 41:921-925.

Frid P, Anisman SV, Popovic N (2007) Congo red and protein aggregation in neurodegenerative diseases. Brain Res Rev 53:135-160.

Fujigasaki H, Uchihara T, Koyano S, Iwabuchi K, Yagishita S, Makifuchi T, Nakamura A, Ishida K, Toru S, Hirai S, Ishikawa K, Tanabe T, Mizusawa H (2000) Ataxin-3 is translocated into the nucleus for the formation of intranuclear inclusions in normal and Machado-Joseph disease brains. Exp Neurol 165:248-256.

Fujigasaki H, Uchihara T, Takahashi J, Matsushita H, Nakamura A, Koyano S, Iwabuchi K, Hirai S, Mizusawa H (2001) Preferential recruitment of ataxin-3 independent of expanded polyglutamine: an immunohistochemical study on Marinesco bodies. J Neurol Neurosurg Psychiatry 71:518-520.
Fujikake N, Nagai Y, Popiel HA, Okamoto Y, Yamaguchi M, Toda T (2008) Heat shock transcription factor 1-activating compounds suppress polyglutamine-induced neurodegeneration through induction of multiple molecular chaperones. J Biol Chem 283:26188-26197.

Furusho K, Yoshizawa T, Shoji S (2005) Ectoine alters subcellular localization of inclusions and reduces apoptotic cell death induced by the truncated Machado-Joseph disease gene product with an expanded polyglutamine stretch. Neurobiol Dis 20:170-178.

Gafni J, Hermel E, Young JE, Wellington CL, Hayden MR, Ellerby LM (2004) Inhibition of calpain cleavage of huntingtin reduces toxicity: accumulation of calpain/caspase fragments in the nucleus. J Biol Chem 279:20211-20220.

Gardian G, Browne SE, Choi DK, Klivenyi P, Gregorio J, Kubiš J, Ryu H, Langley B, Ratan RR, Ferrante RJ, Beal MF (2005) Neuroprotective effects of phenylbutyrate in the N171-82Q transgenic mouse model of Huntington’s disease. J Biol Chem 280:556-563.

Gaspar C, Lopes-Cendes I, De Stefano AL, Maciel P, Silveira I, Coutinho P, MacLeod P, Sequeiros J, Farrer LA, Rouleau GA (1996) Linkage disequilibrium analysis in Machado-Joseph disease patients of different ethnic origins. Hum Genet 98:620-624.

Gatchel JR, Zoghbi HY (2005) Diseases of unstable repeat expansion: mechanisms and common principles. Nat Rev Genet 6:743-755.

Globas C, du Montcel ST, Baliko L, Boesch S, Depondt C, Di Donato S, Durr A, Filla A, Klockgether T, Mariotti C, Melegh B, Rakowicz M, Ribai P, Rola R, Schmitz-Hubsch T, Szymanski S, Timmann D, Van de Warrenburg BP, Bauer P, Schols L (2008) Early symptoms in spinocerebellar ataxia type 1, 2, 3, and 6. Mov Disord 23:2232-2238.

Godavarthi SK, Narender D, Mishra A, Goswami A, Rao SN, Nukina N, Jana NR (2009) Induction of chemokines, MCP-1, and KC in the mutant huntingtin expressing neuronal cells because of proteasomal dysfunction. J Neurochem 108:787-795.

Goehler H, Lalowski M, Stelzl U, Waelter S, Stroedicke M, Worm U, Droege A, Lindenberg KS, Knoblich M, Haenic C, Herbst M, Suopanki J, Scherzinger E, Abraham C, Bauer B, Hasenbank R, Fritzsch a, Ludewig AH, Bussow K, Coleman SH, Gutekunst CA, Landwehrmeyer BG, Lehra ch H, Wanker EE (2004) A protein interaction network links GIT1, an enhancer of huntingtin aggregation, to Huntington’s disease. Mol Cell 15:853-865.

Goldberg YP, Nicholson DW, Rasper DM, Kalchman MA, Koide HB, Graham RK, Bromm M, Kazemi-Esfarjani P, Thornberry NA, Vaillancourt JP, Hayden MR (1996) Cleavage of huntingtin by apopain, a proapoptotic cysteine protease, is modulated by the polyglutamine tract. Nat Genet 13:442-449.

Goti D, Katzen SM, Mez J, Kurtis N, Kiluk J, Ben-Haim L, Jenkins NA, Copeland NG, Kakizuka A, Sharp AH, Ross CA, Mouton PR, Colomer V (2004) A mutant ataxin-3 putative-cleavage fragment in brains of Machado-Joseph disease patients and transgenic mice is cytotoxic above a critical concentration. J Neurosci 24:10266-10279.
Goto J, Watanabe M, Ichikawa Y, Yee SB, Ihara N, Endo K, Igarashi S, Takiyama Y, Gaspar C, Maciel P, Tsuji S, Rouleau GA, Kanazawa I (1997) Machado-Joseph disease gene products carrying different carboxyl termini. Neurosci Res 28:373-377.

Gu W, Ma H, Wang K, Jin M, Zhou Y, Liu X, Wang G, Shen Y (2004) The shortest expanded allele of the MJD1 gene in a Chinese MJD kindred with autonomic dysfunction. Eur Neurol 52:107-111.

Gunawardena S, Her LS, Brusch RG, Laymon RA, Niesman IR, Gordesky-Gold B, Sintasath L, Bonini NM, Goldstein LS (2003) Disruption of axonal transport by loss of huntingtin or expression of pathogenic polyQ proteins in Drosophila. Neuron 40:25-40.

Gusella JF, MacDonald ME (2000) Molecular genetics: unmasking polyglutamine triggers in neurodegenerative disease. Nat Rev Neurosci 1:109-115.

Gwinn-Hardy K, Singleton A, O'Suilleabhain P, Boss M, Nicholl D, Adam A, Hussey J, Critchley P, Hardy J, Farrer M (2001) Spinocerebellar ataxia type 3 phenotypically resembling parkinson disease in a black family. Arch Neurol 58:296-299.

Haacke A, Broadley SA, Boteva R, Tzvetkov N, Hartl FU, Breuer P (2006) Proteolytic cleavage of polyglutamine-expanded ataxin-3 is critical for aggregation and sequestration of non-expanded ataxin-3. Hum Mol Genet 15:555-568.

