REVIEW

Polyglutamine neurodegenerative diseases and regulation of transcription: assembling the puzzle

Brigit E. Riley^{1,3,4} and Harry T. Orr^{1,2,3,5}

¹Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota, Minneapolis, Minnesota 55455, USA; ²Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota 55455, USA;

³Institute of Human Genetics, University of Minnesota, Minneapolis, Minnesota 55455, USA

The polyglutamine disorders are a class of nine neurodegenerative disorders that are inherited gain-of-function diseases caused by expansion of a translated CAG repeat. Even though the disease-causing proteins are widely expressed, specific collections of neurons are more susceptible in each disease, resulting in characteristic patterns of pathology and clinical symptoms. One hypothesis poses that altered protein function is fundamental to pathogenesis, with protein context of the expanded polyglutamine having key roles in disease-specific processes. This review will focus on the role of the disease-causing polyglutamine proteins in gene transcription and the extent to which the mutant proteins induce disruption of transcription.

One of the intriguing developments in human genetics is the identification of a mutational mechanism apparently unique to the human genome, the expansion of unstable nucleotide repeats (Gatchel and Zoghbi 2005). Depending on the genetic context of the unstable repeat, the pathogenic mechanism underlying the disorder can be either a loss-of-function or gain-of-function mutation operating at either the RNA or protein level. A subclass of the unstable repeat disorders is caused by the expansion of an unstable CAG trinucleotide repeat located within the protein encoding region such that the repeat is translated into a stretch of glutamine residues; i.e., the polyglutamine diseases. Although rare as a group, the polyglutamine disorders represent the most common form of inherited neurodegenerative disease. At present, nine disorders make up this class of neurodegenerative disease (Table 1). Initially, it was argued that the genetic similarities among these disorders strongly supported the hypothesis that these disorders shared a common

mechanism of pathogenesis entirely dependent on the toxic properties of the polyglutamine tract. This typically centered on the enhanced ability of polyglutamine peptides to form intranuclear aggregates/inclusions (Ross and Poirer 2004). The presence of these aggregates/inclusions within the nuclei of affected neurons focused attention on the nucleus as the subcellular site important in pathogenesis. After much study, the concept of large aggregates/inclusions of mutant polyglutamine as the pathogenic species has become suspect (Arrasate et al. 2004). However, for many of the polyglutamine disorders, understanding events in the nucleus still remains crucial for comprehending pathogenesis.

Expansion of the polyglutamine tract is the trigger for pathogenesis. Yet, it likely does so by acting in concert with the other amino acids of the "host" protein (Orr 2001). This point is nicely illustrated by studies on SCA1 and AR/SBMA. In the case of SCA1, replacing single amino acids in ataxin-1 outside of its polyglutamine tract dramatically reduced the ability of mutant ataxin-1 (ataxin-1[82Q]) to cause disease in vivo (Klement et al. 1998; Emamian et al. 2003). In SBMA, androgen binding to the ligand-binding region in AR is critical for pathogenesis (Katsuno et al. 2002, 2003; Takeyama et al. 2002).

Central to the hypothesis of "host" protein amino acids having a fundamental role in pathogenesis is the concept that the normal function and protein interactions in which each polyglutamine-disease-associated protein participates are critical aspects of the pathogenic pathway. This review focuses on an examination of the evidence linking the disease-causing polyglutamine proteins to the regulation of transcription. Many transcriptional alterations have been reported early in disease progression for the various polyglutamine diseases (Sugars and Rubinshtein 2003). In addition, mutant polyglutamine proteins have been reported to interfere with a large number of transcription factors. However, it is very hard to sort out primary from secondary effects in these studies. In this review we center the discussion on those polyglutamine proteins where the evidence indi-

[Keywords: Gene expression; neurodegenerative disease; polyglutamine; transcription; trinucleotide repeats]

⁴Present address: Department of Biology, Stanford University, Stanford, CA 94305.

⁵Corresponding author.

E-MAIL orrxx002@umn.edu; FAX (612) 626-7031.

Article is online at <http://www.genesdev.org/cgi/doi/10.1101/gad.1436506>.

Table 1. *The polyglutamine family of neurodegenerative diseases*

Disease	Phenotypes	Gene locus	Protein	Protein subcellular location	Wild-type allele repeat number	Mutant allele repeat number
SBMA	Proximal muscle atrophy	Xq11-12	Androgen receptor	Nuclear and cytoplasmic	6–39	40–63
HD	Psychiatric, cognitive, motor abnormalities	4p16.3	Huntingtin	Cytoplasmic	6–34	36–121
SCA1	Ataxia	6p22-23	Ataxin-1	Nuclear (neurons)	8–44	39–83
SCA2	Ataxia	12q23-24	Ataxin-2	Cytoplasmic	13–33	32–77
SCA3/MJD	Ataxia	14q24-31	Ataxin-3	Cytoplasmic	12–40	54–89
SCA6	Ataxia	19p3	CACNA1A	Cell membrane	4–18	19–33
SCA7	Ataxia, retinal degeneration	3p12-21	Ataxin-7	Nuclear	4–35	37–306
SCA17	Ataxia	2q13	TATA-BP	Nuclear	29–42	47–55
DRPLA	Epilepsy, ataxia, dementia	12q	Atrophin-1	Cytoplasmic	6–36	49–84

cates they normally function to regulate transcription. It is reasoned such studies are more likely to provide mechanistic insight into dysfunctions induced by the disease-associated mutant forms of the polyglutamine proteins.

Precise spatial and temporal patterns of gene expression are crucial for normal development of all cells and tissues as well as the response of differentiated cells to changes in their environment. In the case of the latter point, there is no tissue whose proper function is more dependent on its ability to respond to changes in the environment than the brain. Coordinated transcription requires the synchronization of many events and mechanisms that depend on the regulated trafficking and interaction of numerous proteins. Such proteins include DNA-binding transcription factors, non-DNA-binding coregulators, and components of the basal RNA-polymerase apparatus. More recently, the fact that ubiquitin and the ubiquitin-proteasome system are important for proper control of transcription is becoming increasingly apparent. In addition to the components involved in transcription, eukaryotic gene expression consists of other multiprotein complexes that carry out the additional steps of premessenger RNA processing and export of mRNA to the cytoplasm. Rather than being discrete steps performed by distinct macromolecular complexes, the steps of gene expression are believed to form an extensive coupled network with proteins participating in more than one step (Maniatis and Reed 2002; Reed 2003).

It is important to note that many regulators of transcription contain glutamine-rich activation domains that are typical of an extensive family of highly conserved transcriptional activators. These glutamine-rich activation domains are an important class of protein-protein interacting motifs that enable transcription factors to interact with one another and thus regulate gene expression (Tanese and Tjian 1993). Moreover, of the three polyglutamine disorders (SBMA, SCA6, and SCA17) where the disease-causing mutation occurs within a protein with a known function, two of these proteins have a well-established function involving the regulation of gene expression. These are the androgen receptor (AR; a DNA-binding nuclear receptor) in the

case of SBMA and the TATA-binding protein (a DNA-binding component of the general transcription factor) in SCA17. It is with these two disorders that we start the discussion and proceed to those where the evidence in support of a direct role in transcriptional function/dysfunction is less clear.

