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The Expanding Clinical Universe of Polyglutamine Disease

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Abstract

Polyglutamine (polyQ) diseases are a group of hereditary neurodegenerative disorders caused by expansion of unstable polyQ repeats in their associated disease proteins. To date, the pathogenesis of each disease remains poorly understood, and there are no effective treatments. Growing evidence has indicated that, in addition to neurodegeneration, polyQ-expanded proteins can cause a wide array of abnormalities in peripheral tissues. Indeed, polyQ-expanded proteins are ubiquitously expressed throughout the body and can affect the function of both the central nervous system (CNS) and peripheral tissues. The peripheral effects of polyQ disease proteins include muscle wasting and reduced muscle strength in patients or animal models of spinal and bulbar muscular atrophy (SBMA), Huntington's disease (HD), dentatorubral-pallidoluysian atrophy (DRPLA), and spinocerebellar ataxia type 17 (SCA17). Since skeletal muscle pathology can reflect disease progression and is more accessible for treatment than neurodegeneration in the CNS, understanding how polyQ disease proteins affect skeletal muscle will help elucidate disease mechanisms and the development of new therapeutics. In this review, we focus on important findings in terms of skeletal muscle pathology in polyQ diseases and also discuss the potential mechanisms underlying the major peripheral effects of polyQ disease proteins, as well as their therapeutic implications.

Keywords

CAG repeat expansion; neurodegeneration; peripheral pathology; muscle; protein misfolding

Introduction

Polyglutamine (PolyQ) diseases are a family of neurological disorders that includes Huntington's disease (HD), spinocerebellar ataxia (SCA) 1, 2, 3, 6, 7, and 17, spinobulbar muscular atrophy (SBMA), and dentatorubral-pallidoluysian atrophy (DRPLA) (Bates and others 2015; Orr and Zoghbi 2007; Paulson and others 2017; Ross and others 2014). These are genetically defined, dominantly inherited progressive neurodegenerative diseases caused

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by expanded CAG repeats at distinct gene loci encoding elongated polyQ stretches in the associated disease proteins (Orr and Zoghbi 2007; Paulson and others 2017). Although these polyQ proteins function very differently, expansion of the polyQ repeat can lead to many common pathological features in different polyQ diseases. First, these diseases are late-onset, and symptoms appear at middle age, with deteriorating phenotypes progressing over about 15 to 20 years until death; juvenile cases do exist, however, in accordance with the phenomenon that longer repeat sizes are associated with an earlier age of disease onset. Second, the hallmark of these diseases is the accumulation of abnormally folded proteins in the forms of inclusions and microaggregates, which are predominately present in neurons. Although whether aggregates or inclusions are toxic or protective remains a matter of debate, the formation of polyQ-containing aggregates is correlated with disease progression and results from protein misfolding, a critical polyQ expansion-mediated molecular change that can lead to abnormal protein-protein interaction and a toxic gain-of-function (Lieberman and others 2018). Third, expression of these mutant proteins is widespread throughout the body, but specific populations of neurons are vulnerable and eventually die, leading to different cognitive and motor symptoms (Bates and others 2015; Orr and Zoghbi 2007; Paulson and others 2017; Ross and others 2014).

Although previous research has focused mainly on neuronal degeneration caused by polyQ disease proteins, it has become apparent that polyQ diseases are complicated by peripheral dysfunction and pathology, such as weight loss and skeletal muscle wasting, which are not necessarily associated with changes in brain functions (Carroll and others 2015; van der Burg and others 2009). These features sometimes appear early in the disease course and can contribute substantially to both morbidity and mortality. Indeed, all polyQ proteins are ubiquitously expressed and involved in a variety of cellular functions, among them transcriptional regulation, mitochondrial metabolism, and intracellular signaling pathways (Bates and others 2015; Orr and Zoghbi 2007; Paulson and others 2017; Ross and others 2014). Because polyQ proteins are ubiquitously expressed, it is possible that the peripheral pathology may be caused by the direct effect of mutant proteins on peripheral tissues, in addition to their role in central nervous system (CNS) dysfunction (Huang and others 2015; Lodi and others 2000).

