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The expanding role for chromatin and transcription in polyglutamine disease

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Nine genetic diseases arise from expansion of CAG repeats in seemingly unrelated genes. They are referred to as polyglutamine (polyQ) diseases due to the presence of elongated glutamine tracts in the corresponding proteins. The pathologic consequences of polyQ expansion include progressive spinal, cerebellar, and neural degeneration. These pathologies are not identical, however, suggesting that disruption of protein-specific functions is crucial to establish and maintain each disease. A closer examination of protein function reveals that several act as regulators of gene expression. Here we examine the roles these proteins play in regulating gene expression, discuss how polyQ expansion may disrupt these functions to cause disease, and speculate on the neural specificity of perturbing ubiquitous gene regulators.

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Introduction

The search for causative mechanisms among polyQ diseases continues and, at this time, it remains unclear whether the associated genes impact different points within the same biological pathway, or whether they ultimately affect neurodegeneration via different routes. Many hypotheses regarding the mechanism of polyQ disease have been postulated, one being that dysregulation of transcription is causative. Our understanding, however, of the mechanisms underlying transcriptional and post-transcriptional deregulation in polyQ disease remains incomplete. Thus, we are unable to weigh the contribution of imbalanced gene expression to the corresponding pathology.

Previous studies comparing gene expression profiles among PolyQ disease models have found genes commonly misregulated between diseases, but none have revealed the genes or pathways responsible for neurodegeneration [1,2]. Additionally, it is not clear which changes in gene expression in these early studies reflected primary or secondary effects. Therefore, the questions remain: Is misregulation of crucial genes causative in each polyglutamine disease? Is misregulation of these genes common to multiple diseases? Can we develop therapeutic interventions to alleviate the consequences of misregulated gene expression? Here we review the evidence for polyQ-mediated effects on transcriptional regulation and chromatin modification, and consequent transcriptional dysregulation in polyglutamine diseases.

Polyglutamine expansion diseases and regulation of gene expression

Nine inherited neurodegenerative diseases are a consequence of genetic instability that leads to expansion of CAG repeats in seemingly unrelated genes (Table 1). These CAG repeats cause expanded polyglutamine tracts (polyQ) in the corresponding proteins. Repeat length increases intergenerationally, and increased repeat length correlates with increased severity of disease and reduced time to onset of disease symptoms. PolyQ diseases manifest as progressive degeneration of the spine, cerebellum, brain stem and, in the case of spinocerebellar ataxia 7 (SCA7), the retina and macula. Though they all lead to neural degeneration, different diseases are initially diagnosed by very specific symptoms and patterns of neuronal death. As these diseases progress, extensive neurodegeneration can lead to overlapping patterns of cell death [3]. Currently, no effective treatment for these fatal diseases is available [4] (Table 2).

Early histological and immunohistological analyses showed that polyglutamine-expanded proteins, or even a polyglutamine stretch alone, can form intranuclear aggregates that contain transcriptional regulatory proteins [5]. Titration of these factors seemed a likely cause of polyQ toxicity, but some studies have suggested that these inclusions may sometimes play a protective role [6]. Furthermore, inclusions are not observed in SCA2 [7,8], and intranuclear inclusions are not necessarily indicative or predictive of cell death in polyQ models and patient samples. In addition, although the essential lysine acetyltransferase (KAT) and transcriptional coactivator cAMP-response element-binding (CREB) binding protein (CBP) are sequestered in aggregates formed by mutant Ataxin-3 or huntingtin, they can move in and out of aggregates formed by Ataxin-1 [9]. Thus, localization of

Table 1

Genes affected by polyglutamine expansion and the function of their protein products where known. In some cases repeat expansion affects more than one gene product.

Polyglutamine expansion diseases				
Disease name	Products of expanded gene	Wild-type number of repeats (repeat sequence)	Repeat expansion in disease	Protein function
Huntington disease (HD)	Huntingtin	6–34 (CAG)	36–121	Transcriptial repressor, membrane trafficking, endocytosis.
Spinal and bulbar muscular atrophy (SBMA)/Kennedy's disease	Androgen receptor	9–36 (CAG)	38-62	Nuclear receptor, androgen response.
Dentatorubral-pallidoluysian atrophy	Atrophin 1	7–34 (CAG)	49–88	Nuclear receptor corepressor, transcriptional corepressor.
SCA1	Ataxin-1, alt-ATXN1	6–39 (CAG)	40–82	RNA processing, transcription factor, transcriptional corepressor, general repressor of transcription.
SCA2 and amyotrophic lateral sclerosis (ALS)	Ataxin-2	15–24 (CAG)	27–33 for ALS, 32–200 for SCA2	RNA binding protein.
SCA3, Machado-Joseph disease	Ataxin-3	13–36 (CAG)	61–84	Transcription factor, transcriptional coactivator, transcriptional repressor, histone H2B deubiquitinase.
SCA6	α1A voltage-dependent calcium channel subunit, and α1ACT	4–18 (CAG)	19–33	Voltage-gated calcium channel, transcription factor.
SCA7	Ataxin-7	4–35 (CAG)	36–460	Integral member of SAGA complex, regulation of histone acetylation and ubiquitination.
SCA17	TATA box binding protein (TBP)	25–42 (CAG)	47–63	General transcription factor, member of TFIID complex.

proteins to nuclear inclusions does not always reflect functional sequestration, and may not be a common cause of PolyQ toxicity.

Increasing evidence suggests that PolyQ proteins regulate gene expression and indeed, many of the 9 CAG-expanded genes are transcription factors, transcriptional coactivators, and regulators of RNA stability (Figure 1 and Table 1). Furthermore, analysis of gene expression profiles indicates that a large number of genes are deregulated in mouse models of polyQ disease [10]. We speculate that deregulation of the transcriptional program may be central to polyQ disease etiology. Accordingly, we hypothesize that closer examination of the transcriptional basis for polyQ disease will yield new avenues for therapeutic intervention.

Huntington disease

Huntington disease is caused by polyglutamine expansion of the Huntingtin (Htt) protein [11]. Nearly two decades ago, post-mortem brain samples exhibiting the initial histological signs of Huntington disease showed deregulation of transcripts for enkephalin and substance P before onset of clinical symptoms [12]. These observations suggested that early changes in transcriptional regulation contributed to the onset of clinical symptoms. Subsequently, mouse models for Huntington disease showed altered expression of genes involved in neurotransmission, stress response, and axonal transport before the onset of disease symptoms, suggesting neural-specific deregulation of transcriptional control [13]. Among the many interacting partners of Htt are important transcriptional regulators such as specificity protein 1 (Sp1), TATA-box-binding protein-associated factor II, 130 kDa (TAFII130) [14], CREB, tumor protein p53 (TP53), SIN3 transcription regulator family member A (Sin3a) [15], K (lysine) acetyltransferase 2B (KAT2B/PCAF), CBP, and repressor element 1(RE1)-silencing transcription factor REST [16]. Although CBP and its close homolog E1A binding protein p300 (EP300/p300) are often functionally redundant, and commonly referred to as CBP/p300, polyQ expanded Huntingtin correlates with the degradation of only CBP [17]. CBP is associated with histone H3K27 acetylation, a potential marker for enhancers that are active but not inactive or poised [18••]. Thus, perturbation of gene expression by Htt may occur through changes in epigenetic marks such as H3K27ac.

Studies suggest that polyQ Htt interferes with transcriptional activation by sequestering transcription factors. For example, overexpression of Sp1 and TAFII130 rescues polyQ Htt-mediated inhibition of the dopamine D2