Haacke A, Hartl FU, Breuer P (2007) Calpain inhibition is sufficient to suppress aggregation of polyglutamine-expanded ataxin-3. J Biol Chem 282:18851-18856.

Harper SQ, Staber PD, He X, Eliason SL, Martins IH, Mao Q, Yang L, Kotin RM, Paulson HL, Davidson BL (2005) RNA interference improves motor and neuropathological abnormalities in a Huntington's disease mouse model. Proc Natl Acad Sci U S A 102:5820-5825.

Harris GM, Dodelzon K, Gong L, Gonzalez-Alegre P, Paulson HL (2010) Splice isoforms of the polyglutamine disease protein ataxin-3 exhibit similar enzymatic yet different aggregation properties. PLoS One 5:e13695.

Hathorn T, Snyder-Keller A, Messer A (2011) Nicotinamide improves motor deficits and upregulates PGC-1alpha and BDNF gene expression in a mouse model of Huntington's disease. Neurobiol Dis 41:43-50.

Hayashi M, Kobayashi K, Furuta H (2003) Immunohistochemical study of neuronal intranuclear and cytoplasmic inclusions in Machado-Joseph disease. Psychiatry Clin Neurosci 57:205-213.

Heiser V, Engemann S, Brocker W, Dunkel I, Boeddrich A, Waelter S, Nordhoff E, Lurz R, Schugardt N, Rautenberg S, Herhaus C, Barnickel G, Bottcher H, Lehrach H, Wanker EE (2002) Identification of benzothiazoles as potential polyglutamine aggregation inhibitors of Huntington's disease by using an automated filter retardation assay. Proc Natl Acad Sci U S A 99 Suppl 4:16400-16406.

Heiser V, Scherzinger E, Boeddrich A, Nordhoff E, Lurz R, Schugardt N, Lehrach H, Wanker EE (2000) Inhibition of huntingtin fibrillogenesis by specific antibodies and small molecules: implications for Huntington's disease therapy. Proc Natl Acad Sci U S A 97:6739-6744.

Herbst M, Wanker EE (2006) Therapeutic approaches to polyglutamine diseases: combating protein misfolding and aggregation. Curr Pharm Des 12:2543-2555.
Hockly E, Richon VM, Woodman B, Smith DL, Zhou X, Rosa E, Sathasivam K, Ghazi-Noori S, Mahal A, Lowden PA, Steffan JS, Marsh JL, Thompson LM, Lewis CM, Marks PA, Bates GP (2003) Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. Proc Natl Acad Sci U S A 100:2041-2046.

Hodgson JG, Agopyan N, Gutekunst CA, Leavitt BR, LePiane F, Singaraja R, Smith DJ, Bissada N, McCutcheon K, Nasir J, Jamot L, Li XJ, Smith ME, Rosemond E, Roder JC, Phillips AG, Rubin EM, Hersch SM, Hayden MR (1999) A YAC mouse model for Huntington's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration. Neuron 23:181-192.

Hu J, Matsui M, Gagnon KT, Schwartz JC, Gabillet S, Arar K, Wu J, Bezprozvanny I, Corey DR (2009) Allele-specific silencing of mutant huntingtin and ataxin-3 genes by targeting expanded CAG repeats in mRNAs. Nat Biotechnol 27:478-484.

Hubener J, Vauti F, Funke C, Wolburg H, Ye Y, Schmidt T, Wolburg-Buchholz K, Schmitt I, Gardyan A, Dziessen S, Arnold HH, Nguyen HP, Riess O (2011) N-terminal ataxin-3 causes neurological symptoms with inclusions, endoplasmic reticulum stress and ribosomal dislocation. Brain 134:1925-1942.

Hughes RE, Lo RS, Davis C, Strand AD, Neal CL, Olson JM, Fields S (2001) Altered transcription in yeast expressing expanded polyglutamine. Proc Natl Acad Sci U S A 98:13201-13206.

Ichikawa Y, Goto J, Hattori M, Toyoda A, Ishii K, Jeong SY, Hashida H, Masuda N, Ogata K, Kasai F, Hirai M, Maciel P, Rouleau GA, Sakaki Y, Kanazawa I (2001) The genomic structure and expression of MJD, the Machado-Joseph disease gene. J Hum Genet 46:413-422.

Ikeda H, Yamaguchi M, Sugai S, Aze Y, Narumiya S, Kakizuka A (1996) Expanded polyglutamine in the Machado-Joseph disease protein induces cell death in vitro and in vivo. Nat Genet 13:196-202.

Jacobi H, Hauser TK, Giunti P, Globas C, Bauer P, Schmitz-Hubsch T, Baliko L, Filla A, Mariotti C, Rakowicz M, Charles P, Ribai P, Szymanski S, Infante J, van de Warrenburg BP, Durr A, Timmann D, Boesch S, Fancello R, Rola R, Depondt C, Schols L, Zdzienicka E, Kang JS, Ratzka S, Kremer B, Stephenson DA, Melegh B, Pandolfo M, du Montcel ST, Borkert J, Schulz JB, Klockgether T (2011) Spinocerebellar Ataxia Types 1, 2, 3 and 6: the Clinical Spectrum of Ataxia and Morphometric Brainstem and Cerebellar Findings. Cerebellum.

Jana NR, Dikshit P, Goswami A, Kotliarova S, Murata S, Tanaka K, Nukina N (2005) Co-chaperone CHIP associates with expanded polyglutamine protein and promotes their degradation by proteasomes. J Biol Chem 280:11635-11640.

Jana NR, Nukina N (2004) Misfolding promotes the ubiquitination of polyglutamine-expanded ataxin-3, the defective gene product in SCA3/MJD. Neurotox Res 6:523-533.

Kasumu A, Bezprozvanny I (2010) Deranged Calcium Signaling in Purkinje Cells and Pathogenesis in Spinocerebellar Ataxia 2 (SCA2) and Other Ataxias. Cerebellum.
Kawaguchi Y, Okamoto T, Taniwaki M, Aizawa M, Inoue M, Katayama S, Kawakami H, Nakamura S, Nishimura M, Akiyoshi I, et al., (1994) CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. Nat Genet 8:221-228.

Kayed R, Head E, Thompson JL, McIntire TM, Milton SC, Cotman CW, Glabe CG (2003) Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science 300:486-489.