Skeletal muscle dysfunction is involved in a wide spectrum of age-dependent neurological diseases, such as Alzheimer's and Parkinson's diseases, as well as amyotrophic lateral sclerosis (ALS) (Askanas and Engel 2008; Loeffler and others 2016). Emerging evidence supports the theory that muscle wasting is an important pathological feature of polyQ diseases (Huang and others 2015; Lodi and others 2000; Sassone and others 2009; van der Burg and others 2009; Zielonka and others 2014). Since amelioration of muscle dysfunction can help mitigate a deterioration of symptoms and since the muscle phenotypes are more accessible for treatment than CNS dysfunction, we aim to summarize recent achievements in the identification of common peripheral effects of polyQ proteins on muscle and the mechanisms leading to the skeletal muscle malfunction in polyQ diseases. Understanding the peripheral effects of polyQ proteins could provide insights into the pathogenesis of these diseases and novel therapeutic strategies for polyQ diseases.

Mutant HTT Accumulates in Skeletal Muscle and Reduces Muscle Strength

HD is caused by polyQ expansion in the N-terminal region of huntingtin (HTT), a large, 350-kDa protein implicated in a variety of physiological functions (Saudou and Humbert 2016). PolyQ expansion causes HTT to misfold and aggregate, to become toxic, and to accumulate in the nuclei and processes of neuronal and non-neuronal cells (Bates and others 2015; Ross and others 2014). Skeletal muscle malfunction in HD is a well-documented peripheral pathology among all polyQ diseases (Table 1). In a study of 20 people with HD and matched healthy controls, HD patients were found to have reduced isometric muscle strength by 50% on average when assessed using a handheld dynamometer (Busse and others 2008). A case study reported a marathon runner with 43 CAGs in the HTT gene who developed exercise-induced muscle fatigue as a first sign at the presymptomatic HD stage, before developing typical HD symptoms (Kosinski and others 2007). Muscle damage is thought to be caused by mutant HTT in muscle cells because these cells show the existence of HTT aggregates. For example, Saft et al found HTT inclusions in muscle biopsies of HD patients (Saft and others 2005); Ciammola et al cultured muscle cells from HD patients and observed HTT immunoreactive inclusions in differentiated myotubes (Ciammola and others 2011).

Muscle phenotypes have also been seen in several HD mouse models. In the R6/2 mouse model that expresses an N-terminal mutant HTT fragment, HTT aggregates can be detected as early as 6 weeks in the quadriceps muscle (Sathasivam and others 1999), and more aggregates are formed in quadriceps and hamstrings at 13 weeks (Disatnik and others 2016). Muscle cell cultures revealed that HTT forms aggregates in differentiated myotubes, as seen in HD patients (Orth and others 2003). These inclusions were also detected in the HdhQ150 knock-in mouse model that expresses full-length mutant HTT at the endogenous level; these animals show almost identical aggregates as those seen in R6/2 mice at 12 weeks of age (Moffitt and others 2009; Ribchester and others 2004; Sathasivam and others 1999). In BACHD mice that also express full-length mutant HTT, ultrastructure analyses revealed enlargement of the sarcoplasmic reticulum, the invasion of the myofibrils region by connective tissues, the presence of vacuoles inside the mitochondria, and the appearance of intermyofibrillar glycogen and disorganization of the triads (Valadão and others 2017).

Many studies discovered that the skeletal myopathy in HD patients is associated with changes in mitochondrial function, supporting mitochondrial dysfunction as a key pathogenic factor in HD-related muscle pathogenesis (Reddy 2014). Using ^{31}P magnetic resonance spectroscopy (^{31}P -MRS), one study demonstrated a significant decrease in the phosphocreatine-to-inorganic phosphate ratio in the resting muscle of HD patients compared with control subjects (Koroshetz and others 1997). This was further confirmed by the results from 12 patients (4 presymptomatic gene carriers) (Lodi and others 2000). The latter also observed that, during recovery from exercise, the maximum rate of mitochondrial adenosine triphosphate production was reduced by 44% in symptomatic HD patients and by 35% in presymptomatic HD carriers compared to healthy controls (Lodi and others 2000). Other mitochondrial electron transport chain dysregulations were uncovered through a series of case studies (Turner and others 2007). Ciammola et al confirmed that muscular cell cultures from HD patients show increased lactate and striking mitochondrial structural abnormalities

(Ciammola and others 2011). Mouse models also yielded strong evidence supporting mitochondrial dysfunction in HD. R6/2 mice not only showed muscle fiber atrophy and increased fuchsinophilic aggregates, but also decreased cytochrome *c* oxidase activity (Gizatullina and others 2006).

