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Toward understanding Machado–Joseph disease

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ABSTRACT

Machado–Joseph disease (MJD), also known as spinocerebellar ataxia type 3 (SCA3), is the most common inherited spinocerebellar ataxia and one of many polyglutamine neurodegenerative diseases. In MJD, a CAG repeat expansion encodes an abnormally long polyglutamine (polyQ) tract in the disease protein, ATXN3. Here we review MJD, focusing primarily on the function and dysfunction of ATXN3 and on advances toward potential therapies. ATXN3 is a deubiquitinating enzyme (DUB) whose highly specialized properties suggest that it participates in ubiquitin-dependent proteostasis. By virtue of its interactions with VCP, various ubiquitin ligases and other ubiquitin-linked proteins, ATXN3 may help regulate the stability or activity of many proteins in diverse cellular pathways implicated in proteotoxic stress response, aging, and cell differentiation. Expansion of the polyQ tract in ATXN3 is thought to promote an altered conformation in the protein, leading to changes in interactions with native partners and to the formation of insoluble aggregates. The development of a wide range of cellular and animal models of MJD has been crucial to the emerging understanding of ATXN3 dysfunction upon polyQ expansion. Despite many advances, however, the principal molecular mechanisms by which mutant ATXN3 elicits neurotoxicity remain elusive. In a chronic degenerative disease like MJD, it is conceivable that mutant ATXN3 triggers multiple, interconnected pathogenic cascades that precipitate cellular dysfunction and eventual cell death. A better understanding of these complex molecular mechanisms will be important as scientists and clinicians begin to focus on developing effective therapies for this incurable, fatal disorder.

Contents

Abbreviations: ATXN3, ataxin-3; bZIP, basic leucine zipper motif; CBPC, REB binding protein; cDNA, complementary DNA; CHIP, C-terminus of Hsc70 interacting protein; CK2, casein kinase 2; CMV, cytomegalovirus; CNS, central nervous system; CREB, cAMP-response element binding; DRPLA, dentatorubral pallidoluysian atrophy; DUB, deubiquitinating enzyme; ERAD, endoplasmic reticulum-associated degradation; FOXO, forkhead box O; HD, Huntington disease; HDAC, histone deacetylase; HDL2, Huntington disease-like 2; HSF1, heat-shock factor 1; HSP, heat-shock protein; Htt, huntingtin; IGF1, insulin/insulin-like growth factor 1; JD, Josephin domain; Kv, voltage-activated potassium; LNA, locked nucleic acid; MITOL, mitochondrial ubiquitin ligase; MJD, Machado–Joseph disease; MRI, magnetic resonance imaging; NCIs, neuronal cytoplasmic inclusions; NCOR1, nuclear receptor co-repressor 1; NEDD8, neural precursor cell expressed developmentally downregulated 8; NES, nuclear export signal; NLS, nuclear localization signal; NNIs, neuronal nuclear inclusions; p97, ATPase p97; PCAF, p300/CREBBP associated factor; PLIC1, protein linking IAP to the cytoskeleton; PNA, peptide nucleic acid; polyQ, polyglutamine; Prnp, prion protein; RNAi, RNA interference; ROS, reactive oxygen species; SCA, spinocerebellar ataxia; SBMA, spinal bulbar muscular atrophy; shRNAs, short hairpin RNAs; SNPs, single nucleotide polymorphisms; SOD, superoxide dismutase; STRs, single tandem repeats; SUMO, small ubiquitin-like modifier; Ub, ubiquitin; Ubl, ubiquitin-like; UIM, ubiquitin interacting motif; UPS, ubiquitin proteasome system; UTR, untranslated region; VCP, valosin-containing protein; YAC, yeast artificial chromosome; 17-AAG, 17-allylamino-17-demethoxygeldanamycin.