SBMA: neurodegeneration linked to a nuclear receptor

Spinal bulbar muscular atrophy (SBMA, or Kennedy's disease) is an X-linked motor neuron disease caused by the expansion of a polyglutamine tract within the AR (La Spada et al. 1991). The AR is a nuclear receptor that regulates the expression of genes in response to the presence of androgens. Nuclear receptors are a family of transcription factors that switch between active and inactive states by the binding of a ligand to a conserved C-terminal ligand-binding domain (Mangelsdorf et al. 1995). In addition, nuclear receptors have a conserved DNA-binding domain for sequence-specific binding to the regulatory region of genes whose expression they regulate. Nuclear receptors also have a less-conserved activation domain in their N-terminal regions. The AR polyglutamine tract is located within the N-terminal activation domain. Normal, wild-type alleles are highly polymorphic, having 6–39 glutamine repeats. Expansion of the AR-polyglutamine tract to ≥ 40 repeats causes SBMA, an adult-onset neurodegenerative disease affecting brain stem and motor neurons. Although some SBMA patients show mild signs of partial androgen insensitivity (gynecomastia and testicular atrophy) they do not have a phenotype consistent with loss of AR function (testicular feminization). An interesting aspect of SBMA is that it essentially affects only males. In fact, there are reported cases of females who are homozygous for AR with an expanded polyglutamine tract (Schmidt et al. 2002). These individuals show very mild signs of SBMA, indicating perhaps a high androgen level is a critical aspect of SBMA pathogenesis.

In 2002, two reports appeared—one using a transgenic mouse model of SBMA (Katsuno et al. 2002) and the other a *Drosophila* model (Takeyama et al. 2002), in which the mutant phenotype was androgen dependent. In transgenic mice expressing intact AR with an ex-

panded polyglutamine tract, only males developed motor neuron disease that was rescued by castration. Moreover, upon administration of testosterone to female mutant AR transgenic mice, they developed disease. Both the mouse and fly studies were interpreted as demonstrating that binding of androgen to the polyglutamine-expanded AR and the subsequent translocation of AR to the nucleus, both aspects of normal AR function, were required for onset of motor neuron disease.

Subsequently, a study was performed in which the SBMA transgenic mice were treated with two androgen antagonists (Katsuno et al. 2003). One agent, leuprorelin, was found to be very effective in rescuing all aspects of the disease phenotype. Leuprorelin is a luteinizing releasing hormone agonist that reduces release of testosterone from the testis and thereby reduces circulating levels of testosterone. This result supported the concept that ligand-induced nuclear translocation of mutant AR is a crucial aspect of SBMA pathogenesis. The second drug used to treat the SBMA mice, flutamide, had no effect on motor neuron disease. Flutamide has a very high affinity for AR and functions as an androgen antagonist by competing with testosterone for binding to AR. While flutamide suppresses the androgen-dependent transactivation activity of AR, it does not reduce plasma testosterone nor does it block nuclear translocation of mutant AR in either the mouse or *Drosophila* (Katsuno et al. 2002, 2003; Takeyama et al. 2002). Thus, SBMA pathogenesis seems to be dependent on the translocation of mutant AR to the nucleus yet independent of ligand-induced activation of gene expression by AR.

SCA 17: neurodegeneration and the TATA-box-binding protein (TBP)

Expansion of the glutamine tract beyond 42 in the TBP results in an autosomal dominant form of spinocerebellar ataxia type 17 (SCA17) (Koide et al. 1999; Rolfs et al. 2003). SCA17 is a progressive neurodegenerative disease with an onset typically in midlife. In addition to ataxia, patients with SCA17 suffer from dementia and, in some cases, epilepsy. At a pathological level, SCA17 consists of marked cerebella atrophy and, to a lesser extent, atrophy of the cerebral cortex.

TBP has long been known to be a general transcription factor and a crucial component of the core transcriptional complex, TFIID, which plays two important roles in the initiation of transcription for most eukaryotic genes (Gill and Tjian 1992). Assembly of the TFIID complex is dependent on interactions between TBP and multiple TBP-associated factors. The TFIID complex is the first general transcription complex to bind to DNA, and this step is essential for initiating transcription by RNA polymerase II. TBP is the component of the TFIID complex that directs the complex to DNA by binding to the TATA-box. Which of these functions of TBP are disrupted by expansion of its polyglutamine tract associated with SCA17 is not known. Regardless, the fact that an expansion of the polyglutamine tract in TBP is associ-

ated with the neurodegenerative disease SCA17 strongly suggests disruption of an essential part of transcriptional initiation is at the heart of pathogenesis. Thus, of all of the polyglutamine disorders, SCA17 presents the clearest example of the paradox faced in understanding the molecular basis of each polyglutamine disease: How is it that a mutation in a widely expressed protein, and in some cases a protein with a function critical in many cell types, leads to a neurodegenerative disease that affects a restricted set of neurons? As we see from studies on SCA17, perhaps understanding the precise role of TBP in the TFIID/GTC complex in neurons will provide the answer.

SCA 7: a role in cell-specific chromatin structure

Similar to the other polyglutamine disorders, spinocerebellar ataxia type 7 (SCA7) is an autosomal dominant neurodegenerative disease (David et al. 1997). SCA7 is clinically unique in that it is the only polyglutamine disorder in which the retina is affected, eventually resulting in blindness (Enevoldson et al. 1994). Insight into the molecular basis of SCA7 has come largely from studies on the function of ataxin-7 in rod-photoreceptors.

It was recently observed that ataxin-7, the protein mutated in SCA7, is a subunit of the GCN5 histone acetyltransferase complexes TFIIIC (the TATA-binding protein-free TBP-associated factor-containing complex) and STAGA (the SPT3/TAF GCN5 complex) (Helmlinger et al. 2004). In retinas of SCA7 transgenic mice, with mutant ataxin-7 as a component of these GCN5 histone acetyltransferase complexes, there is an increased recruitment of the complexes to certain promoters and a subsequent hyperacetylation of histone H3 at the promoters of a subset of genes specifically expressed in rod photoreceptors (Helmlinger et al. 2006). Importantly, this hyperacetylation leads to a down-regulation of transcription of these genes. Together with previous studies, these results indicate that rods uniquely require chromatin condensation for the proper level of expression of a set of genes required for rod differentiation and function (Neophytou et al. 2004; Zhang et al. 2004). By a mechanism yet to be determined, expansion of the polyglutamine tract in ataxin-7, a component of GCN5 histone acetyltransferase complexes, enhances their recruitment to rod-specific genes and thus alters chromatin structure at these genes.

Crucial to the hypothesis put forward by Helmlinger et al. (2006) is the idea that mutant ataxin-7 enhances the localization of TFIIIC/STAGA complexes to rod-specific genes rather than affecting complex assembly or HAT activity per se. In contrast, studies on the yeast STAGA homolog SAGA suggested that expression of mutant ataxin-7 disrupted SAGA assembly and decreased HAT activity (McMahon et al. 2005; Palhan et al. 2005). It was further suggested that a photoreceptor-specific disruption in gene expression was associated with changes in the function of the photoreceptor-specific transcription activator CRX (La Spada et al. 2001). It was reported that in mice overexpressing mutant ataxin-7, mutant ataxin-7 interacted with CRX and

induced its decrease, as well as a decrease in CRX-mediated gene expression. However, a subsequent study using a mouse knockin model of SCA7, where an expanded CAG repeat was introduced into the endogenous mouse *Sca7* gene, found substantial disruption of photoreceptor gene expression without changes in CRX levels or changes in the expression of several genes whose expression is known to be CRX-mediated (Yoo et al. 2003). Together these results provide a very important lesson. While basic pathways associated with the polyglutamine proteins can be elucidated from model systems that employ lower organisms and/or the overexpression of mutant protein, the specifics of how the mutant protein alters function are better examined by using accurate genetic mammalian in vivo models.