Skeletal Muscle Dysfunction in Other PolyQ Diseases

SBMA, or Kennedy's disease, presents another example of polyQ expansion-mediated muscle atrophy. SBMA is caused by a polymorphic CAG repeat expansion in the first exon of the coding region of the androgen receptor (AR) gene, which encodes a steroid receptor-thyroid receptor. A study of 233 patients concluded that muscular weakness associated with SBMA occurred predominantly in the lower limbs in middle age (Cox and others 2000). Studies using muscle biopsy revealed myogenic changes in SBMA patients, including myotubes with a reduced number of nuclei, impaired fusion, and contractile structures that were not responsive to androgen treatment (Malena and others 2013; Querin and others 2016). Using immunochemistry, a study of 19 patients found that mutant AR accumulates in the nucleus of skeletal muscle and causes depletion of mitochondrial mass (Borgia and others 2017). Interestingly, muscle atrophy in SBMA was associated with a glycolytic-to-oxidative fiber-type switch and elevated lipid metabolism (Rocchi and others 2016).

The skeletal muscle alterations and disability seen in SBMA patients were confirmed by a variety of mouse models. The AR113 knock-in mouse model, which expresses full-length mutant AR, verified androgen-dependent myopathy with downregulated expression of CLCN1, the skeletal muscle sodium channel alpha-subunit, and decreased urinary tract myotonic discharges (Yu and others 2006). In this mouse model, the muscle exhibits diminished glycolysis, altered mitochondrial function, and an impaired response to exercise (Giorgetti and others 2016). Administration of insulin-like growth factor 1 (IGF-1) in skeletal muscle can ameliorate SBMA-associated behavioral and histopathological abnormalities (Palazzolo and others 2009). Using a gene silencing technique to suppress mutant AR in skeletal muscle in AR113 and BAC transgenic mice prevented weight loss, motor phenotypes, muscle pathology, motor dysfunction, and also dramatically extended survival time (Cortes and others 2014; Giorgetti and others 2016; Lieberman and others 2014). On the other hand, overexpression of AR selectively in skeletal muscle showed hormone-dependent myopathy and motor axon loss (Monks and others 2007).

In DRPLA, which is caused by an unstable CAG repeat in the atrophin-1 gene coding region, muscle atrophy is also evident. In a case report of a 9-year-old male DRPLA patient, muscle biopsy revealed significant histological changes, such as an absence of type IIB fibers and a predominance of type I fibers, with an increase in lipid droplets (Cox and others 2000). Studies of in vivo muscle energy metabolism on DRPLA patients showed a reduced phosphocreatine-to-inorganic phosphate ratio at rest and a reduction in the maximum rate of mitochondrial adenosine triphosphate production in muscle (Lodi and others 2000).

Although patients with spinocerebellar ataxia (SCA) 1, 2, 3, 6, 7, and 17 all present with body weight loss and suspicion of muscle atrophy, the muscle phenotypes have not been clearly demonstrated in these patients; however, by generating SCA17 knock-in mice that

express mutant TATA-box-binding protein (TBP) with 105Q, these authors have previously reported striking muscle degeneration in the SCA17 mice (Huang and others 2015) (Fig. 1). Since SCA17 is a very rare disease and the largest CAG repeat in SCA17 patients was found to be 66 (van Roon-Mom and others 2005), it is possible that CAG repeats >66 in TBP are very deleterious to humans and could cause severe muscle atrophy that does not lead to viable birth or survival after birth. The SCA17 mouse model suggests that a large polyQ repeat (105Q) in TBP may preferentially cause muscle degeneration. This study also suggests that peripheral phenotypes in some polyQ diseases are polyQ repeat length dependent and offer a rationale for examining peripheral phenotypes of other SCA diseases when a large polyQ repeat is expressed.

Potential Mechanisms of Muscle Atrophy in PolyQ Diseases

Muscles require neuronal innervation to function, and the neuromuscular junction, innervated by motor neurons, transmits synaptic signals to the muscle fiber, causing muscle contraction. Since mutant polyQ proteins preferentially accumulate in neurons and affect neuronal function, some have speculated that muscle weakness and atrophy could be caused by dysfunction of motor neurons and denervation (Yu and others 2006). However, there has been a growing appreciation of muscle cells as a primary target in polyQ diseases (Fig. 2). Indeed, both myopathy and neurogenic atrophy features are seen in muscle biopsies of SBMA patients (Sorarù and others 2008).

