Polyglutamine Neurodegeneration: Expanded Glutamines Enhance Native Functions

Harry T. Orr
Institute for Translational Neuroscience, Department of laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN 55455, USA

Abstract

An intriguing set of neurodegenerative disease are the nine disorders caused by the expansion of a unstable trinucleotide CAG repeat where the repeat is located within the coding of the affected gene, i.e. the polyglutamine (polyQ) diseases. A gain-of-function mechanism for toxicity in polyQ diseases is widely thought to have a major role in pathogenesis. Yet, the specific nature of this gain-of-function is a matter of considerable discussion. The basic issue concerns whether toxicity stems from the native or normal function of the affected protein versus a novel function induced by polyQ expansion. For at least three of the polyQ disease considerable evidence is accumulating that pathology is mediated by a polyQ-induced exaggeration of a native function of the host protein.

Twenty years ago one of the first unstable nucleotide repeat mutations identified was the CAG expansion causing spinal and bulbar muscular atrophy (SBMA/Kennedy disease) [1]. SBMA subsequently proved to be the first member of a group of nine progressive neurodegenerative disorders now known as the polyglutamine (polyQ) diseases [2]. Along with SBMA, the polyQ diseases include Huntington disease, dentatorubral-pallidoluysian atrophy, and spinocerebellar ataxia (SCA) 1, 2, 3, 6, 7 and 17. As a group, the polyQ diseases are one of the more common causes of inherited neurodegeneration.

Like most neurodegenerative diseases, the polyQ disorders are progressive and have the accumulation of mutant protein aggregates as a pathological hallmark. The extent to which these accumulations of mutant protein are pathogenic or protective has evolved over the years and remains under considerable investigation and discussion [3]. While the polyQ stretch alone can be toxic *in vivo*, for three of the polyQ disorders highlighted here recent studies demonstrate that an expanded polyQ alone is not sufficient to induce neurodegeneration, i.e. residues and regions of the host protein are also critical for pathogenesis. These three disorders provide a strong connection between host protein framework and induction of disease and, thus, argue that the native biochemistry and function are relevant for understanding disease mechanism. Such a link between an affected protein's normal function and pathogenesis very likely is the basis for the fact that these and other neurodegenerative disorders vary considerably in terms of the region of the CNS they target.

Corresponding author: Harry T. Orr, Ph.D., Institute for Translational Neuroscience, University of Minnesota, Wallin Medical Bioscience Building, 2101 Sixth Street S.E., Minneapolis, MN 5545, orrxx002@umn.edu.

SBMA – The paradigm for linking normal function to pathogenesis

In SBMA the unstable polyQ is located within the androgen receptor (AR) gene located on the X-chromosome [1]. SBMA is a late-onset progressive disorder in which motor neurons in the brainstem and spinal cord in only males degenerate [4]. This latter point, that SBMA is a disease essentially restricted to males, is accentuated by the finding that females homozygous for mutant alleles of the AR have a subclinical presentation of mild symptoms, clearly showing that the disease is influenced by sex-specific factors possibly levels of circulating androgen [5].

Upon generation of SBMA animal models displaying the same male bias in presentation as seen in human patients, it became possible to test directly whether the sex-specific factor important in SBMA was indeed level of circulating androgen. In both a *Drosophila* and a transgenic mouse model of SBMA, neurodegeneration is linked to the presence of circulating testosterone as is normally present only in males [6,7]. Thus, along with an expanded polyQ tract in the AR, the normal AR ligand is required for manifestation of disease. Nedelsky et al. recently utilized *Drosophila* genetics to further dissect and characterize the normal interactions and components of the AR/androgen pathway critical for toxicity [8••]. These and earlier results provide a solid platform for exploring the therapeutic potential of hormonal intervention for SBMA.

In contrast to many of the polyQ diseases where less is known about the native function and biochemistry of the protein affected, the normal structure/function of AR is well characterized. AR is a nuclear hormone that resides in the cytoplasm in an inactive form. Upon binding androgen, the hormone-receptor complex translocates to the nucleus, binds to DNA at specific recognition sites upstream of its target genes. Expression or repression of these genes occurs through the interaction of two co-regulator regions of AR with other transcription factors. As shown previously, Nedelsky and colleagues found that ligand binding was necessary for expanded polyQ AR to cause degeneration of *Drosophila* adult photoreceptors and larval motor neurons [8••]. They further showed that upon binding androgen mutant AR had to translocate to the nucleus and bind to DNA to cause degeneration. Lastly, it was found that one of the interaction regions of AR, the AF-2 transactivation domain, is required for toxicity and that several known AF-2 interacting proteins are modifiers of degeneration in a genetic screen. The results of this study show that the mutant AR pathogenic pathway induced by expansion of the polyQ tract overlaps considerably with the normal AR-ligand binding pathway (Figure 1). Nedelsky et al. went on to suggest that disease is induced by the amplification of a yet unidentified aspect of normal AR function involving the AF-2 transduction domain. This idea is supported by their observation that lies overexpressing wild type AR show some signs of disease [8••].

