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Machado-Joseph Disease / Spinocerebellar Ataxia Type 3

Clévio Nóbrega[1] and Luís Pereira de Almeida[1,2]
[1]*CNC - Center for Neurosciences & Cell Biology, University of Coimbra;*
[2]*Faculty of Pharmacy, University of Coimbra, Coimbra, Portugal*

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 subscore (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).

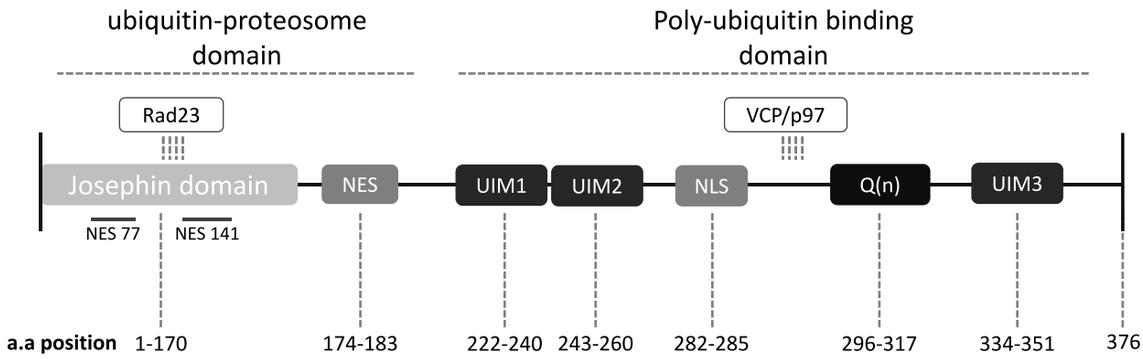

Fig. 1. **Structure of the ataxin-3 protein.** Ataxin-3 is mainly composed of a highly conserved N-terminal domain (Josephin), encoding a predicted ubiquitin-specific protease with the catalytic triad of amino acids (Cys14, His119, and Asn136), a nuclear export signal (NES), followed by a flexible C-terminal 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 (Tait 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. Ultra structurally, 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.