Kayed R, Sokolov Y, Edmonds B, McIntire TM, Milton SC, Hall JE, Glabe CG (2004) Permeabilization of lipid bilayers is a common conformation-dependent activity of soluble amyloid oligomers in protein misfolding diseases. J Biol Chem 279:46363-46366.

Kaytor MD, Byam CE, Tousey SK, Stevens SD, Zoghbi HY, Orr HT (2005) A cell-based screen for modulators of ataxin-1 phosphorylation. Hum Mol Genet 14:1095-1105.

Kettner M, Willwohl D, Hubbard GB, Rub U, Dick EJ, Jr., Cox AB, Trottier Y, Auburger G, Braak H, Schultz C (2002) Intranuclear aggregation of nonexpanded ataxin-3 in marinesco bodies of the nonhuman primate substantia nigra. Exp Neurol 176:117-121.

Kim DH, Rossi JJ (2007) Strategies for silencing human disease using RNA interference. Nat Rev Genet 8:173-184.

Klement IA, Skinner PJ, Kaytor MD, Yi H, Hersch SM, Clark HB, Zoghbi HY, Orr HT (1998) Ataxin-1 nuclear localization and aggregation: role in polyglutamine-induced disease in SCA1 transgenic mice. Cell 95:41-53.

Klinke I, Minnerop M, Schmitz-Hubsch T, Hendriks M, Klockgether T, Wullner U, Helmstaedter C (2010) Neuropsychological features of patients with spinocerebellar ataxia (SCA) types 1, 2, 3, and 6. Cerebellum 9:433-442.

Knott AB, Perkins G, Schwarzenbacher R, Bossy-Wetzel E (2008) Mitochondrial fragmentation in neurodegeneration. Nat Rev Neurosci 9:505-518.

Kurdistan SK, Tavazoie S, Grunstein M (2004) Mapping global histone acetylation patterns to gene expression. Cell 117:721-733.

La Spada AR, Fu YH, Sopher BL, Libby RT, Wang X, Li LY, Einum DD, Huang J, Possin DE, Smith AC, Martinez RA, Koszdzin KL, Treuting PM, Ware CB, Hurley JB, Ptacek LJ, Chen S (2001) Polyglutamine-expanded ataxin-7 antagonizes CRX function and induces cone-rod dystrophy in a mouse model of SCA7. Neuron 31:913-927.

Lansbury PT, Lashuel HA (2006) A century-old debate on protein aggregation and neurodegeneration enters the clinic. Nature 443:774-779.

Lastres-Becker I, Rub U, Auburger G (2008) Spinocerebellar ataxia 2 (SCA2). Cerebellum 7:115-124.

Lathrop RH, Casale M, Tobias DJ, Marsh JL, Thompson LM (1998) Modeling protein homopolymeric repeats: possible polyglutamine structural motifs for Huntington's disease. Proc Int Conf Intell Syst Mol Biol 6:105-114.

Lessing D, Bonini NM (2008) Polyglutamine genes interact to modulate the severity and progression of neurodegeneration in Drosophila. PLoS Biol 6:e29.

Li F, Macfarlan T, Pittman RN, Chakravarti D (2002) Ataxin-3 is a histone-binding protein with two independent transcriptional corepressor activities. J Biol Chem 277:45004-45012.
Lim J, Crespo-Barreto J, Jafar-Nejad P, Bowman AB, Richman R, Hill DE, Orr HT, Zoghbi HY (2008) Opposing effects of polyglutamine expansion on native protein complexes contribute to SCA1. Nature 452:713-718.

Lim J, Hao T, Shaw C, Patel AJ, Szabo G, Rual JF, Fisk CJ, Li N, Smolyar A, Hill DE, Barabasi AL, Vidal M, Zoghbi HY (2006) A protein-protein interaction network for human inherited ataxias and disorders of Purkinje cell degeneration. Cell 125:801-814.

Lima L, Coutinho P (1980) Clinical criteria for diagnosis of Machado-Joseph disease: report of a non-Azoren Portuguese family. Neurology 30:319-322.

Lombardi MS, Jaspers L, Sproukman C, Geller C, Taroni F, Di Maria E, Donato SD, Kaemmerer WF (2009) A majority of Huntington’s disease patients may be treatable by individualized allele-specific RNA interference. Exp Neurol 217:312-319.

Lysenko L, Grewal RP, Ma W, Peddareddygar LR (2010) Homozygous Machado Joseph Disease: a case report and review of literature. Can J Neurol Sci 37:521-523.

Macedo-Ribeiro S, Cortes L, Maciel P, Carvalho AL (2009) Nucleocytoplasmic shuttling activity of ataxin-3. PLoS One 4:e5834.

Maciel P, Costa MC, Ferro A, Rousseau M, Santos CS, Gaspar C, Barros J, Rouleau GA, Coutinho P, Sequeiros J (2001) Improvement in the molecular diagnosis of Machado-Joseph disease. Arch Neurol 58:1821-1827.

Maciel P, Gaspar C, DeStefano AL, Silveira I, Coutinho P, Radvany J, Dawson DM, Sudarsky L, Guimaraes J, Loureiro JE, et al., (1995) Correlation between CAG repeat length and clinical features in Machado-Joseph disease. Am J Hum Genet 57:54-61.

Martindale D, Hackam A, Wieczorek A, Ellerby L, Wellington C, McCutcheon K, Singaraja R, Kazemi-Esfarjani P, Devon R, Kim SU, Bredesen DE, Tufaro F, Hayden MR (1998) Length of huntingtin and its polyglutamine tract influences localization and frequency of intracellular aggregates. Nat Genet 18:150-154.

Maruyama H, Nakamura S, Matsuyama Z, Sakai T, Doyu M, Sobue G, Seto M, Tsujihata M, Oh-i T, Nishio T, et al., (1995) Molecular features of the CAG repeats and clinical manifestation of Machado-Joseph disease. Hum Mol Genet 4:807-812.

Masino L, Musi V, Menon RP, Fusi P, Kelly G, Frenkiel TA, Trottier Y, Pastore A (2003) Domain architecture of the polyglutamine protein ataxin-3: a globular domain followed by a flexible tail. FEBS Lett 549:21-25.

Matos CA, de Macedo-Ribeiro S, Carvalho AL (2011) Polyglutamine diseases: The special case of ataxin-3 and Machado-Joseph disease. Prog Neurobiol.