SCA1: corepressors and remodeling at sites of transcription

Spinocerebellar ataxia type 1 (SCA1) was the first of the autosomal dominant ataxias for which the gene was cloned (Orr et al. 1993). Typical clinical features of SCA1 in patients include gait ataxia, dysarthria, and bulbar dysfunction, with death usually between 10 and 15 yr after the onset of symptoms. Despite the protein ataxin-1 being widely expressed in the central nervous system, the most frequently seen and most severe pathological alterations are restricted to loss of Purkinje cells in the cerebellar cortex, as well as loss of neurons in the inferior olivary nuclei, the cerebellar dentate nuclei and the red nuclei.

Normally ataxin-1, the product of the SCA1 gene, is prominently located in the nuclei of neurons (Servadio et al. 1995). Indication that SCA1 pathogenesis was due to alterations in nuclear function began with the observation that for mutant ataxin-1 to cause disease, it had to enter the nucleus of Purkinje cells (Klement et al. 1998). Consequent studies revealed that wild-type ataxin-1 has properties consistent with a role in the regulation of gene expression in the nucleus. These include the ability to bind RNA (Yue et al. 2001) and to shuttle between the nucleus and cytoplasm (Irwin et al. 2005). Subsequently, gene profiling analyses of SCA1 transgenic animals showed a decrease in numerous genes during early development of Purkinje cells (Lin et al. 2000; Serra et al. 2004). Specifically, the glutamate transporter EAAT4 was down-regulated, as well as four other genes that localized to the dendritic tree of Purkinje cells, the primary site of pathology in SCA1 (Serra et al. 2004). The down-regulation of specific neuronal genes occurred before the onset of detectable SCA1 pathology, hinting at the possibility that decreased transcription of specific neuronal genes mediates early cytotoxicity of SCA1. A genetic screen in *Drosophila* aimed at identifying modulators of SCA1 toxicity reported enhanced neurodegeneration of a SCA1 *Drosophila* model when genes encoding transcriptional corepressors were reduced (Fernandez-Funez et al. 2000).

Two groups have confirmed the ability of ataxin-1, independent of glutamine repeat length, to repress tran-

scription when tethered to artificial promoters (Tsai et al. 2004; Okazawa et al. 2002). In 2002, one of these groups showed the ability of mutant ataxin-1[82Q] to repress transcription was enhanced in the presence of PQBP-1 (polyQ-binding protein) (Okazawa et al. 2002). PQBP-1 has been described as a binding partner of the active, phosphorylated form of the CTD (C-terminal domain) of Pol II, the neuronal transcription factor Brn-2 (Waragai et al. 1999), the RNA splicing factor U5-15kDa, and the RNA-binding protein NpwBP (Komuro et al. 1999a,b). The interaction between mutant ataxin-1[82Q] and PQBP-1 decreased the phosphorylation of Pol II, suggesting a possible mechanism for the decrease in transcription.

In addition to demonstrating ataxin-1's ability to mediate transcriptional repression and bind chromosomes, Ron Evans's group (Tsai et al. 2004) showed an interaction of ataxin-1 with the corepressors, silencing mediator of retinoid and thyroid hormone receptors (SMRT) and histone deacetylase 3 (HDAC3). There was enhanced *Drosophila* eye neurodegeneration when SMRTER (*Drosophila* homolog of SMRT) and mutant ataxin-1[82Q] flies were crossed compared with mutant ataxin-1[82Q] alone (Tsai et al. 2004). The investigators concluded that perturbation of corepressor-dependent transcriptional pathways by mutant ataxin-1[82Q] contributes to SCA1 pathogenesis (Tsai et al. 2004). Transcriptional regulation is highly dynamic, and the release of SMRT and its paralog, N-CoR, coincides with the acquisition of co-activators and the activation of transcription (Privalsky 2004). Perhaps mutant ataxin-1[82Q] impairs this association/dissociation of SMRT/N-CoR from sites of transcription.

The roles of regions outside the polyglutamine stretch in mediating mutant ataxin-1 toxicity have been established; however, two recent reports have underscored the importance of ataxin-1's AXH (ataxin-1 and HMG-box protein 1) domain in mediating transcriptional regulatory events and neurodegeneration (Mizutani et al. 2005; Tsuda et al. 2005). Overexpression of mutant ataxin-1 resulted in a reduction of the transcription factor Senseless (Sens)/Gfi-1 in Purkinje cells. The investigators demonstrated that this decrease in Sens/Gfi-1 activity was a result of decreased protein levels, not RNA levels. Mutant ataxin-1[82Q] interacts with Sens/Gfi-1 via ataxin-1's AXH domain, and deletion of the AXH domain abrogated the decrease in Sens/Gfi-1 activity. It was also shown that if the proteasome was pharmacologically inhibited, there was an increase in ubiquitinated Sens/Gfi-1, suggesting that ataxin-1 enhanced the degradation of Sens/Gfi-1 via the ubiquitin proteasome system. This is interesting in light of the second report in which the level of Boat (Brother of ataxin-1) was reduced in the Purkinje cells of SCA1 transgenic mice (Mizutani et al. 2005). It was not demonstrated that this was due to enhanced proteasomal degradation, but it seems probable in light of the Sens/Gfi-1 result. Boat also contains an AXH domain important for Boat's interaction with SMRT and ability to repress transcription (Mizutani et al. 2005).

In *Drosophila*, a Boat-ataxin-1 interaction reduced the neurotoxicity associated with mutant ataxin-1[82Q] suggesting the decreased levels of Boat observed in SCA1 transgenic mice could contribute to SCA1 pathology.

Regulation of gene expression is highly coordinated and the dynamic properties of chromatin exert a regulatory role. SUMOylation has been shown to facilitate a "hit and run" mode of interaction/regulation of gene expression (Johnson 2004; Muller et al. 2004). Previously, it was shown that mutant ataxin-1[82Q] redistributed PML oncogenic domains (PODs) to large mutant ataxin-1[82Q] foci or nuclear inclusions (NIs) (Skinner et al. 1997). In addition to SUMOylated PML, PODs contain other SUMOylated proteins including transcriptional corepressors (Borden 2002). Ataxin-1 was shown to be SUMOylated on at least five lysine residues, two of which are in the AXH domain (Riley et al. 2005). Ataxin-1 SUMOylation was dependent on the length of the polyglutamine tract, the ability of ataxin-1 to be phosphorylated at serine776 and the integrity of ataxin-1's nuclear localization signal. Ataxin-1's dependence on phosphorylation and nuclear localization is reminiscent of other nuclear body proteins, namely, PML, Sp100, and HDAC4 (Johnson, 2004). Most targets of SUMOylation are nuclear proteins with many having a role in gene transcription (Seeler and Dejean 2003). Supporting this is the observation that SUMOylation of PML, Sp100, and HDAC4 controls their nucleocytoplasmic trafficking as well as their ability to function as transcriptional corepressors. These results suggest that ataxin-1's SUMOylation could be linked to its ability to regulate transcription.