For HD, it is still an open question whether HD-related skeletal muscle pathology is a secondary event resulting from neuronal abnormalities or is primarily caused by mutant HTT in muscle cells. That said, expression of mutant polyQ in the myocardial cells in *Drosophila melanogaster* also resulted in polyQ length-dependent cardiac defects, including recurrent asystolic periods and a near-complete lack of cardiac contractility (Melkani and others 2013). Mouse models have been valuable tools to identify the primary target site for the peripheral effects of polyQ disease proteins. Although the preceding studies suggest a role for muscle dysfunction as a component of SBMA motor neuronopathy, work on a BAC (bacterial artificial chromosome) transgenic mouse model of SBMA indicated that removal of polyQ-AR from skeletal muscle alone was sufficient to prevent the development of systemic and neuromuscular SBMA phenotypes (Cortes and others 2014). Other strong evidence for the primary effects of polyQ proteins in muscles is that conditional knock-in SCA17 mice, which selectively express mutant TBP in muscle cells, show muscle atrophy and weakness phenotypes similar to the knock-in mice that express mutant TBP ubiquitously in the whole body (Huang and others 2015). Also, SCA17 KI mice at 3 months of age show muscle degeneration and phenotypes prior to the development of typical neurological symptoms (Huang and others 2015), further suggesting the primary and important contributions of muscle atrophy to the severe phenotypes of SCA17 mice. It should also be noted that skeletal muscle is a major source of trophic support for innervating motor neurons and contributes to neuron survival, synaptic activity, and axonal function (Funakoshi and others 1995).

As for molecular changes in myocytes caused by polyQ disease proteins, it seems that key pathways governing protein metabolism, apoptosis, and autophagy are altered. As discussed

above, mitochondrial abnormalities are seen in the muscle cells expressing expanded polyQ proteins in different polyQ diseases, which are in accordance with a variety of metabolic alterations. In SCA17 knock-in mice, enlarged and swollen mitochondria are abundant in myoblasts, providing ultrastructural evidence for mitochondrial abnormalities and dysfunction (Huang and others 2015).

Robust activation of macroautophagy is reported in myocytes in HD and SBMA mouse models (Rusmini and others 2015; She and others 2011), raising the possibility that overactivity of this pathway may be deleterious. SBMA patients and knock-in mice display impaired glycolysis, the upregulation of autophagy-related transcription factor EB, and enhancement of mTOR signaling in the muscle tissues (Rocchi and others 2016). Activation of caspase cascades was found in myocytes expressing mutant polyQ proteins. For example, in the HD R6/2 mouse model, the mRNA level of several caspase genes (CASPASE-3/7, -8, and -9) were elevated (She and others 2011). However, it remains to be investigated whether increased caspase activity is specific to overexpressed transgenic mutant Htt, as other polyQ disease mouse models have not shown such increased caspase activities in their muscle tissues.

The wide range of cellular effects of polyQ proteins in muscles is likely due to both nuclear and cytoplasmic toxicity of polyQ proteins. It is well known that mutant Htt can affect transcription of a large number of genes (Bates and others 2015; Ross and others 2014). A study using skeletal muscle from eight HD patients revealed a transition of gene expression from fast-twitch to slow-twitch muscle fiber types (Strand and others 2007). This trend was also found in R6/2 and HdhQ150 mice (Strand and others 2005). Mutant polyQ proteins form aggregates in muscle cells in the same manner as in the brain. The toxic effects of the inclusion bodies may disturb the homeostasis of muscle cells, which can contribute to muscle atrophy. Mutant Htt in the cytoplasm is also found to interact with a variety of proteins, mediating gain-of-function toxicity (Li and Li 2004; Saudou and Humbert 2016). For SBMA, DRPLA, and SCA17, the nuclear effects of mutant polyQ proteins may play a predominant role in muscle atrophy and dysfunction, as these disease proteins are transcription factors or transcription corepressors. For example, mutant AR protein may repress transcription of peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1 α), a transcriptional coactivator that regulates expression of nuclear-encoded mitochondrial proteins, resulting in impairment of mitochondrial function (Ranganathan and others 2009). Expanded polyQ-containing AR interacts with the transcription coactivator CRE response element-binding protein (CREB)-binding protein (CBP) to interfere with CBP-dependent transcription (McCampbell and others 2000). Mutant AR with expanded polyQ also interferes with the function of transcription factor TFEB to impair autophagy (Cortes and others 2014). In SCA17 knock-in mice, an expanded polyQ repeat (105Q) reduces the association of MyoD, a muscle-specific transcription factor, with TBP and DNA promoters, resulting in decreases in the expression of a number of muscle-specific proteins (Huang and others 2015). Taken together, multiple cellular functions in muscles can be affected by expanded polyQ proteins via gene transcriptional dysregulation and/or cytoplasmic toxicity, leading to muscle atrophy and malfunction (Fig. 3).