Matsumoto M, Yada M, Hatakeyama S, Ishimoto H, Tanimura T, Tsuji S, Kakizuka A, Kitagawa M, Nakayama KI (2004) Molecular clearance of ataxin-3 is regulated by a mammalian E4. Embo J 23:659-669.

Mauri PL, Riva M, Ambu D, De Palma A, Secundo F, Benazzi L, Valtorta M, Tortora P, Fusi P (2006) Ataxin-3 is subject to autolytic cleavage. Febs J 273:4277-4286.

McCampbell A, Taylor JP, Taye AA, Robitschek J, Li M, Walcott J, Merry D, Chai Y, Paulson H, Sobue G, Fischbeck KH (2000) CREB-binding protein sequestration by expanded polyglutamine. Hum Mol Genet 9:2197-2202.
Menzies FM, Huebener J, Renna M, Bonin M, Riess O, Rubinsztein DC (2010) Autophagy induction reduces mutant ataxin-3 levels and toxicity in a mouse model of spinocerebellar ataxia type 3. Brain 133:93-104.

Michalik A, Van Broeckhoven C (2003) Pathogenesis of polyglutamine disorders: aggregation revisited. Hum Mol Genet 12 Spec No 2:R173-186.

Miller VM, Nelson RF, Gouvion CM, Williams A, Rodriguez-Lebrón E, Harper SQ, Davidson BL, Rebagliati MR, Paulson HL (2005) CHIP suppresses polyglutamine aggregation and toxicity in vitro and in vivo. J Neurosci 25:9152-9161.

Miller VM, Xia H, Marrs GL, Gouvion CM, Lee G, Davidson BL, Paulson HL (2003) Allele-specific silencing of dominant disease genes. Proc Natl Acad Sci U S A 100:7195-7200.

Minamiyama M, Katsuno M, Adachi H, Waza M, Sang C, Kobayashi Y, Tanaka F, Doyu M, Inukai A, 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.

Morfini G, Pigino G, Brady ST (2005) Polyglutamine expansion diseases: failing to deliver. Trends Mol Med 11:64-70.

Mueller T, Breuer P, Schmitt I, Walter J, Evert BO, Wullner U (2009) CK2-dependent phosphorylation determines cellular localization and stability of ataxin-3. Hum Mol Genet 18:3334-3343.

Munoz E, Rey MJ, Mila M, Cardozo A, Ribalta T, Tolosa E, Ferrer I (2002) Intranuclear inclusions, neuronal loss and CAG mosaicism in two patients with Machado-Joseph disease. J Neurol Sci 200:19-25.

Nagai Y, Fujikake N, Ohno K, Higashiyama H, Popiel HA, Rahadian J, Yamaguchi M, Strittmatter WJ, Burke JR, Toda T (2003) Prevention of polyglutamine oligomerization and neurodegeneration by the peptide inhibitor QBPI in Drosophila. Hum Mol Genet 12:1253-1259.

Nagai Y, Fujikake N, Popiel HA, Wada K (2010) Induction of molecular chaperones as a therapeutic strategy for the polyglutamine diseases. Curr Pharm Biotechnol 11:188-197.

Nagai Y, Inui T, Popiel HA, Fujikake N, Hasegawa K, Urade Y, Goto Y, Naiki H, Toda T (2007) A toxic monomeric conformer of the polyglutamine protein. Nat Struct Mol Biol 14:332-340.

Nascimento-Ferreira I, Santos-Ferreira T, Sousa-Ferreira L, Auregan G, Onofre I, Alves S, Dufour N, Colomer Gould VF, Koeppen A, Deglon N, Pereira de Almeida L (2011) Overexpression of the autophagic beclin-1 protein clears mutant ataxin-3 and alleviates Machado-Joseph disease. Brain 134:1400-1415.

Nucifora FC, Jr., Sasaki M, Peters MF, Huang H, Cooper JK, Yamada M, Takahashi H, Tsuji S, Troncoso J, Dawson VL, Dawson TM, Ross CA (2001) Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. Science 291:2423-2428.

Okuro M, Fujiki N, Kotorii N, Ishimaru Y, Sokoloff P, Nishino S (2010) Effects of paraxanthine and caffeine on sleep, locomotor activity, and body temperature in orexin/ataxin-3 transgenic narcoleptic mice. Sleep 33:930-942.
Ona VO, Li M, Vonsattel JP, Andrews LJ, Khan SQ, Chung WM, Frey AS, Menon AS, Li XJ, Stieg PE, Yuan J, Penney JB, Young AB, Cha JH, Friedlander RM (1999) Inhibition of caspase-1 slows disease progression in a mouse model of Huntington's disease. Nature 399:263-267.

Orrenius S, Zhivotovsky B, Nicotera P (2003) Regulation of cell death: the calcium-apoptosis link. Nat Rev Mol Cell Biol 4:552-565.

Padiath QS, Srivastava AK, Roy S, Jain S, Brahmachari SK (2005) Identification of a novel 45 repeat unstable allele associated with a disease phenotype at the MJD1/SCA3 locus. Am J Med Genet B Neuropsychiatr Genet 138B:124-126.

Panov AV, Gutekunst CA, Leavitt BR, Hayde MR, Burke JR, Strittmatter WJ, Greenamyre JT (2002) Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. Nat Neurosci 5:731-736.

Paulson HL (1999) Protein fate in neurodegenerative proteinopathies: polyglutamine diseases join the (mis)fold. Am J Hum Genet 64:339-345.

Paulson HL, Das SS, Crino PB, Perez MK, Patel SC, Gotsdiner D, Fischbeck KH, Pittman RN (1997a) Machado-Joseph disease gene product is a cytoplasmic protein widely expressed in brain. Ann Neurol 41:453-462.

Paulson HL, Perez MK, Trottier Y, Trojanowski JQ, Subramony SH, Das SS, Vig P, Mandel JL, Fischbeck KH, Pittman RN (1997b) Intranuclear inclusions of expanded polyglutamine protein in spinocerebellar ataxia type 3. Neuron 19:333-344.

Perez MK, Paulson HL, Pendse SJ, Saionz SJ, Bonini NM, Pittman RN (1998) Recruitment and the role of nuclear localization in polyglutamine-mediated aggregation. J Cell Biol 143:1457-1470.

Pfister EL, Kennington L, Straubhaar J, Wagh S, Liu W, DiFiglia M, Landwehrmeyer B, Vonsattel JP, Zamore PD, Aronin N (2009) Five siRNAs targeting three SNPs may provide therapy for three-quarters of Huntington's disease patients. Curr Biol 19:774-778.