Huntington disease: disruption of glutamine-rich transcription factors

Huntington disease (HD), the most prevalent of the polyglutamine neurodegenerative disorders, is a fatal inherited neurodegenerative disorder affecting the cerebral cortex and striatum. HD is characterized clinically by a typically late-age-at-onset and progressive loss of motor and cognitive functions. The age of onset of HD correlates with the length of the polyglutamine tract in the N-terminal region of the huntingtin protein. The first indication that alterations in nuclear function underlie HD pathogenesis came from a study demonstrating that for the N-terminal polyglutamine fragment of huntingtin to be toxic, it had to enter the nucleus (Saudou et al. 1998).

Two transcriptional pathways are more extensively implicated in HD, the CBP/p300 and Sp1 pathways. These are transcription factors whose functions are vital for the expression of many genes. The postulated relationship between CBP and HD stems from studies showing that CBP is found in polyglutamine aggregates (see Kazantsev et al. 1999). Consequently, it was demonstrated that huntingtin and CBP interact via their polyglutamine stretches, that huntingtin with an expanded polyglutamine tract interferes with CBP-activated gene

expression, and that overexpression of CBP rescued polyglutamine-induced toxicity in cultured cells (Nucifora et al. 2001; Steffan et al. 2001). Mutant huntingtin was also shown to interact with the acetyltransferase domain of CBP and inhibit the acetyltransferase activity of CBP, p300, and the p300/CBP-associated factor P/CAF (Steffan et al. 2001). These observations prompted a hypothesis whereby the pathogenic process was linked to the state of histone acetylation; specifically, mutant huntingtin induced a state of decreased histone acetylation and thus altered gene expression. Support for this hypothesis was obtained in a *Drosophila* HD model expressing an N-terminal fragment of huntingtin with an expanded polyglutamine tract in the eye. Administration of inhibitors of histone deacetylase arrested the neurodegeneration and lethality (Steffan et al. 2001). Protective effects of HDAC inhibitors have been reported for other polyglutamine disorders, prompting the concept that at least some of the observed effects in polyglutamine disorders are due to alterations in histone acetylation (Hughes 2002). This has led to several preclinical studies (see Ferrante et al. 2003; Hockly et al. 2003; Minamiyama et al. 2004; Gardian et al. 2005). It remains to be seen whether HDAC inhibitors, such as FDA-approved SAHA, have use for the treatment of HD and the other polyglutamine disorders. It is perhaps important to note that the evidence linking histone acetylation to polyglutamine pathogenesis is based for the most part on work performed using a fragment of the mutant polyglutamine protein. Thus, the biological relevance of this work is dependent on the extent to which pathogenesis fundamentally rests on properties of the polyglutamine tract.

Studies published in 2002 revealed that the N-terminal fragment of huntingtin and intact huntingtin interact with Sp1 (Dunah et al. 2002; Li et al. 2002a), a transcriptional activator that binds to upstream GC-rich elements in certain promoters. It is the glutamine-rich transactivation domain of Sp1 that selectively binds and directs core components of the general transcriptional complex such as TFIID, TBP and other TBP-associated factors (TAF_{II}s) to Sp1-dependent sites of transcription. Intriguingly, one study showed that both Sp1 and TAF_{II}130, a Sp1 coactivator, interact with full-length huntingtin and this interaction was enhanced by increasing the polyglutamine tract length in huntingtin (Dunah et al. 2002). These investigators went on to perform some additional analyses, the sum of which provide a very tantalizing link between the actions of mutant huntingtin and a negative effect on Sp1-mediated transcription. For example, in the presence of mutant huntingtin, the interaction between Sp1 and TAF_{II}130 was decreased in postmortem human HD brain and mutant huntingtin interfered with the DNA binding of Sp1.

In vitro transcription studies have gone on to show that in addition to targeting Sp1, mutant huntingtin targets TFIID and TFIIF, members of the core transcriptional complex (Zhai et al. 2005). Mutant huntingtin was shown to interact with the RAP30 subunit of TFIIF. Notably, overexpression of RAP30 alleviated both mutant huntingtin-induced toxicity and transcriptional repres-

sion of the dopamine D2 receptor gene. These results indicate that mutant huntingtin may interfere with multiple components of the transcription machinery.

Further indication that huntingtin functions in gene transcription comes from a recent study demonstrating SUMOylation of the N-terminal fragment of huntingtin in *Drosophila* (Steffan et al. 2004). SUMOylation of this huntingtin fragment reduced its ability to form aggregates, promoted its capacity to repress transcription, and enhanced its ability to induce neurodegeneration in *Drosophila*.

DRPLA: corepressor dysfunction

Dentatorubral-pallidoluysian atrophy (DRPLA) is a progressive neurodegenerative disease caused by the expansion of polyglutamine repeats within the atrophin-1 protein. Clinical manifestations of DRPLA include chorea, a lack of coordination, ataxia, and dementia. Studies have shown that in patients and DRPLA transgenic mice, there is an accumulation of an N-terminal cleavage fragment of mutant atrophin-1 within the nuclei of neurons. While the function of atrophin-1 is unknown, the protein contains a nuclear localization signal within its N terminus and a putative nuclear export signal (Nucifora et al. 2003). In tissue culture cells, truncation of atrophin-1 increases nuclear localization of the N-terminal fragment and toxicity.

The strongest evidence that atrophin-1 has a role in the regulation of transcription comes from work in *Drosophila* (Zhang et al. 2002). From a screen to identify *Drosophila* mutants having characteristics of human diseases, the fly homolog of human atrophin-1 was identified. *Drosophila atrophin* was found to interact genetically with the transcription repressor *even-skipped* and is required for its repressive activity. Both human atrophin-1 and *Drosophila atrophin* repress transcription. Expansion of the polyglutamine tract in atrophin-1 reduced its ability to repress transcription. From these observations, it was suggested that atrophin-1 can function as a transcriptional corepressor, and the deregulation of this activity by an expanded polyglutamine tract contributes to the neurodegeneration seen in DRPLA.

SCA3: a link to ubiquitin-proteasome regulation of transcription?

Spinocerebellar ataxia type 3 (SCA3), also known as Machado Joseph disease (MJD), is the most common of the autosomal dominantly inherited ataxias with several genetic features that distinguish it from many of the other polyglutamine disorders. In contrast to HD and SCA1, where the repeat threshold for mutant alleles is ~40, in SCA3 the repeat threshold for the mutant alleles is >50 repeats. Moreover, although other polyglutamine disorders behave as pure dominant diseases, SCA3/MJD homozygous patients have a more severe disease presentation than individuals having only a single mutant allele.

Ataxin-3 contains an N-terminal Josephin domain (JD) with recently ascribed ubiquitin protease activity (Bur-

nett et al. 2003; Scheel et al. 2003), two ubiquitin interacting motifs (UIMs) capable of binding ubiquitin (Chai et al. 2004; Burnett et al. 2003; Donaldson et al. 2003) followed by a polyglutamine stretch, and a C-terminal variable domain. The crystal structure of the ataxin-3 JD provided insight into the potential function of ataxin-3 as a polyubiquitin chain editing protein by demonstrating a tight connection between polyubiquitin binding and the deubiquitylating activity of ataxin-3 (Mao et al. 2005; Nicastro et al. 2005). Thus, there are considerable structural data indicating that ataxin-3 has a role in the ubiquitin and/or the ubiquitin-proteasome system.