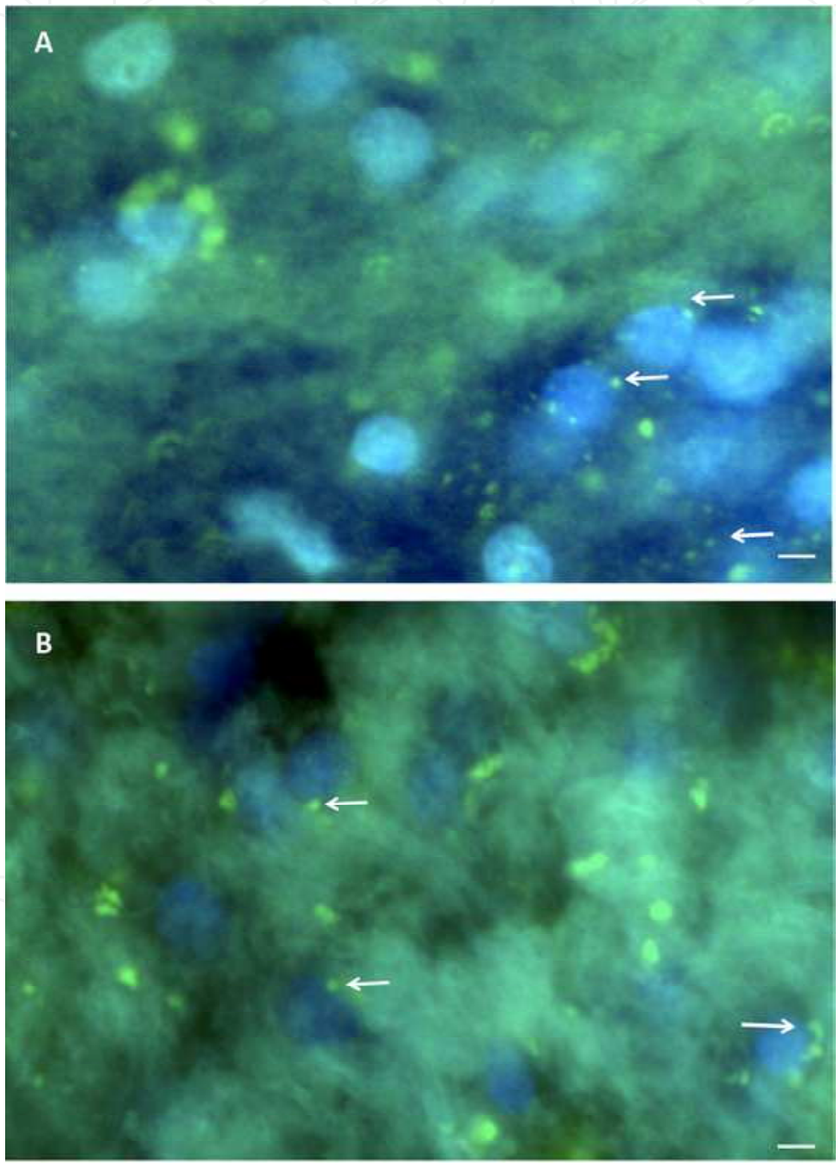

Fig. 2. **Intranuclear inclusions in the striatum of Machado Joseph disease patients.** (A) Fluorescence analysis shows ataxin-3 reaction intranuclear inclusions (green) in the neurons of the striatum of postmortem brain samples of MJD patients (white arrows). (B) Fluorescence microscopy analysis shows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

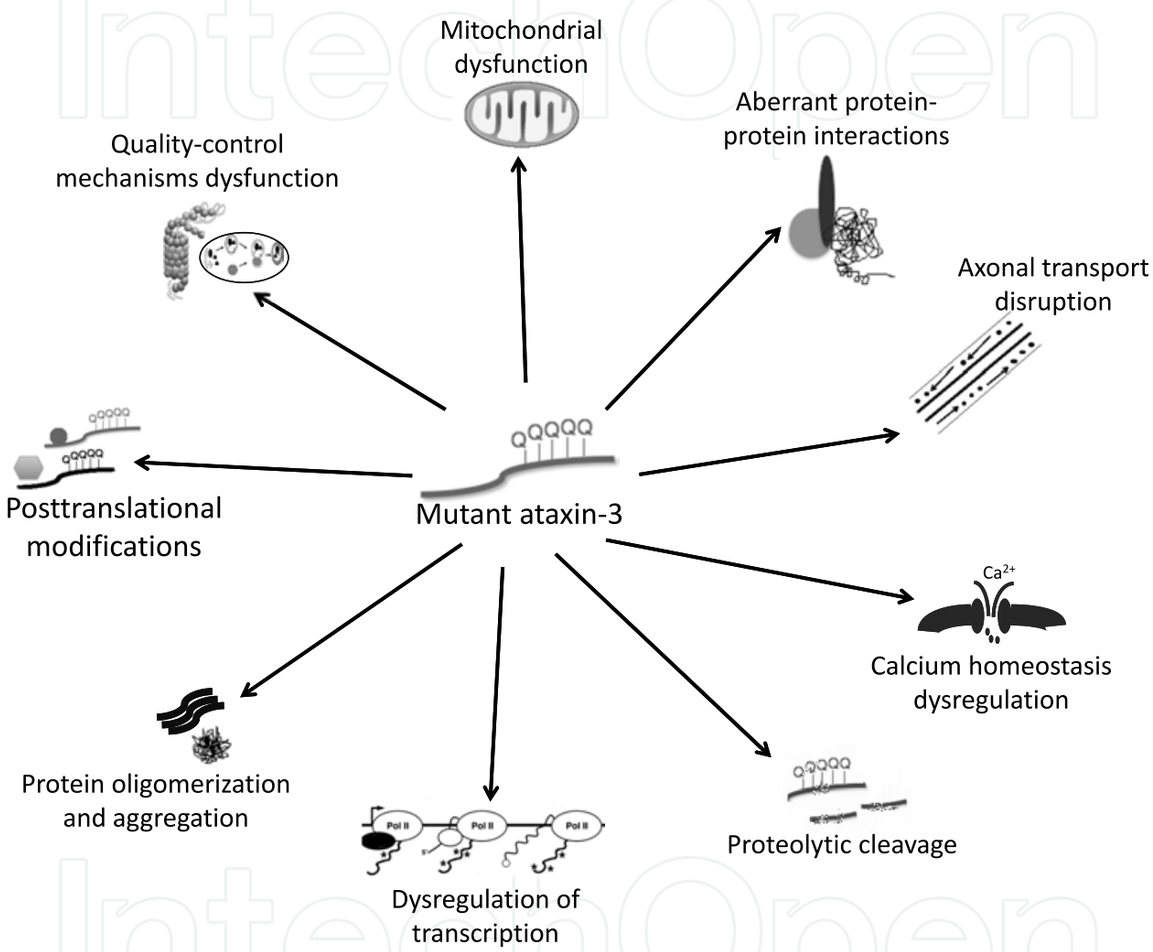

Fig. 3. **Mechanisms of pathogenesis in Machado-Joseph disease**. Several events and mechanisms could contribute to pathogenesis in MJD and other polyglutamine diseases. The presence of mutant ataxin-3 with an expanded tract in the cellular environment, triggers several events that lead to neurodegeneration in selective areas of the brain. For the neuronal cytoxicity 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 mjd1a 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-pallidoluysian atrophy, (Uchihara et al., 2001) and in neuronal intranuclear hyaline inclusion disease (Takahashi et al., 2001). It is also found in Marinesco 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 mechanism 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 (McCampbell 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 lymphoblast's 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 Ca2+ 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).