Pickford F, Masliah E, Britschgi M, Lucin K, Narasimhan R, Jaeger PA, Small S, Spencer B, Rockenstein E, Levine B, Wyss-Coray T (2008) The autophagy-related protein beclin 1 shows reduced expression in early Alzheimer disease and regulates amyloid beta accumulation in mice. J Clin Invest 118:2190-2199.

Poirier MA, Li H, Macosko J, Cai S, Amzel M, Ross CA (2002) Huntingtin spheroids and protofibrils as precursors in polyglutamine fibrilization. J Biol Chem 277:41032-41037.

Prediger RD (2010) Effects of caffeine in Parkinson's disease: from neuroprotection to the management of motor and non-motor symptoms. J Alzheimers Dis 20 Suppl 1:S205-220.

Qin Q, Inatome R, Hotta A, Kojima M, Yamamura H, Hirai H, Yoshizawa T, Tanaka H, Fukami K, Yanagi S (2006) A novel GTPase, CRAG, mediates promyelocytic leukemia protein-associated nuclear body formation and degradation of expanded polyglutamine protein. J Cell Biol 172:497-504.

Ralph GS, Radcliffe PA, Day DM, Cathy JM, Leroux MA, Lee DC, Wong LF, Bilsland LG, Greensmith L, Kingsman SM, Mitrophanous KA, Mazarakis ND, Azzouz M (2005)
Silencing mutant SOD1 using RNAi protects against neurodegeneration and extends survival in an ALS model. Nat Med 11:429-433.

Ranum LP, Lundgren JK, Schut LJ, Ahrens MJ, Perlman S, Aita J, Bird TD, Gomez C, Orr HT (1995) Spinocerebellar ataxia type 1 and Machado-Joseph disease: incidence of CAG expansions among adult-onset ataxia patients from 311 families with dominant, recessive, or sporadic ataxia. Am J Hum Genet 57:603-608.

Raoul C, Abbas-Terki T, Bensadoun JC, Guillot S, Haase G, Szulc J, Henderson CE, Aebischer P (2005) Lentiviral-mediated silencing of SOD1 through RNA interference retards disease onset and progression in a mouse model of ALS. Nat Med 11:423-428.

Ravikumar B, Vacher C, Berger Z, Davies JE, Luo S, Oroz LG, Scaravilli F, Easton DF, Duden R, O’Kane CJ, Rubinsztein DC (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.

Riess O, Rub U, Pastore A, Bauer P, Schols L (2008) SCA3: neurological features, pathogenesis and animal models. Cerebellum 7:125-137.

Riley BE, Orr HT (2006) Polyglutamine neurodegenerative diseases and regulation of transcription: assembling the puzzle. Genes Dev 20:2183-2192.

Robertson AL, Headey SJ, Saunders HM, Ecroyd H, Scanlon MJ, Carver JA, Bottomley SP (2010) Small heat-shock proteins interact with a flanking domain to suppress polyglutamine aggregation. Proc Natl Acad Sci U S A 107:10424-10429.

Rodrigues AJ, do Carmo Costa M, Silva TL, Ferreira D, Bajanca F, Logarinho E, Maciel P (2010) Absence of ataxin-3 leads to cytoskeletal disorganization and increased cell death. Biochim Biophys Acta 1803:1154-1163.

Rodrigues AJ, Neves-Carvalho A, Ferro A, Rokka A, Corthals G, Logarinho E, Maciel P (2009) ATX-3, CDC-48 and UBXN-5: a new trimolecular complex in Caenorhabditis elegans. Biochem Biophys Res Commun 386:575-581.

Rodriguez-Lebron E, Denovan-Wright EM, Nash K, Lewin AS, Mandel RJ (2005) Intrastriatal rAAV-mediated delivery of anti-huntingtin shRNAs induces partial reversal of disease progression in R6/1 Huntington’s disease transgenic mice. Mol Ther 12:618-633.

Rosenberg RN (1992) Machado-Joseph disease: an autosomal dominant motor system degeneration. Mov Disord 7:193-203.

Ross CA (1997) Intranuclear neuronal inclusions: a common pathogenic mechanism for glutamine-repeat neurodegenerative diseases? Neuron 19:1147-1150.

Ross CA, Poirier MA (2005) Opinion: What is the role of protein aggregation in neurodegeneration? Nat Rev Mol Cell Biol 6:891-898.

Ross CA, Poirier MA, Wanker EE, Amzel M (2003) Polyglutamine fibrillogenesis: the pathway unfolds. Proc Natl Acad Sci U S A 100:1-3.

Rub U, Brunt ER, Deller T (2008) New insights into the pathoanatomy of spinocerebellar ataxia type 3 (Machado-Joseph disease). Curr Opin Neurol 21:111-116.

Rub U, Brunt ER, Petrasch-Parwez E, Schols L, Theegarten D, Auburger G, Seidel K, Schultz C, Gierga K, Paulson H, van Broeckhoven C, Deller T, de Vos RA (2006a)
Degeneration of ingestion-related brainstem nuclei in spinocerebellar ataxia type 2, 3, 6 and 7. Neuropathol Appl Neurobiol 32:635-649.

Rub U, de Vos RA, Brunt ER, Sebesteny T, Schols L, Auburger G, Bohl J, Ghebremedhin E, Gierga K, Seidel K, den Dunnen W, Heinsen H, Paulson H, Deller T (2006b) Spinocerebellar ataxia type 3 (SCA3): thalamic neurodegeneration occurs independently from thalamic ataxin-3 immunopositive neuronal intranuclear inclusions. Brain Pathol 16:218-227.

Sanchez I, Mahlke C, Yuan J (2003) Pivotal role of oligomerization in expanded polyglutamine neurodegenerative disorders. Nature 421:373-379.

Saudou F, Finkbeiner S, Devys D, Greenberg ME (1998) Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. Cell 95:55-66.

Scaglione KM, Zavodszky E, Todi SV, Patury S, Xu P, Rodriguez-Lebron E, Fischer S, Konen J, Djarmati A, Peng J, Gestwicki JE, Paulson HL (2011) Ube2w and Ataxin-3 Coordinately Regulate the Ubiquitin Ligase CHIP. Mol Cell 43:599-612.