The ubiquitin and ubiquitin-proteasome pathways are known to modulate transcription in several ways. An intriguing role for the ubiquitin-proteasome system is its proposed role in modulating gene transcription in response to changes in signal transduction (Freeman and Yamamoto 2001; Nawaz and O'Malley 2004). In the case of the nuclear receptor superfamily, transcriptional activity requires proteasome-dependent degradation of the receptors at the promoters of target genes. The concept that is developing is one where the ubiquitin-proteasome system modulates transcription by promoting the remodeling and turnover of receptor-transcription complexes, that is, a continuous recycling process (Freeman and Yamamoto 2001).

At this time evidence that ataxin-3 has a nuclear function—let alone a role in transcription—is limited. Ataxin-3 is reported to localize to the nucleus and interact with the nuclear matrix (Tait et al. 1998). Similar to other polyglutamine proteins, ataxin-3 sequesters transcription factors into NIs. One study has presented a detailed analysis of mechanisms whereby ataxin-3 may regulate transcription (Li et al. 2002b). These investigators showed that the C terminus of ataxin-3 containing the polyglutamine stretch is the region responsible for interaction with CBP, p300, and PCAF. Mutant ataxin-3 interacted more efficiently than did wild-type ataxin-3, and, as expected, repressed CBP, p300, and P/CAF-mediated transcription. The C-terminal polyglutamine repeat was also able to repress CRE-mediated transcription, though a direct interaction between CREB and phospho-CREB was not detected.

Ataxin-3 is unique from the other polyglutamine diseases in that wild-type ataxin-3 expression in *Drosophila* protects neurons from toxicity initiated by other polyglutamine-expanded proteins (Warrick et al. 2005). This protection afforded by wild-type ataxin-3 was dependent on active proteasomes and both the UIM and ubiquitin protease domains of ataxin-3. Perhaps the remodeling/recycling of transcriptional networks is ultimately perturbed in these polyglutamine diseases, and by controlling ubiquitylation, ataxin-3 alleviates the obstruction in assembly/disassembly at specific promoters.

SCA6: calcium channel and transcription regulation

Spinocerebellar ataxia type 6 (SCA6) is one of several inherited neurological disorders due to a mutation in the gene encoding the $\alpha 1A$ transmembrane subunit of the

Figure 1. A simplified diagram showing various transcriptional complexes. Depicted are the core transcription complex (TFIID/GTC) that binds to the TATA-box, RNA polymerase II (Pol II), 5' upstream binding factors (UTC) that would include the nuclear receptors and Sp1 that binds to GC-rich elements, and the coregulator complexes (coactivators and corepressors) that interact with the DNA-binding complexes. In addition, two free complexes that impact upon these complexes at the promoter are the GCN5 histone acetyltransferase complex (TFTC) and the proteasome along with ubiquitin (ub) chains. Placed on this schematized diagram are each of the polyglutamine disorders discussed. Their position indicates where the respective proteins may act to disrupt transcription. The degree of red shading reflects the extent to which the evidence supports their placement (darkest indicates the strongest evidence).

P/Q type voltage-gated calcium channel *CACNA1A* (Pietrobon 2002). The SCA6 mutation is an expansion of a polyglutamine tract located in the cytoplasmic C terminus of the intact $\alpha 1A$ protein. Whereas the other polyglutamine disorders are caused by mutant alleles with polyglutamine tracts of ~ 35 repeats and greater, the pathological range of SCA6 mutant alleles is 19–33 glutamines (Riess et al. 1997; Zhuchenko et al. 1997). This led to the suggestion that perhaps SCA6 is an atypical polyglutamine disease.

Taking a cue from previous demonstrations that the C terminus of the $\alpha 1A$ polypeptide has a critical role in channel function (Walker and De Waard 1998), Kordasiewicz et al. (2006) recently showed that a C-terminal fragment containing the polyglutamine tract is cleaved from the endogenous $\alpha 1A$ protein and localizes to the nucleus. Moreover, in transfected tissue culture cells and neurons, these investigators found that the polyglutamine-mediated toxicity of the C-terminal $\alpha 1A$ fragment was dependent on its localization to the nucleus. Although the role of the $\alpha 1A$ C-terminal fragment in the nucleus is unknown, these interesting results indicate

that SCA6 pathogenesis likely includes nuclear processes.

Closing comments

As highlighted in this review, there is substantial evidence linking the function of the polyglutamine disease-associated proteins with the regulation of gene transcription. Not surprisingly, given that regulation of transcription involves many different types of proteins, a variety of mechanisms have been suggested by which the polyglutamine proteins impact upon transcription (Fig. 1). These include altering the function of a very specific DNA-binding factor like the AR (SBMA), general DNA-binding proteins like TBP (SCA17), Sp1, TFIID and TFIIF (HD), chromatin structure (SCA7), coregulators (HD, SCA1, and DRPLA), and possibly the ubiquitin-proteasome system (SCA3). It is also important to note that in the case of some of the polyglutamine proteins, there is evidence they impact other biological processes important for neuronal function, for example, intracellular trafficking (Gunawardena and Goldstein 2005) and the mitochondrial/energy metabolism (Browne and Beal 2004). The ability of proteins to function in multiple systems is well known. Thus, whether a polyglutamine protein functions in one pathway should not be viewed as evidence that it does not function in other systems. The goal should be to determine if one pathway has a greater impact on pathogenesis over the others.

A final point concerns the extent to which the present understanding of the role of these polyglutamine proteins as transcriptional regulators explains the cellular specificity that typically characterizes each disease. Admittedly there is still a long way to go. Disrupting the function of a broadly used transcription factor, for example, TBP, Sp1, and CBP, seems to offer little mechanistic insight into cellular specificity. Returning to the concept of the importance of "host" protein sequences in pathogenesis, it is these sequences that vary between the polyglutamine proteins. It is reasonable to suggest that interactions dependent on "host" protein sequences bring about the specific cellular pattern of pathogenesis that distinguishes each of the polyglutamine disorders from the others. Support for this idea comes from recent work on SCA1 (Tsuda et al. 2005). Ataxin-1 interacts via its AXH domain with the transcription coregulator Gfi-1 and Gfi-1 expression in the cerebellar cortex is specific to Purkinje cells. Furthermore, partial loss of Gfi-1 function enhanced mutant ataxin-1-induced pathogenesis.

Acknowledgments

The work from our laboratory was supported by grants NS22920 and NS45667 from NINDS/NIH.

References

- Arrasate, M., Mitra, S., Schweitzer, E.S., Segal, M.R., and Finkbeiner, S. 2004. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. *Nature* 431: 805–810.