SCA – Unbalanced normal function leads to ataxia

Spinocerebellar ataxia type 1 (SCA1) is one of the polyQ disorders where the host protein, Ataxin-1 (ATXN1), is a novel protein whose function was unknown. Subsequent to cloning the SCA1 gene in 1993 [9], studies have identified several functional/structural motifs in ATXN1. These include the AXH domain that folds into an OB-fold that consists of a putative RNA-binding and a second ligand-binding surface [10], a nuclear localization signal (NLS) [11] that overlaps with or is immediately adjacent to a 14-3-3 binding site [12] and a UHM ligand motif (ULM) present in proteins associated with RNA splicing [13•]. Not surprisingly, ATXN1 is reported to interact with RNA, several regulators of transcription, and RNA splicing factors RBM17 and U2AF65 [13•,14••]. Interestingly, mutating the NLS of ATXN1 such that transport of the protein to the nucleus of neurons is dramatically reduced prevents ATXN1 with an expanded polyQ tract from causing disease [11].

An important advance in understanding SCA1 pathogenesis came with the observation that ATXN1 normally forms multimeric complexes with other proteins in the nucleus and that expansion of the polyQ tract shifts the *status quo* by enhancing certain functional pathways perhaps at the expense of others [14••]. At the center of the imbalance in complex formation induced by mutant ATXN1 are the complexes it forms with the the splicing factor RBM17 (RNA-binding motif protein 17) and the transcription repressor Capicua (Cic). PolyQ expansion in ATXN1 enhances its interaction with RBM17 [14••]. Furthermore, additional evidence indicates that the RBM17/ATXN1 complex is toxic. The biological effect on Cic of ATXN1 polyQ expansion is much more complex. First, in a fly model of SCA1 overexpresion of Cic was protective [15], while in mice partial loss of Cic prolonged life span [16••]. It seems that for some Cic gene targets expanded ATXN1 causes a loss of function while at other targets polyQ-expanded ATXN1 enhances Cic binding inducing a state of hyper-repression. In the mouse, it is postulated that the hyper-repressive effect of expanded polyQ ATXN1 is toxic [16••].

In addition to polyQ expansion, phosphorylation of the Ser residues at position 776 in ATXN1 favors its interaction with RBM17 [14••]. Ser 776 is one of seven endogenous sites of phosphorylation in ATXN1 [17,18]. Phosphorylation of Ser 776 stabilizes ATXN1 and, in the cytoplasm, binding of 14-3-3 blocks dephosphorylation of Ser 776 as well as the transport of ATXN1 to the nucleus [19]. Previous work showed that placing a phosphorylation-resistant Ala at position 776 dramatically decreases the ability of ATXN1 with an expanded polyQ to cause neurodegeneration *in vivo* [17]. On the other hand a potentially phospho-mimicking Asp at residue 776, a substitution that enhances wild type ATXN1's interaction with RBM17 [14••], enhances ATXN1 induced pathogenesis such that even ATXN1 with a wild type, unexpanded polyQ becomes pathogenic [20•]. Together these results indicate that phosphorylation of Ser 776 in ATXN1 as well as its subsequent interaction with RBM17 has a critical role in pathogenesis.

Moreover, mild exercise likely involving the Cic pathway in the brainstem improves survival in a mouse model of SCA1 in absence of improving the cerebellar motor dysfunction [16••]. While more vigorous motor activity that engages the cerebellum might restore motor function, it is intriguing to speculate that distinct ATXN1 complexes, i.e. cellular pathways, contribute to disease in different regions of the CNS. Such a hypothesis is supported by the ability of a partial loss of 14-3-3 to improve cerebellar phenotypes and not brainstem phenotypes [21].

HD – Increased ciliogenesis?