Schaffar G, Breuer P, Boteva R, Behrends C, Tzvetkov N, Strippel N, Sakahira H, Siegers K, Hayer-Hartl M, Hartl FU (2004) Cellular toxicity of polyglutamine expansion proteins: mechanism of transcription factor deactivation. Mol Cell 15:95-105.

Scheel H, Tomiuk S, Hofmann K (2003) Elucidation of ataxin-3 and ataxin-7 function by integrative bioinformatics. Hum Mol Genet 12:2845-2852.

Schilling B, Gafni J, Torcassi C, Cong X, Row RH, LaFevre-Bernt MA, Cusack MP, Ratovitski T, Hirschhorn R, Ross CA, Gibson BW, Ellerby LM (2006) Huntingtin phosphorylation sites mapped by mass spectrometry. Modulation of cleavage and toxicity. J Biol Chem 281:23686-23697.

Schilling G, Becher MW, Sharp AH, Jinnah HA, Duan K, Kotzuk JA, Slunt HH, Ratovitski T, Cooper JK, Jenkins NA, Copeland NG, Price DL, Ross CA, Borchelt DR (1999) Intranuclear inclusions and neuritic aggregates in transgenic mice expressing a mutant N-terminal fragment of huntingtin. Hum Mol Genet 8:397-407.

Schmidt T, Landwehrmeyer GB, Schmitt I, Trotter T, Auburger G, Laccone F, Klockgether T, Volpel M, Epplen JT, Schols L, Riess O (1998) An isoform of ataxin-3 accumulates in the nucleus of neuronal cells in affected brain regions of SCA3 patients. Brain Pathol 8:669-679.

Schollefield J, Greenberg LJ, Weinberg MS, Arbuthnot PB, Abdelgany A, Wood MJ (2009) Design of RNAi hairpins for mutation-specific silencing of ataxin-7 and correction of a SCA7 phenotype. PLoS One 4:e7232.

Schols L, Bauer P, Schmidt T, Schulte T, Riess O (2004) Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. Lancet Neurol 3:291-304.

Schulte J, Sepp KJ, Wu C, Hong P, Littleton JT (2011) High-Content Chemical and RNAi Screens for Suppressors of Neurotoxicity in a Huntington's Disease Model. PLoS One 6:e23841.

Schulz JB, Borkert J, Wolf S, Schmitz-Hubsch T, Rakowicz M, Mariotti C, Schols L, Timmann D, van de Warrenburg B, Durr A, Pandolfo M, Kang JS, Mandly AG, Nagele T, Grisoli M, Boguslawska R, Bauer P, Klockgether T, Hauser TK (2010) Visualization,
quantification and correlation of brain atrophy with clinical symptoms in spinocerebellar ataxia types 1, 3 and 6. Neuroimage 49:158-168.

Seidel K, den Dunnen WF, Schultz C, Paulson H, Frank S, de Vos RA, Brunt ER, Deller T, Kampinga HH, Rub U (2010) Axonal inclusions in spinocerebellar ataxia type 3. Acta Neuropathol 120:449-460.

Shen L, Tang JG, Tang BS, Jiang H, Zhao GH, Xia K, Zhang YH, Cai F, Tan LM, Pan Q (2005) Research on screening and identification of proteins interacting with ataxin-3. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 22:242-247.

Shibata M, Lu T, Furuya T, Degterev A, Mizushima N, Yoshimori T, MacDonald M, Yankner B, Yuan J (2006) Regulation of intracellular accumulation of mutant Huntingtin by Beclin 1. J Biol Chem 281:14474-14485.

Shimohata M, Shimohata T, Igarashi S, Naruse S, Tsuji S (2005) Interference of CREB-dependent transcriptional activation by expanded polyglutamine stretches--augmentation of transcriptional activation as a potential therapeutic strategy for polyglutamine diseases. J Neurochem 93:654-663.

Shimohata T, Nakajima T, Yamada M, Uchida C, Onodera O, Naruse S, Kimura T, Koide R, Nozaki K, Sano Y, Ishiguro H, Sakoe K, Ooshima T, Sato A, Ikeuchi T, Oyake M, Sato T, Aoyagi Y, Hozumi I, Nagatsu T, Takiyama Y, Nishizawa M, Goto J, Kanazawa I, Davidson I, Tanese N, Takahashi H, Tsuji S (2000a) Expanded polyglutamine stretches interact with TAFII130, interfering with CREB-dependent transcription. Nat Genet 26:29-36.

Shimohata T, Onodera O, Tsuji S (2000b) Interaction of expanded polyglutamine stretches with nuclear transcription factors leads to aberrant transcriptional regulation in polyglutamine diseases. Neuropathology 20:326-333.

Sittler A, Lurz R, Lueder G, Priller J, Lehrach H, Hayer-Hartl MK, Hartl FU, Wanker EE (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.

Soong BW, Paulson HL (2007) Spinocerebellar ataxias: an update. Curr Opin Neurol 20:438-446.

Steffan JS, Bodai L, Pallos J, Poelman M, McCampbell A, Apostol BL, Kazantsev A, Schmidt E, Zhu YZ, Greenwald M, Kurokawa R, Housman DE, Jackson GR, Marsh JL, Thompson LM (2001) Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in Drosophila. Nature 413:739-743.

Stevanin G, Cancel G, Durr A, Chneiweiss H, Dubourg O, Weissbach J, Cann HM, Agid Y, Brice A (1995) The gene for spinal cerebellar ataxia 3 (SCA3) is located in a region of approximately 3 cM on chromosome 14q24.3-q32.2. Am J Hum Genet 56:193-201.

Stott K, Blackburn JM, Butler PJ, Perutz M (1995) Incorporation of glutamine repeats makes protein oligomerize: implications for neurodegenerative diseases. Proc Natl Acad Sci U S A 92:6509-6513.

Sudarsky L, Coutinho P (1995) Machado-Joseph disease. Clin Neurosci 3:17-22.
Szebenyi G, Morfini GA, Babcock A, Gould M, Selkoe K, Stenoien DL, Young M, Faber PW, MacDonald ME, McPhaul MJ, Brady ST (2003) Neuropathogenic forms of huntingtin and androgen receptor inhibit fast axonal transport. Neuron 40:41-52.