- Borden, K. 2002. Pondering the promyelocytic leukemia protein (PML) puzzle: Possible functions for PML nuclear bodies. *Mol. Cell. Biol.* **22**: 5259–5269.
- Browne, S.E. and Beal, M.F. 2004. The energetics of Huntington's disease. *Neurochem. Res.* **29**: 531–546.
- Burnett, B., Li, F., Randall, N., and Pittman, R.N. 2003. The polyglutamine neurodegenerative protein ataxin-3 binds polyubiquitinated proteins and has ubiquitin protease activity. *Hum. Mol. Genet.* **12**: 3195–3205.
- Chai, Y., Berke, S.S., Cohen, R.E., and Paulson, H.L. 2004. Polyubiquitin binding by the polyglutamine disease protein Ataxin-3 links its normal function to protein surveillance pathways. *J. Biol. Chem.* **279**: 3605–3611.
- David, G., Abbas, N., Stevanin, G., Durr, A., Yvert, G., Cancel, G., Weber, C., Imbert, G., Saudou, F., Antoniou, E., et al. 1997. Cloning of the SCA7 gene reveals a highly unstable CAG repeat expansion. *Nat. Genet.* **17**: 65–70.
- Donaldson, K.M., Wei Li, W., Ching, K.A., Batalov, S., Chih-Cheng Tsai, C.-C., and Joazeiro, C.A.P. 2003. Ubiquitin-mediated sequestration of normal cellular proteins into polyglutamine aggregates. *Proc. Natl. Acad. Sci.* **100**: 8892–8897.
- Dunah, A.W., Jeong, H., Griffin, A., Kim, Y.-M., Standaert, D.G., Hersch, S.M., Mouradian, M.M., Young, A.B., Tanese, N., and Dimitri Krainc, D. 2002. Sp1 and TAFII130 transcriptional activity disrupted in early Huntington's disease. *Science* **296**: 2238–2243.
- Emamian, E.S., Kaytor, M.D., Duvick, L.A., Zu, T., Susan, K., Tousey, S.K., Zoghbi, H.Y., Clark, H.B., and Orr, H.T. 2003. Serine 776 of ataxin-1 is critical for polyglutamine-induced disease in SCA1 transgenic mice. *Neuron* **38**: 375–387.
- Enevoldson, T.P., Sanders, M.D., and Harding, A.E. 1994. Autosomal dominant cerebellar ataxia with pigmentary macular dystrophy. A clinical and genetic study of eight families. *Brain* **117**: 445–460.
- Fernandez-Funez, P., Nino-Rosales, M.L., de Gouyon, B., She, W.C., Luchak, J.M., Martinez, P., Turiegano, E., Benito, J., Capovilla, M., Skinner, P.J., et al. 2000. Identification of genes that modify ataxin-1-induced neurodegeneration. *Nature* **408**: 101–106.
- Ferrante, R.J., Kubilus, J.K., Lee, J., Ryu, H., Beesen, A., Zucker, B., Smith, K., Kowall, N.W., Ratan, R.R., Luthi-Carter, R., et al. 2003. Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington's disease mice. *J. Neurosci.* **23**: 9418–9427.
- Freeman, B.C. and Yamamoto, K.R. 2001. Continuous recycling: A mechanism for modulatory signal transduction. *Trends Biochem. Sci.* **26**: 285–290.
- Gardian, G., Browne, S.E., Choi, D.K., Klivenyi, P., Gregorio, J., Kubilus, J.K., Ryu, H., Langley, B., Ratan, R.R., Ferrante, R.J., et al. 2005. Neuroprotective effects of phenylbutyrate in the N171-82Q transgenic mouse model of Huntington's disease. *J. Biol. Chem.* **280**: 556–563.
- Gatchel, J.R. and Zoghbi, H.Y. 2005. Diseases of unstable repeat expansion: Mechanism and common principles. *Nat. Rev. Genet.* **6**: 743–755.
- Gill, G. and Tjian, R. 1992. Eukaryotic coactivators associated with the TATA box binding protein. *Curr. Opin. Genet. Dev.* **2**: 236–242.
- Gunawardena, S. and Goldstein, L.S. 2005. Polyglutamine diseases and transport problems: Deadly traffic jams on neuronal highways. *Arch. Neurol.* **62**: 46–51.
- Helmlinger, D., Hardy, S., Sasorith, S., Klein, F., Robert, F., Weber, C., Miguet, L., Potier, N., Van-Dorselaer, A., Wurtz, J.M., et al. 2004. Ataxin-7 is a subunit of GCN5 histone acetyltransferase-containing complexes. *Hum. Mol. Genet.* **13**: 1257–1265.
- Helmlinger, D., Hardy, S., Abou-Sleymane, G., Eberlin, A., Bowman, A.B., Gansmüller, A., Picaud, S., Zoghbi, H.Y., Trotter, Y., Tora, L., et al. 2006. Glutamine-expanded ataxin-7 alters TFTC/STAGA recruitment and chromatin structure leading to photoreceptor dysfunction. *PLoS Biol.* **4**: 432–445.
- Hockly, E., Richon, V.M., Woodman, B., Smith, D.L., Zhou, X., Rosa, E., Sathasivam, K., Ghazi-Noori, S., Mahal, A., Lowden, P.A., et al. 2003. Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. *Proc. Natl. Acad. Sci.* **100**: 2041–2046.
- Hughes, R.E. 2002. Polyglutamine disease: Acetyltransferases awry. *Curr. Biol.* **12**: R141–R143.
- Irwin, S., Vandelft, M., Howell, J.L., Graczyk, J., Orr, H.T., and Truant, R. 2005. RNA association and nucleocytoplasmic shuttling by ataxin-1. *J. Cell Sci.* **118**: 233–242.
- Johnson, E. 2004. Protein modification by SUMO. *Annu. Rev. Biochem.* **73**: 355–382.
- Katsuno, M., Adachi, H., Kume, A., Li, M., Nakagomi, Y., Niwa, H., Sang, C., Kobayashi, Y., Doyu, M., and Sobue, G. 2002. Testosterone reduction prevents phenotypic expression in a transgenic mouse model of spinal and bulbar muscular atrophy. *Neuron* **35**: 843–854.
- Katsuno, M., Adachi, H., Doyu, M., Minamiyama, M., Sang, C., Kobayashi, Y., Inukai, A., and Sobue, G. 2003. Leuprorelin rescues polyglutamine-dependent phenotypes in a transgenic mouse model of spinal and bulbar muscular atrophy. *Nat. Med.* **9**: 768–773.
- Kazantsev, A., Preisinger, E., Dranovsky, A., Goldgaber, D., and Housman, D. 1999. Insoluble detergent-resistant aggregates form between pathological and nonpathological lengths of polyglutamine in mammalian cells. *Proc. Natl. Acad. Sci.* **96**: 11404–11409.
- Klement, I.A., Skinner, P.J., Kaytor, M.D., Yi, H., Hersch, S.M., Clark, H.B., Zoghbi, H.Y., and Orr, H.T. 1998. Ataxin-1 nuclear localization and aggregation: Role in polyglutamine-induced disease in SCA1 transgenic mice. *Cell* **95**: 41–53.
- Koide, R., Kobayashi, S., Shimohata, T., Ikeuchi, T., Maruyama, M., Saito, M., Yamada, M., Takahashi, H., and Tsuji, S. 1999. A neurological disease caused by an expanded CAG trinucleotide repeat in the TATA-binding protein gene: A new polyglutamine disease. *Hum. Mol. Genet.* **18**: 2047–2053.
- Komuro, A., Saeki, M., and Kato, S. 1999a. Npw38, a novel protein possessing a WW domain capable of activating basal transcription. *Nucleic Acids Res.* **27**: 1957–1965.
- . 1999b. Association of two nuclear proteins, Npw38 and NpwBP, via the interaction between WW domain and a novel proline-rich motif containing glycine and arginine. *J. Biol. Chem.* **274**: 36513–36519.
- Kordasiewicz, H.B., Thompson, R.M., Clark, H.B., and Gomez, C.M. 2006. C-termini of P/Q-type Ca²⁺ channel α subunits translocate to nuclei and promote polyglutamine-mediated toxicity. *Hum. Mol. Genet.* **15**: 1587–1599.
- La Spada, A.R., Wilson, E.M., Lubahn, D.B., Harding, A.E., and Fischbeck, K.H. 1991. Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. *Nature* **352**: 77–79.
- La Spada, A.R., Fu, Y.H., Sopher, B.L., Libby, R.T., Wang, X., Li, L.Y., Einum, D.D., Huang, J., Possin, D.E., Smith, A.C., et al. 2001. Polyglutamine-expanded ataxin-7 antagonizes CRX function and induces cone-rod dystrophy in a mouse model of SCA7. *Neuron* **31**: 913–927.
- Li, S.-H., Cheng, A.L., Zhou, H., Lam, S., Rao, M., Li, H., and Li, X.-J. 2002a. Interaction of Huntington disease protein with transcriptional activator Sp1. *Mol. Cell. Biol.* **22**: 1277–1287.