Perhaps the more prevalent and widely known polyQ disorder is Huntington disease (HD) where the unstable CAG repeat is located in first exon of the huntingtin (*HTT*) gene [21]. Clinically, the loss and dysfunction of neurons in the striatum and deep layers of the cortex characterize HD. Symptomatically, HD patients suffer from cognitive, psychiatric, and motor abnormalities. Over the years a number of cellular pathways and proteins have come forward as targets of wild type and mutant Htt [23,24]. One of the first Htt interacting proteins identified is the huntingtin-associated protein 1 (HAP1) [25]. Subsequently, Hap1 was found to interact the p150[Glued] subunit of dynactin and the pericentriole protein PCM1 [26]. A potential biological relevance of these interactions recently came to light with the observation that Htt/HAP1, impact PCM1's role in ciliogenesis raising the possibility that HD is at least to some extent a ciliopathy [27••].

Cilia fall into two functional/structural groups; nonmotile primary cilia consisting of nine outer microtubule pairs in a (9 + 0 axoneme) configuration and motile cilia with nine outer microtubule pairs, inner and outer dynein arms, and a pair of central microtubules in a (9 + 2

axoneme) configuration. In the brain, primary cilia are on all neurons and glia. On neurons, primary cilia are located on the cell body or proximal portion of the dendrite where they are believed to have a role in sensing the extracelluar environment and subsequent signal transduction. Motile cilia in the brain are located on ependynmal cells lining the lateral ventricles where they are crucial for maintaining proper flow of the cerebral spinal fluid.

Although formation of primary and motile cilia differs, the biogenesis of each form of cilia depends on proper trafficking of proteins to the pericentriolar material (PCM). Specifically, if the pericentriolar material protein 1 (PCM1) does not localize to the PCM ciliogenesis is reduced. Keryer et al. made two key observations linking Htt function to ciliogenesis [27••]. First, they found that depletion of Htt in cultured striatal cells using RNAi resulted in a dispersion of PCM1 away from the centrosome and a decease in the number of cells with primary cilia. Moreover, Keryer et al. found that mice lacking Htt in ependymal cells also had an altered distribution of PCM1 and hydrocephalus, a phenotype previously found in mice having a disruption in ciliary function [27]. In contrast to decreased ciliary function with loss of Htt, expression of Htt with an expanded polyQ resulted in hypermorphic cilia and ciliary dysfunction. Again, in both cultured striatal cells and in mice mutant Htt had a similar effect. With mutant Htt, localization of PCM1 was enhanced at the centriole and the length of primary cilia was increased [27••]. Increased localization of PCM1 to the ependymal zone of the lateral ventricle was found in HD patient brain material. Importantly, this altered accumulation of PCM1 directly correlated with severity of pathology. Keryer et al. went on to show that in HD mice CSF flow was altered using an organotypic preparation that included the lateral ventricle. Intriguingly, in the brain of $Hdh^{Q111/Q111}$ mice migration of neuroblasts was altered relatively to the lateral ventricle. In HD mice, alterations in PCM1 and cilia seemed to be an early event with some abnormalities detected as young as 1 month of age.

These latter findings raise the intriguing possibility that in HD migration of developing neurons is abnormal. If indeed HD proves to be a ciliopathy, having a developmental component to pathogenesis would be in line with other ciliopathies [29]. There is suggestive evidence of abnormal neurodevelopment in HD based on HD mutation carriers having a reduced intracranial volume compared to non-carriers prior to onset of disease [30]. In a mouse model of SCA1, data support a link between abnormal development and neurodegeneration in the adult. Expressing a mutant allele of ATXN1 during early postnatal development compromises Purkinje cell development that contributes to the severity of the neurodegeneration in adult mice [31].

Concluding comments

The results for the three polyQ disorders outlined here illustrate the evidence in support of the hypothesis that pathogenesis induced by polyQ expansion is linked to the native function of the host protein, specifically an enhanced level of a normal function (Figure 2). That such a pathogenic mechanism likely extends beyond these three disorders is suggested by the observations that an increase in wild type gene number and presumably function underlies some forms of Alzheimer and Parkinson disease [32,33]. Recently, Kratter and Finkbeiner nicely outlined how this hypothesis might be envisioned at a protein conformation level [34•]. First, likes many proteins, the polyQ host protein normally adopts multiple conformations each associated with a particular function and/or set of protein interactions. Normally the proportion of each confirmation is dynamically regulated by reversible post-translational modifications such as phosphorylation. However, in the presence of an expanded polyQ one confirmation becomes stabilized and, thus, the associated function(s) is accentuated possibly at the expense of others. It is worth noting that a polyQ$_{17}$ stretch in the exon 1 fragment of HTT was found to assume multiple conformations, indicating that at

least a wild type polyQ tract imparts conformational flexibility to a protein [35•]. Regardless, a hope is that as the native functions and pathways for each disease-associated polyQ protein are identified this will lead to additional therapeutic targets.