Therapeutic Implications

Muscle atrophy and malfunction can affect vital functions of multiple organs and significantly exacerbate the neurological symptoms of polyQ diseases. Alleviation and treatment of muscle atrophy and other peripheral effects may be a crucial therapeutic approach for polyQ diseases. Similar to neurons, muscle cells are postmitotic cells incapable of rapid self-renewal and are susceptible to different types of cellular stress and misfolded proteins. However, treating muscle atrophy is presumably more feasible than treating neuronal atrophy because muscle tissues are accessible to the administration of drugs or chemicals and medical intervention. Based on the common features of mitochondrial dysfunction and abnormalities in muscle tissues in polyQ diseases, drugs that improve mitochondrial function and energy metabolism should help alleviate muscle atrophy. Strategies to enhance PGC-1 α activity, the master regulator of mitochondrial biogenesis, may improve skeletal muscle function. Since mTOR signaling is increased by polyQ disease proteins, antagonist drugs that reduce mTOR activity could be beneficial for mitigating the toxic effects of mutant polyQ proteins in skeletal muscle cells. Based on the theory that heat shock machinery modulation could suppress mutant Htt aggregation, expression of an active heat-shock transcription factor 1 (HSF1) isoform in peripheral tissues of R6/2 mice was found to result in a significant improvement of mouse life span (Fujimoto and others 2005).

The divergent mechanisms of toxicity in polyQ myopathy, however, suggest that potential treatments targeting a single downstream pathway are likely to be incomplete or unsuccessful. Thus, targeting the mutant polyQ protein itself as the proximal mediator of disease has attracted much recent attention. In the SBMA disease mouse model, gene silencing techniques, such as antisense oligonucleotides and the Cre-loxP system, were applied to selectively suppress the expression of mutant polyQ-AR in skeletal muscle (Cortes and others 2014). These strategies rescued deficits in muscle weight, fiber size, and grip strength, reversed changes in muscle gene expression, and extended the life span of mutant mice (Cortes and others 2014; Giorgetti and others 2016; Lieberman and others 2014). The recently developed gene editing tool, CRISPR/Cas9, holds great promise for precisely depleting mutant polyQ proteins (Yang and others 2017). In fact, removing the expression of mutant Htt in HD mouse brain showed beneficial effects on motor function and reduction of neuropathology (Yang and others 2017). Since CRISPR/Cas9 expression in muscle cells can be readily achieved by viral transduction and since this gene targeting does not require continuous administration of therapeutic reagents, CRISPR/Cas9 is a particularly attractive approach that can permanently eliminate polyQ protein expression and its associated toxicity. Given that muscle tissues are accessible to a variety of therapeutic approaches, treatment of muscle phenotypes in polyQ diseases could be an effective strategy.