- Li, F., Macfarlan, T., Pittman, R.N., and Chakravarti, D. 2002b. Ataxin-3 is a histone-binding protein with two independent transcriptional corepressor activities. *J. Biol. Chem.* **277**: 45004–45012.
- Lin, X., Antalffy, B., Kang, D., Orr, H.T., and Zoghbi, H.Y. 2000. Polyglutamine expansion downregulates specific neuronal genes before pathologic changes in SCA1. *Nat. Neurosci.* **3**: 157–163.
- Mangelsdorf, D.J., Thummel, C., Beato, M., Herrlich, P., Günther Schütz, G., Kazuhiko Umesono, K., Bruce Blumberg, B., Kastner, P., Mark, M., Chambon, P., et al. 1995. The nuclear receptor superfamily: The second decade. *Cell* **83**: 835–839.
- Maniatis, T. and Reed, R. 2002. An extensive network of coupling among gene expression machines. *Nature* **416**: 499–506.
- Mao, Y., Senic-Matuglia, F., Di Fiore, P.P., Polo, S., Hodson, M.E., and De Camilli, P. 2005. Deubiquitinating function of ataxin-3: Insights from the solution structure of the Josephin domain. *Proc. Natl. Acad. Sci.* **102**: 12700–12705.
- McMahon, S.J., Pray-Grant, M.G., Schieltz, D., Yates, J.R., and Grant, P.A. 2005. Polyglutamine-expanded spinocerebellar ataxia-7 protein disrupts normal SAGA and SLIK histone acetyltransferase activity. *Proc. Natl. Acad. Sci.* **102**: 8478–8482.
- Minamiyama, M., Katsuno, M., Adachi, H., Waza, M., Sang, C., Kobayashi, Y., Tanaka, F., Doyu, M., Inukai, A., and Sobue, G. 2004. Sodium butyrate ameliorates phenotypic expression in a transgenic mouse model of spinal and bulbar muscular atrophy. *Hum. Mol. Genet.* **13**: 1183–1192.
- Mizutani, A., Wang, L., Rajan, H., Vig, P.J.S., Alaynick, W.A., Thaler, J.P., and Tsai, C.-C. 2005. Boat, an AXH domain protein, suppresses the cytotoxicity of mutant ataxin-1. *EMBO J.* **24**: 3339–3351.
- Muller, S., Ledl, A., and Schmidt, D. 2004. SUMO: A regulator of gene expression and genome integrity. *Oncogene* **23**: 1998–2008.
- Nawaz, Z. and O'Malley, B.W. 2004. Urban renewal in the nucleus: Is protein turnover by proteasomes absolutely required for nuclear receptor-regulated transcription? *Mol. Endocrinol.* **18**: 493–499.
- Neophytou, C., Vernallis, A.B., Smith, A., and Raff, M.C. 1997. Muller-cell-derived leukaemia inhibitory factor arrests rod photoreceptor differentiation at a postmitotic pre-rod stage of development. *Development* **124**: 2345–2354.
- Nicastro, G., Menon, R.P., Masino, L., Knowles, P.P., McDonald, N.Q., and Pastore, A. 2005. The solution structure of the Josephin domain of ataxin-3: Structural determinants for molecular recognition. *Proc. Natl. Acad. Sci.* **102**: 10493–10498.
- Nucifora Jr., F.C., Sasaki, M., Peters, M.F., Huang, H., Cooper, J.K., Yamada, M., Takahashi, H., Tsuji, S., Troncoso, J., Dawson, V.L., et al. 2001. Interference by huntingtin and atrophin-1 with CBP-mediated transcription leading to cellular toxicity. *Science* **291**: 2423–2428.
- Nucifora Jr., F.C., Ellerby, L.M., Wellington, C.L., Wood, J.D., Herring, W.J., Sawa, A., Hayden, M.R., Dawson, V.L., Dawson, T.M., and Ross, C.A. 2003. Nuclear localization of a non-caspase truncation product of atrophin-1, with an expanded polyglutamine repeat, increases cellular toxicity. *J. Biol. Chem.* **278**: 13047–13055.
- Okazawa, H., Rich, T., Chang, A., Lin, X., Waragai, M., Kajikawa, M., Enokido, Y., Komuro, A., Kato, S., Shibata, M., et al. 2002. Interaction between mutant ataxin-1 and PQBP-1 affects transcription and cell death. *Neuron* **34**: 701–713.
- Orr, H.T. 2001. Beyond the Qs in the polyglutamine diseases. *Genes & Dev.* **15**: 925–932.
- Orr, H.T., Chung, M.-Y., Banji, S., Kwiatkowski Jr., T.J., Servadio, A., Beaudet, A.L., McCall, A.E., Duvick, L.A., Ranum, L.P.W., and Zoghbi, H.Y. 1993. Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. *Nat. Genet.* **4**: 221–226.
- Palhan, V.B., Chen, S., Peng, G.H., Tjernberg, A., Gamper, A.M., Fan, Y., Chait, B.T., La Spada, A.R., and Roeder, R.G. 2005. Polyglutamine-expanded ataxin-7 inhibits STAGA histone acetyltransferase activity to produce retinal degeneration. *Proc. Natl. Acad. Sci.* **102**: 8472–8477.
- Pietrobon, D. 2002. Calcium channels and channelopathies of the central nervous system. *Mol. Neurobiol.* **25**: 31–50.
- Privalsky, M. 2004. The role of corepressors in transcriptional regulation by nuclear hormone receptors. *Annu. Rev. Physiol.* **66**: 315–360.
- Reed, R. 2003. Coupling transcription, splicing and mRNA export. *Curr. Opin. Cell Biol.* **15**: 326–331.
- Riess, O., Schols, L., Bottger, H., Nolte, D., Vieira-Saecker, A.M., Schimming, C., Kreuz, F., Macek Jr., M., Krebsova, A., Macek, M.S., et al. 1997. SCA6 is caused by moderate CAG expansion in the $\alpha 1A$ -voltage-dependent calcium channel gene. *Hum. Mol. Genet.* **6**: 1289–1293.
- Riley, B.E., Zoghbi, H.Y., and Orr, H.T. 2005. SUMOylation of the polyglutamine protein, ataxin-1 is dependent on a functional nuclear localization signal. *J. Biol. Chem.* **280**: 21942–21948.
- Rolfs, A., Koeppen, A., Bauer, I., Bauer, P., Buhlmann, S., Topka, H., Schols, L., and Riess, O. 2003. Clinical features and neuropathology of autosomal dominant spinocerebellar ataxia (SCA17). *Ann. Neurol.* **54**: 367–375.
- Ross, C.A. and Poirer, M.A. 2004. Protein aggregation and neurodegenerative disease. *Nat. Med.* **10**: S10–S17.
- Saudou, F., Finkbeiner, S., Devys, D., and Greenberg, M.E. 1998. Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. *Cell* **95**: 55–66.
- Scheel, H., Tomiuk, S., and Kay Hofmann, K. 2003. Elucidation of ataxin-3 and ataxin-7 function by integrative bioinformatics. *Hum. Mol. Genet.* **12**: 2845–2852.
- Schmidt, B.J., Greenberg, C.R., Allingham-Hawkins, D.J., and Sproggs, E.L. 2002. Expression of X-linked bulbospinal muscular atrophy (Kennedy's disease) in two homozygous women. *Neurology* **59**: 770–772.
- Seeler, J.-S. and Dejean, A. 2003. Nuclear and unclear functions of SUMO. *Nat. Rev. Cell Biol.* **4**: 690–699.
- Serra, H.G., Byam, C.E., Lande, J.D., Tousey, S.K., Zoghbi, H.Y., and Orr, H.T. 2004. Gene profiling links SCA1 pathophysiology to glutamate signaling in Purkinje cells of transgenic mice. *Hum. Mol. Genet.* **13**: 2535–2543.
- Servadio, A., Koshy, B., Armstrong, D., Antalffy, B., Orr, H.T., and Zoghbi, H.Y. 1995. Expression analysis of the ataxin-1 protein in tissues from normal and spinocerebellar ataxia type 1 individuals. *Nat. Genet.* **10**: 94–98.
- Skinner, P.J., Koshy, B., Klement, I.A., Helin, K., Servadio, A., Zoghbi, H.Y., and Orr, H.T. 1997. SCA1 pathogenesis involves alterations in nuclear matrix associated structures. *Nature* **389**: 971–974.
- Steffan, J.S., Bodai, L., Pallos, J., Poelman, M., McCampbell, A., Apostol, B.L., Kazantsev, A., Schmidt, E., Zhu, Y.Z., Greenwald, M., et al. 2001. Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in *Drosophila*. *Nature* **413**: 739–743.
- Steffan, J.S., Agrawal, N., Pallos, J., Rockabrand, E., Trotman, L.C., Slepko, N., Illes, K., Lukacovich, T., Zhu, Y.-Z., Cattaneo, E., et al. 2004. SUMO modification of huntingtin and Huntington's disease pathology. *Science* **304**: 100–104.