Acknowledgments

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• of special interest

•• of outstanding interest

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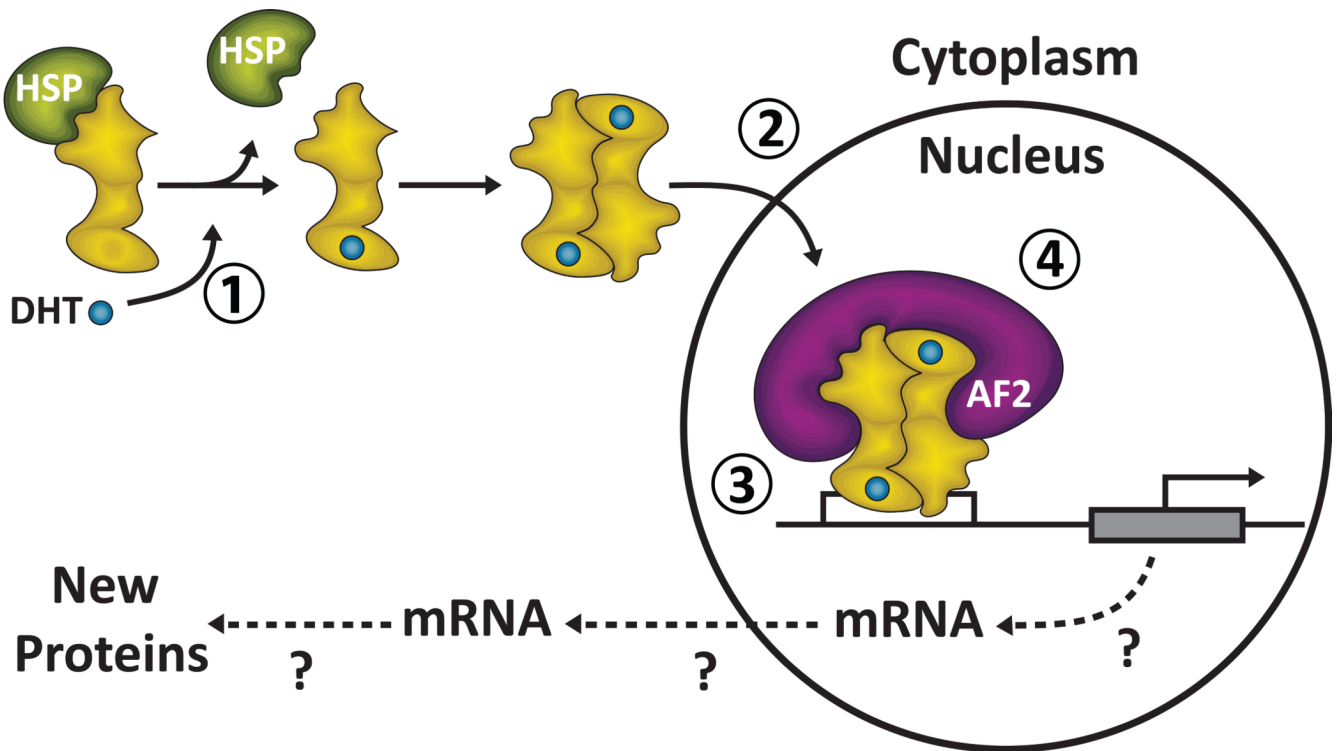
Figure 1. Schematic Depiction of the Minimum Elements of the Native Ligand-Dependent AR Pathway Required for Pathogenesis
To induce pathogenesis AR with an expanded polyQ must (1) Ligand binds to AR inducing a conformation change that releases the bound chaperone, uncovers the NLS and creates the AF-2 binding surface. Presumably mutant AR forms a dimer prior to (2) AR and bound ligand translocate to the nucleus. (3) AR and bound ligand bind to DNA targets sites. (4) AF-2 interacting co-regulators bind. It remains unclear the