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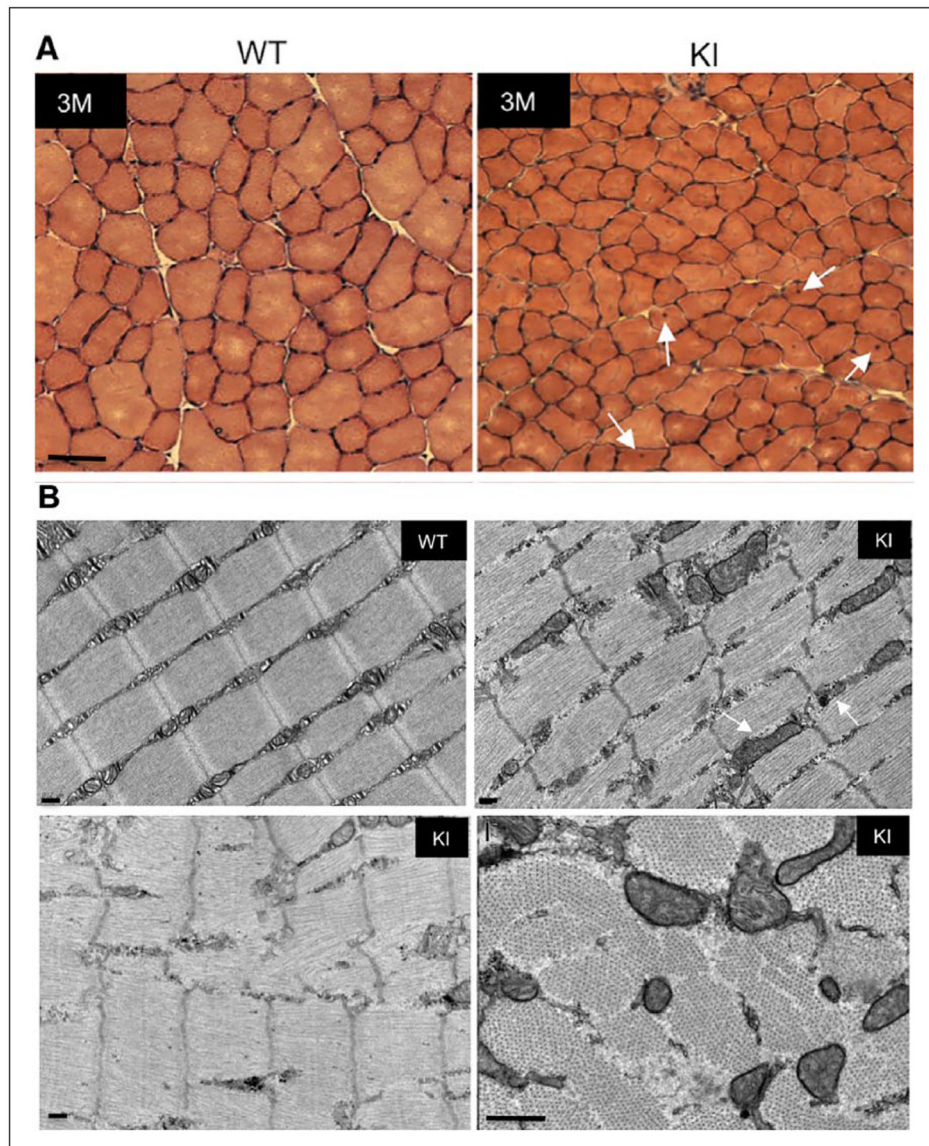


Figure 1. Mutant TATA-binding protein (TBP) causes muscle atrophy in SCA17 knock-in mice. (A) Hematoxylin and eosin (H&E) cross-section staining of tibialis anterior muscles from 3-month-old SCA17 KI (spinocerebellar ataxia 17 knock-in) mice showing a decrease in myofibril size, including severe muscle atrophy and cells containing central nuclei (white arrow), a feature of muscle degeneration. Scale bars, 50 μ m. (B) Electron microscopy of WT (wild type) and SCA17 KI tibialis anterior muscles. In KI muscle, Z bands are destroyed and mitochondria are swollen, abnormally shaped, and enlarged. Scale bars, 0.2 μ m. From the author's publication (Huang and others 2015).