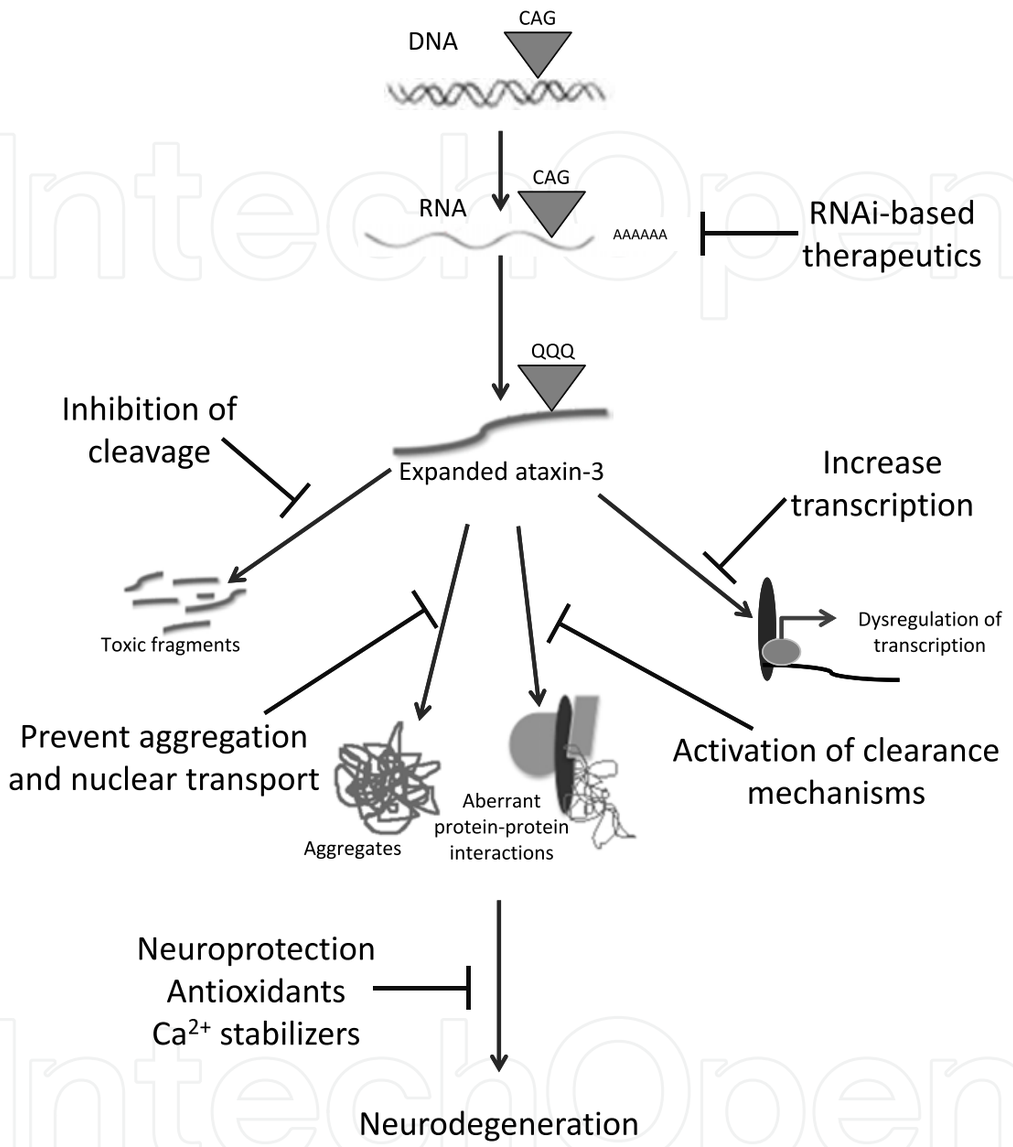

Fig. 4. **Potential therapeutic strategies to Machado-Joseph disease.** Expansion of the polyglutamine tract of ataxin-3 initiates a cascade of events that culminates with the accumulation of insoluble inclusions and degenerations in selected neurons. The strategies that can be used to treat MJD or other 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 bellow 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 esther improves motor coordination in a transgenic model of MJD (Menzies et al., 2010). The rapamycin esther 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; Sanchéz 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 esther	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^{2+} signaling, improved motor performance and prevented neuronal cell loss in pontine nuclei and *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_{2^*} and H_2O_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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Phone: +385 (51) 770 447
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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