extent to which if any downstream events (depicted by dashed lines) such as target gene transcription and subsequent steps contribute to pathogenesis.
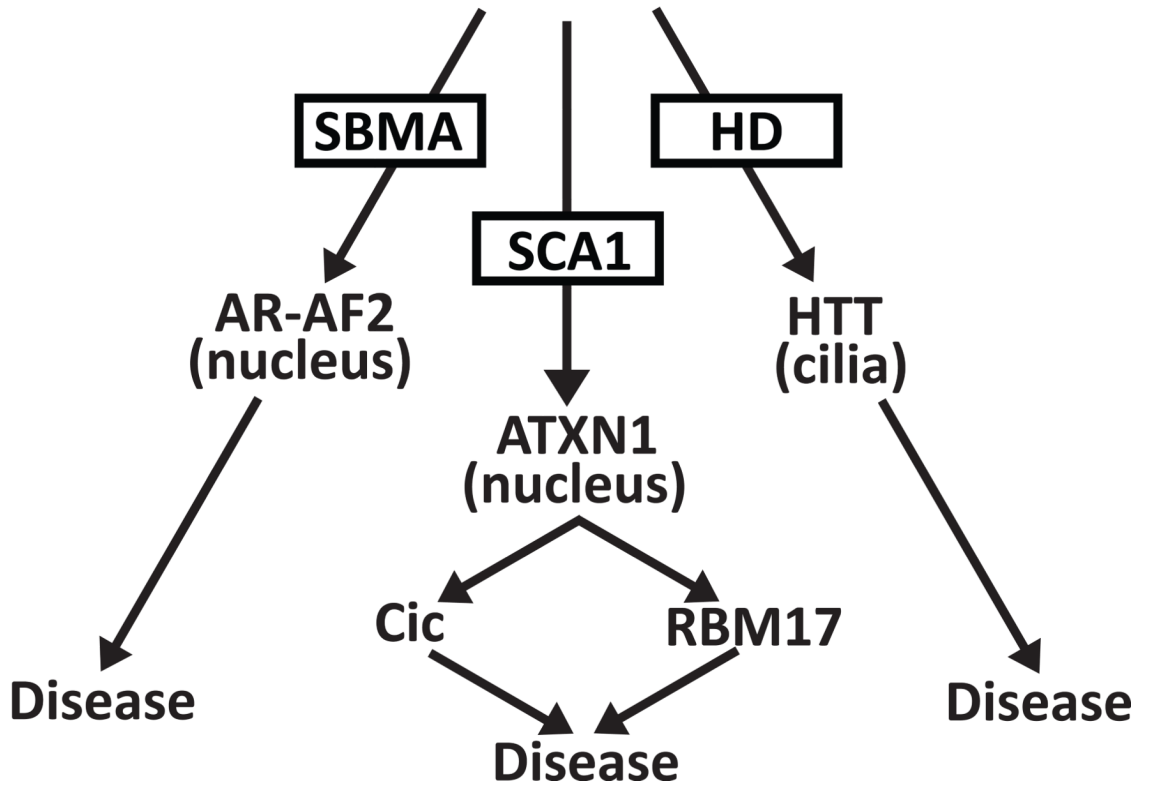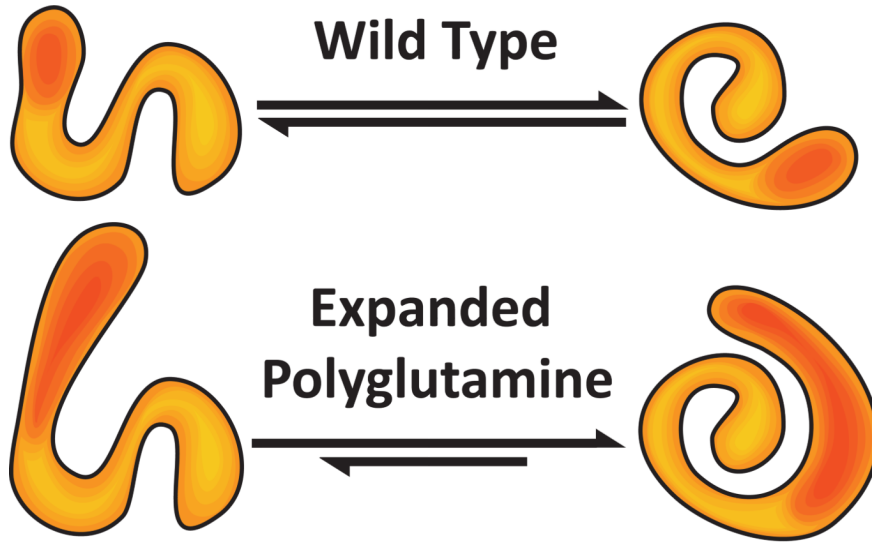
Wild Type

Expanded Polyglutamine

SBMA

HD

SCA1

AR-AF2
(nucleus)

HTT
(cilia)

ATXN1
(nucleus)

Disease

Cic

RBM17

Disease

Disease

Figure 2. A Hypothesis in which the Consequence of Expanded PolyQ is to Enhance a Native Function
Normally the polyQ host exists in a equilibrium of multiple conformations each of which sub serves a native function. Upon expansion of the polyQ (red shaded portion) one native conformation predominates and its associated function is now enhanced in a disease-specific manner.