Tait D, Riccio M, Sittler A, Scherzinger E, Santi S, Ognibene A, Maraldi NM, Lehrach H, Wanker EE (1998) Ataxin-3 is transported into the nucleus and associates with the nuclear matrix. Hum Mol Genet 7:991-997.

Takahashi J, Tanaka J, Arai K, Funata N, Hattori T, Fukuda T, Fujigasaki H, Uchihara T (2001) Recruitment of nonexpanded polyglutamine proteins to intranuclear aggregates in neuronal intranuclear hyaline inclusion disease. J Neuropathol Exp Neurol 60:369-376.

Takahashi T, Katada S, Onodera O (2010) Polyglutamine diseases: where does toxicity come from? what is toxicity? where are we going? J Mol Cell Biol 2:180-191.

Takahashi T, Kikuchi S, Katada S, Nagai Y, Nishizawa M, Onodera O (2008) Soluble polyglutamine oligomers formed prior to inclusion body formation are cytotoxic. Hum Mol Genet 17:345-356.

Takahashi-Fujigasaki J, Breidert T, Fujigasaki H, Duyckaerts C, Camonis JH, Brice A, Lebre AS (2011) Amyloid precursor-like protein 2 cleavage contributes to neuronal intranuclear inclusions and cytotoxicity in spinocerebellar ataxia-7 (SCA7). Neurobiol Dis 41:33-42.

Takiyama Y, Nishizawa M, Tanaka H, Kawashima S, Sakamoto H, Karube Y, Shimazaki H, Soutome M, Endo K, Ohta S, et al., (1993) The gene for Machado-Joseph disease maps to human chromosome 14q. Nat Genet 4:300-304.

Tanaka M, Machida Y, Nukina N (2005) A novel therapeutic strategy for polyglutamine diseases by stabilizing aggregation-prone proteins with small molecules. J Mol Med 83:343-352.

Tanaka M, Morishima I, Akagi T, Hashikawa T, Nukina N (2001) Intra- and intermolecular beta-pleated sheet formation in glutamine-repeat inserted myoglobin as a model for polyglutamine diseases. J Biol Chem 276:45470-45475.

Tang TS, Slow E, Lupu V, Stavrovskaya IG, Sugimori M, Linas R, Kristal BS, Hayden MR, Bezprowzanny I (2005) Disturbed Ca2+ signaling and apoptosis of medium spiny neurons in Huntington's disease. Proc Natl Acad Sci U S A 102:2602-2607.

Tang TS, Tu H, Chan EY, Maximov A, Wang Z, Wellington CL, Hayden MR, Bezprowzanny I (2003) Huntingtin and huntingtin-associated protein 1 influence neuronal calcium signaling mediated by inositol-(1,4,5) triphosphate receptor type 1. Neuron 39:227-239.

Tao RS, Fei EK, Ying Z, Wang HF, Wang GH (2008) Casein kinase 2 interacts with and phosphorylates ataxin-3. Neurosci Bull 24:271-277.

Tarlac V, Storey E (2003) Role of proteolysis in polyglutamine disorders. J Neurosci Res 74:406-416.

Taroni F, DiDonato S (2004) Pathways to motor incoordination: the inherited ataxias. Nat Rev Neurosci 5:641-655.

Taylor JP, Hardy J, Fischbeck KH (2002) Toxic proteins in neurodegenerative disease. Science 296:1991-1995.
Taylor JP, Tanaka F, Robitschek J, Sandoval CM, Taye A, Markovic-Plese S, Fischbeck KH (2003) Aggresomes protect cells by enhancing the degradation of toxic polyglutamine-containing protein. Hum Mol Genet 12:749-757.

Thakur AK, Wetzel R (2002) Mutational analysis of the structural organization of polyglutamine aggregates. Proc Natl Acad Sci U S A 99:17014-17019.

Todi SV, Winborn BJ, Scaglione KM, Blount JR, Travis SM, Paulson HL (2009) Ubiquitination directly enhances activity of the deubiquitinating enzyme ataxin-3. Embo J 28:372-382.

Todi SV, Paulson HL (2011) Balancing act: deubiquitinating enzymes in the nervous system. Trends Neurosci.

Torashima T, Koyama C, Iizuka A, Mitsumura K, Takayama K, Yanagi S, Oue M, Yamaguchi H, Hirai H (2008) Lentivector-mediated rescue from cerebellar ataxia in a mouse model of spinocerebellar ataxia. EMBO Rep 9:393-399.

Trottier Y, Cancel G, An-Gourfinkel I, Lutz Y, Weber C, Brice A, Hirsch E, Mandel JL (1998) Heterogeneous intracellular localization and expression of ataxin-3. Neurobiol Dis 5:335-347.

Tsuda H, Jafar-Nejad H, Patel AJ, Sun Y, Chen HK, Rose MF, Venken KJ, Botas J, Orr HT, Bellen HJ, Zoghbi HY (2005) The AXH domain of Ataxin-1 mediates neurodegeneration through its interaction with Gfi-1/Senseless proteins. Cell 122:633-644.

Uchihara T, Fujigasaki H, Koyano S, Nakamura A, Yagishita S, Iwabuchi K (2001) Non-expanded polyglutamine proteins in intranuclear inclusions of hereditary ataxias--triple-labeling immunofluorescence study. Acta Neuropathol 102:149-152.

Ueda H, Goto J, Hashida H, Lin X, Oyanagi K, Kawano H, Zoghbi HY, Kanazawa I, Okazawa H (2002) Enhanced SUMOylation in polyglutamine diseases. Biochem Biophys Res Commun 293:307-313.

van Bilsen PH, Jaspers L, Lombardi MS, Odekerken JC, Burright EN, Kaemmerer WF (2008) Identification and allele-specific silencing of the mutant huntingtin allele in Huntington's disease patient-derived fibroblasts. Hum Gene Ther 19:710-719.

Vellai T (2009) Autophagy genes and ageing. Cell Death Differ 16:94-102.

Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, Rowan MJ, Selkoe DJ (2002) Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature 416:535-539.

Walsh R, Storey E, Stefani D, Kelly L, Turnbull V (2005) The roles of proteolysis and nuclear localisation in the toxicity of the polyglutamine diseases. A review. Neurotox Res 7:43-57.

Wang H, Jia N, Fei E, Wang Z, Liu C, Zhang T, Fan J, Wu M, Chen L, Nukina N, Zhou J, Wang G (2007) p45, an ATPase subunit of the 19S proteasome, targets the polyglutamine disease protein ataxin-3 to the proteasome. J Neurochem 101:1651-1661.