- Sugars, K.L. and Rubinsztein, D.C. 2003. Transcriptional abnormalities in Huntington disease. *Trends Genet.* **19**: 233–238.
- Tait, D., Riccio, M., Sittler, A., Scherzinger, E., Santi, S., Ognibene, A., Maraldi, N.M., Lehrach, H., and Wankler, E.E. 1998. Ataxin-3 is transported into the nucleus and associates with the nuclear matrix. *Hum. Mol. Genet.* **7**: 991–997.
- Takeyama, K., Ito, S., Yamaoto, A., Tanimoto, H., Furutani, T., Kanuka, H., Miura, M., Tabata, T., and Kato, S. 2002. Androgen-dependent neurodegeneration by polyglutamine-expanded human androgen receptor in *Drosophila*. *Neuron* **35**: 855–864.
- Tanese, N. and Tjian, R. 1993. Coactivators and TAFs: A new class of eukaryotic transcription factors that connect activators to the basal machinery. *Cold Spring Harb. Symp. Quant. Biol.* **58**: 179–185.
- Tsai, C.C., Kao, H.Y., Mitzutani, A., Banayo, E., Rajan, H., McKeown, M., and Evans, R.M. 2004. Ataxin 1, a SCA1 neurodegenerative disorder protein, is functionally linked to the silencing mediator of retinoid and thyroid hormone receptors. *Proc. Natl. Acad. Sci.* **101**: 4047–4052.
- Tsuda, H., Jafar-Nejad, H., Patel, A.J., Sun, Y., Chen, H.-K., Rose, M.F., Venken, K.J.T., Botas, J., Orr, H.T., Hugo, J., et al. 2005. The AXH domain in mammalian/*Drosophila* Ataxin-1 mediates neurodegeneration in spinocerebellar ataxia 1 through its interaction with Gfi-1/Senseless proteins. *Cell* **122**: 633–644.
- Walker, D. and De Waard, M. 1998. Subunit interaction sites in voltage-dependent Ca²⁺ channels: Role in channel function. *Trends Neurosci.* **21**: 148–154.
- Waragai, M., Lammers, C.H., Takeuchi, S., Imafuku, I., Udagawa, Y., Kanazawa, I., Kawabata, M., Mouradian, M.M., and Okazawa, H. 1999. PQBP-1, a novel polyglutamine tract-binding protein, inhibits transcription activation by Brn-2 and affects cell survival. *Hum. Mol. Genet.* **8**: 977–987.
- Warrick, J.M., Morabito, L.M., Bilen, J., Gordesky-Gold, B., Faust, L.Z., Paulson, H.L., Nancy, M., and Bonini, N.M. 2005. Ataxin-3 suppresses polyglutamine neurodegeneration in *Drosophila* by a ubiquitin-associated mechanism. *Mol. Cell* **18**: 37–48.
- Yoo, S.Y., Pennesi, M.E., Weeber, E.J., Xu, B., Atkinson, R., Chen, S., Armstrong, D.L., Wu, S.M., Sweatt, J.D., and Zoghbi, H.Y. 2003. SCA7 knockin mice model human SCA7 and reveal gradual accumulation of mutant ataxin-7 in neurons and abnormalities in short-term plasticity. *Neuron* **37**: 383–401.
- Yue, S., Serra, H., Zoghbi, H.Y., and Orr, H.T. 2001. The SCA1 protein, ataxin-1, has RNA-binding activity that is inversely affected by the length of its polyglutamine tract. *Hum. Mol. Genet.* **10**: 25–30.
- Zhai, W., Jeong, H., Cui, L., Krainc, D., and Tjian, R. 2005. In vitro analysis of Huntingtin-mediated transcriptional repression reveals multiple transcription factor targets. *Cell* **123**: 1241–1253.
- Zhang, S., Xu, L., Lee, J., and Xu, T. 2002. *Drosophila* atrophin homolog functions as a transcription corepressor in multiple developmental processes. *Cell* **108**: 45–56.
- Zhang, J., Gray, J., Wu, L., Leone, G., Rowan, S., Cepko, C.L., Zhu, X., Craft, C.M., and Dyer, M.A. 2004. Rb regulates proliferation and rod photoreceptor development in the mouse retina. *Nat. Genet.* **36**: 351–360.
- Zhuchenko, O., Bailey, J., Bonnen, P., Ashizawa, T., Stockton, D.W., Amos, C., Dobyns, W.B., Subramony, S.H., Zoghbi, H.Y., and Lee, C.C. 1997. Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the $\alpha 1A$ -voltage-dependent calcium channel. *Nat. Genet.* **15**: 62–69.

Polyglutamine neurodegenerative diseases and regulation of transcription: assembling the puzzle

Brigit E. Riley and Harry T Orr

Genes Dev. 2006, **20**:

Access the most recent version at doi:[10.1101/gad.1436506](https://doi.org/10.1101/gad.1436506)

References

This article cites 83 articles, 26 of which can be accessed free at:
<http://genesdev.cshlp.org/content/20/16/2183.full.html#ref-list-1>

License

Email Alerting Service

Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article or [click here](#).

Focused on your science.