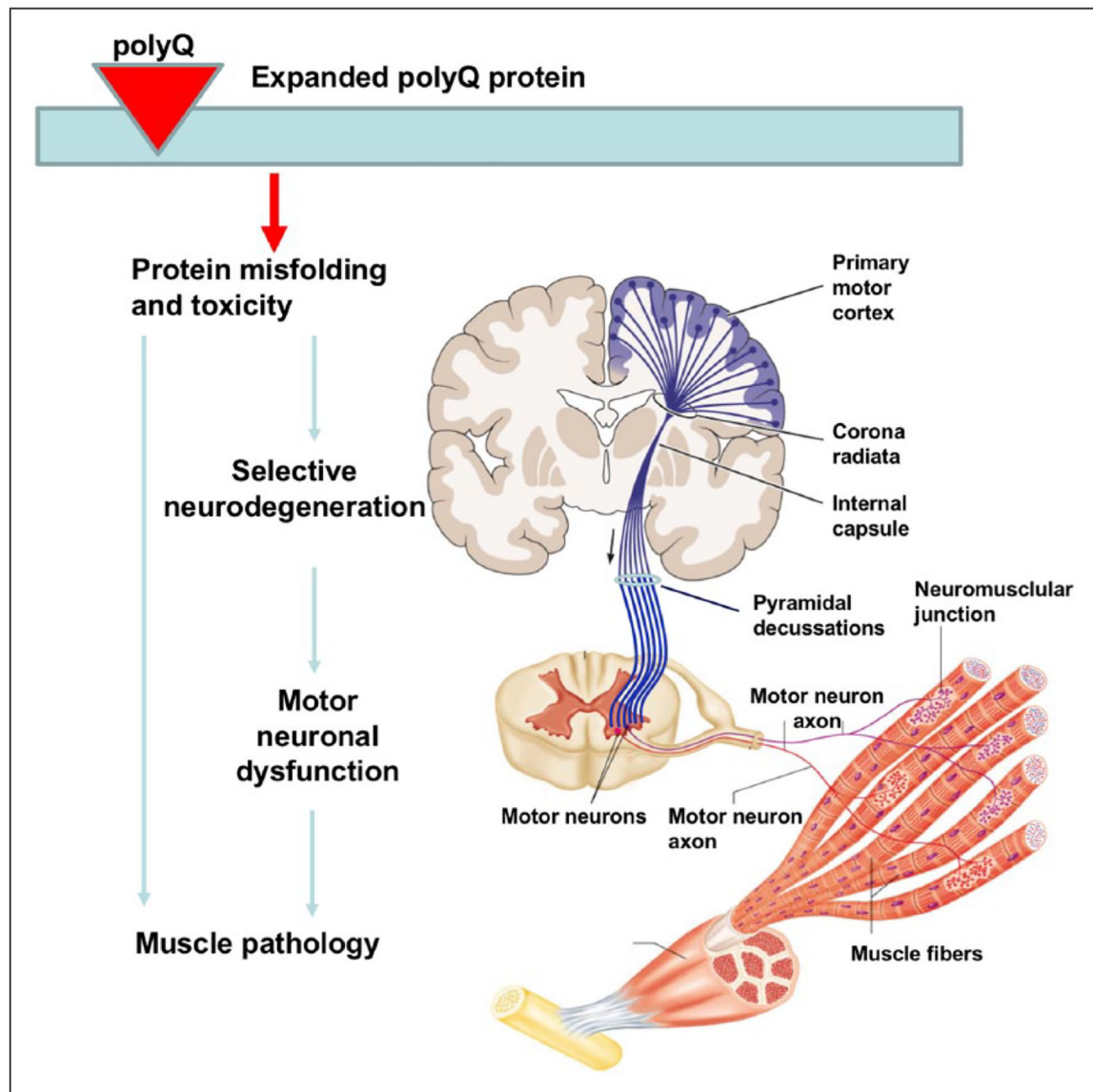


Figure 2.

PolyQ disease protein-mediated muscle pathology. Expansion of polyQ repeats can cause protein misfolding and accumulation in the neuronal and muscle cells, resulting in neuronal dysfunction and direct toxicity in muscle cells. Both nuclear and cytoplasmic toxicity of polyQ proteins contributes to muscle pathology.