Wang Q, Li L, Ye Y (2006) Regulation of retrotranslocation by p97-associated deubiquitinating enzyme ataxin-3. J Cell Biol 174:963-971.

Wanker EE (2000) Protein aggregation and pathogenesis of Huntington's disease: mechanisms and correlations. Biol Chem 381:937-942.
Warrick JM, Morabito LM, Bilen J, Gordesky-Gold B, Faust LZ, Paulson HL, Bonini NM (2005) Ataxin-3 suppresses polyglutamine neurodegeneration in Drosophila by a ubiquitin-associated mechanism. Mol Cell 18:37-48.

Wellington CL, Ellerby LM, Hackam AS, Margolis RL, Trifiro MA, Singaraja R, McCutcheon K, Salvesen GS, Propp SS, Broom M, Rowland KJ, Zhang T, Rasper D, Roy S, Thornberry N, Pinsky L, Kakizuka A, Ross CA, Nicholson DW, Bredesen DE, Hayden MR (1998) Caspase cleavage of gene products associated with triplet expansion disorders generates truncated fragments containing the polyglutamine tract. J Biol Chem 273:9158-9167.

Williams A, Jahreiss L, Sarkar S, Saiki S, Menzies FM, Ravikumar B, Rubinsztein DC (2006) Aggregate-prone proteins are cleared from the cytosol by autophagy: therapeutic implications. Curr Top Dev Biol 76:89-101.

Winborn BJ, Travis SM, Todi SV, Scaglione KM, Xu P, Williams AJ, Cohen RE, Peng J, Paulson HL (2008) The deubiquitinating enzyme ataxin-3, a polyglutamine disease protein, edits Lys63 linkages in mixed linkage ubiquitin chains. J Biol Chem 283:26436-26443.

Wolfgang WJ, Miller TW, Webster JM, Huston JS, Thompson LM, Marsh JL, Messer A (2005) Suppression of Huntington's disease pathology in Drosophila by human single-chain Fv antibodies. Proc Natl Acad Sci U S A 102:11563-11568.

Wu J, Tang T, Bezprozvanny I (2006) Evaluation of clinically relevant glutamate pathway inhibitors in in vitro model of Huntington's disease. Neurosci Lett 407:219-223.

Xia H, Mao Q, Eliason SL, Harper SQ, Martins IH, Orr HT, Paulson HL, Yang L, Kotin RM, Davidson BL (2004) RNAi suppresses polyglutamine-induced neurodegeneration in a model of spinocerebellar ataxia. Nat Med 10:816-820.

Xie Y, Hayden MR, Xu B (2010) BDNF overexpression in the forebrain rescues Huntington's disease phenotypes in YAC128 mice. J Neurosci 30:14708-14718.

Yamada M, Hayashi S, Tsuji S, Takahashi H (2001) Involvement of the cerebral cortex and autonomic ganglia in Machado-Joseph disease. Acta Neuropathol 101:140-144.

Yamada M, Sato T, Tsuji S, Takahashi H (2008) CAG repeat disorder models and human neuropathology: similarities and differences. Acta Neuropathol 115:71-86.

Yamada M, Tsuji S, Takahashi H (2000) Pathology of CAG repeat diseases. Neuropathology 20:319-325.

Yamamoto Y, Hasegawa H, Tanaka K, Kakizuka A (2001) Isolation of neuronal cells with high processing activity for the Machado-Joseph disease protein. Cell Death Differ 8:871-873.

Yamanaka T, Miyazaki H, Oyama F, Kurosawa M, Washizu C, Doi H, Nukina N (2008) Mutant Huntingtin reduces HSP70 expression through the sequestration of NF-Y transcription factor. Embo J 27:827-839.

Yoshida H, Yoshizawa T, Shibasaki F, Shoji S, Kanazawa I (2002) Chemical chaperones reduce aggregate formation and cell death caused by the truncated Machado-Joseph disease gene product with an expanded polyglutamine stretch. Neurobiol Dis 10:88-99.

Young JE, Gouw L, Propp S, Sopher BL, Taylor J, Lin A, Hermel E, Logvinova A, Chen SF, Chen S, Bredesen DE, Truant R, Ptacek LJ, La Spada AR, Ellerby LM (2007)
Proteolytic cleavage of ataxin-7 by caspase-7 modulates cellular toxicity and transcriptional dysregulation. J Biol Chem 282:30150-30160.

Yu YC, Kuo CL, Cheng WL, Liu CS, Hsieh M (2009) Decreased antioxidant enzyme activity and increased mitochondrial DNA damage in cellular models of Machado-Joseph disease. J Neurosci Res 87:1884-1891.

Zala D, Bensadoun JC, Pereira de Almeida L, Leavitt BR, Gutekunst CA, Aebischer P, Hayden MR, Deglon N (2004) Long-term lentiviral-mediated expression of ciliary neurotrophic factor in the striatum of Huntington's disease transgenic mice. Exp Neurol 185:26-35.

Zhang X, Smith DL, Meriin AB, Engemann S, Russel DE, Roark M, Washington SL, Maxwell MM, Marsh JL, Thompson LM, Wanker EE, Young AB, Housman DE, Bates GP, Sherman MY, Kazantsev AG (2005) A potent small molecule inhibits polyglutamine aggregation in Huntington's disease neurons and suppresses neurodegeneration in vivo. Proc Natl Acad Sci U S A 102:892-897.

Zhang Y, Engelman J, Friedlander RM (2009) Allele-specific silencing of mutant Huntington's disease gene. J Neurochem 108:82-90.

Zoghbi HY, Orr HT (2000) Glutamine repeats and neurodegeneration. Annu Rev Neurosci 23:217-247.

Zoghbi HY, Orr HT (2009) Pathogenic mechanisms of a polyglutamine-mediated neurodegenerative disease, spinocerebellar ataxia type 1. J Biol Chem 284:7425-7429.

Zuccato C, Ciammola A, Rigamonti D, Leavitt BR, Goffredo D, Conti L, MacDonald ME, Friedlander RM, Silani V, Hayden MR, Timmusk T, Sipione S, Cattaneo E (2001) Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. Science 293:493-498.
The purpose of this book has been to depict as many biochemical, genetic and molecular advances as possible, in the vast field of the spinocerebellar ataxias.

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