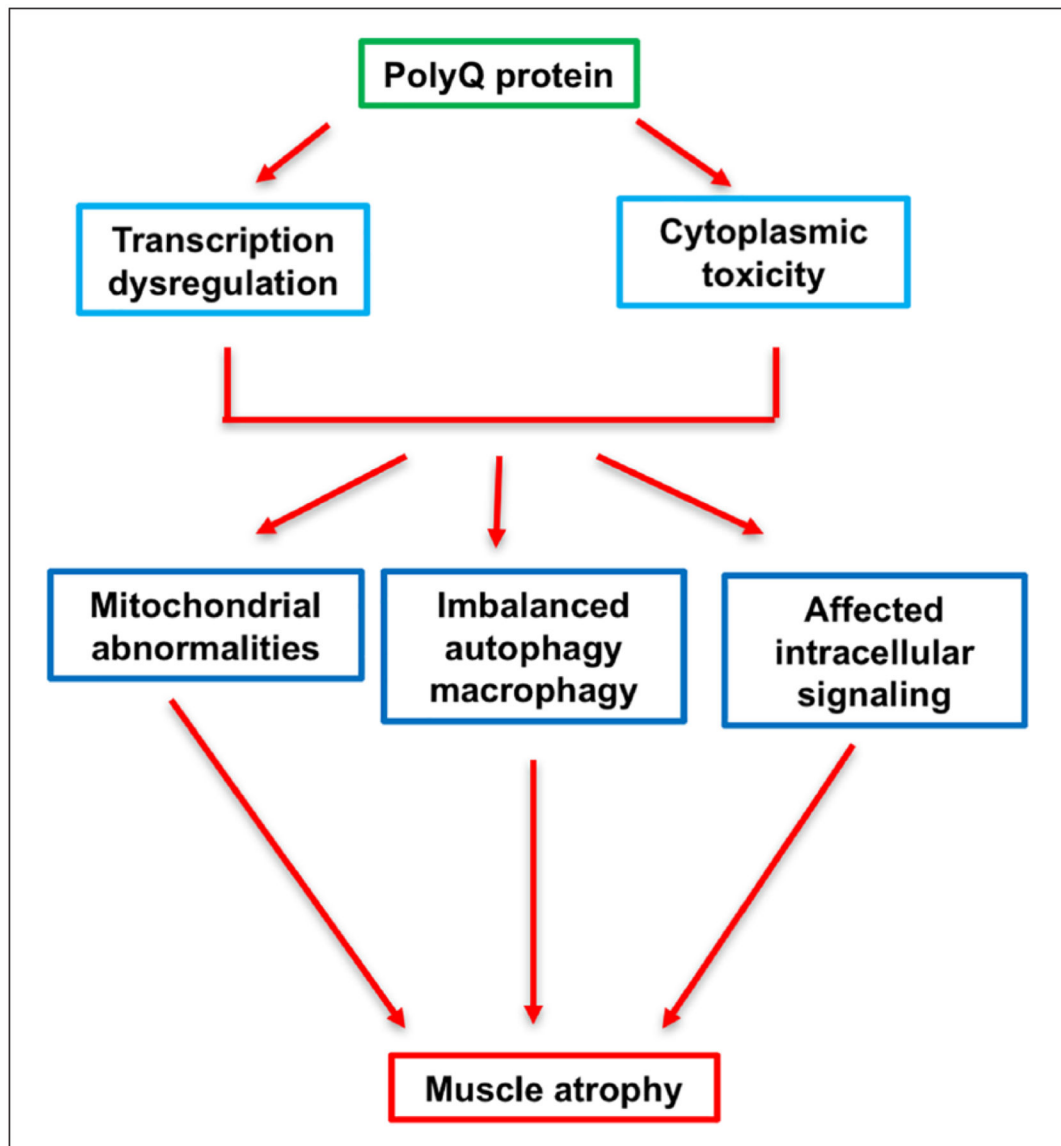


Figure 3.

Multiple pathological pathways for muscle pathology. Mutant polyQ repeats with expanded polyQ repeats can affect gene transcription and cytoplasmic function, leading to multiple pathways that cause muscle atrophy.

Table 1.
Summary of the CAG/Polyglutamine Repeat Expansion Diseases with Peripheral Pathology.

Disease	Protein	Normal Glutamine Repeats	Expanded Glutamine Repeats	Protein Function	Protein Expression	Most Affected Neurons	Most Affected Peripheral Tissue
Huntington disease (HD)	Huntingtin	6–35	39–250	Likely scaffold protein	Ubiquitous	Striatal neurons	Muscle
Spinal and bulbar muscular atrophy (SBMA)	Androgen receptor	5–34	37–70	Transcription factor	Ubiquitous	Motor neurons	Muscle
Dentatorubral pallidoluysian atrophy (DRPLA)	Atrophin-1	3–38	49–88	Transcription corepressor	Ubiquitous	Brainstem, cerebellar, and deep midbrain structures	Muscle
Spinocerebellar Ataxia type 17 (SCA17)	TATA-binding protein (TBP)	25–43	45–66	Transcription factor	Ubiquitous	Striatal neurons, cerebellar Purkinje cells	Muscle