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1. Introduction

Many hereditary neurodegenerative diseases manifest later in life and are characterized by the progressive and selective loss of neuronal cell bodies, axons, dendrites and/or synapses. For decades scientists have sought to clinically define specific neurodegenerative diseases and their genetic causes in order to achieve a molecular diagnosis, offer presymptomatic and prenatal testing to affected families, generate cellular and animal models toward understanding pathogenic mechanisms and facilitate the development of potential therapies. Studies over the past 20 years have established that an unusual type of mutation, dynamic repeat expansions, cause many inherited neurodegenerative diseases.

Among the dynamic repeat expansion diseases, the polyglutamine (polyQ) disorders caused by CAG repeat expansions represent the most common class, although each polyglutamine disease is relatively rare. In all polyQ diseases the CAG repeat expansion is translated into an abnormally long stretch of glutamine residues in the corresponding disease protein. Spinal bulbar muscular atrophy (SBMA) was the first discovered polyQ disease, identified 20 years ago (La Spada et al., 1991). Since then nine additional polyQ diseases have been identified: the spinocerebellar ataxias (SCA) types 1, 2, 3 (also known as Machado–Joseph disease), 6, 7 and 17, dentatorubral-pallidoluysian atrophy (DRPLA), Huntington disease (HD), and, most recently, Huntington disease-like 2 (HDL2). All polyQ diseases are dominantly inherited disorders except SBMA, which is X-linked. The current review focuses on MJD/SCA3 and its disease protein, ataxin-3 (ATXN3).

Development of rational, targeted therapies for these diseases will be facilitated by knowing the pathogenic mechanism of the disease-causing mutation. As a class, polyQ diseases share certain features that suggest a general toxic mechanism triggered by expanded polyQ, which might be targetable in class-wide therapeutics. All 10 polyglutamine diseases are characterized by selective neurodegeneration in the central nervous system (CNS) despite widespread expression of the disease proteins. Indeed there is little correlation between the expression pattern of polyQ proteins and the sites of CNS pathology. The disease proteins are widely expressed throughout the CNS with two notable exceptions: the $CACNA1_A$ calcium channel subunit in SCA6, which is mainly expressed in affected cerebellar Purkinje cells, and the androgen receptor in SBMA, which is primarily expressed in vulnerable motor neurons. Another shared feature of polyQ disease proteins is their propensity to misfold, oligomerize, and form intracellular aggregates and inclusions that constitute a pathological disease hallmark. The misfolding and aggregation of polyQ disease proteins have been targets of some proposed therapeutic strategies (Bauer and Nukina, 2009; Di Prospero and Fischbeck, 2005; Matos et al., 2011; Williams and Paulson, 2008).

Despite these shared features, however, each polyQ disease is a distinctive disorder with characteristic symptomatology and pathology occurring in specific brain regions. PolyQ disease proteins differ in size, cellular localization and biological function, suggesting that the toxic effect of a given polyQ expansion depends on the specific protein context and that the particular details of pathogenesis may be unique to each disease.

Here we review Machado–Joseph disease (MJD), also known as spinocerebellar ataxia type 3 (SCA3), focusing primarily on the molecular properties of the disease protein, ATXN3, both in normal and pathogenic contexts, and on recent progress toward therapeutic development for this fatal disorder.

2. MJD

2.1. Clinical features

The discovery of MJD (OMIM#109150) illustrates the difficulty of defining a disease as a single entity when variable symptoms themselves represent a hallmark of the disease. MJD was first described in Northern American families of Azorean ancestry. Between 1972 and 1977 the disease was identified in four families, reported as four distinct entities named "Machado disease" (Nakano et al., 1972), "nigro-spino-dentatal degeneration" (Woods and Schaumburg, 1972), "Joseph disease" (Rosenberg et al., 1976), and "Azorean disease of the nervous system" (Romanul et al., 1977). In 1975, Coutinho and Andrade studied 15 families from the Azorean Islands and proposed that the above mentioned diseases were simply variations of the same clinical disorder (Coutinho and Andrade, 1978). They defined it as "Machado–Joseph disease," a single disorder characterized by an unusually high degree of clinical variability.

Most frequently in affected individuals, a slowly progressive "ataxia-plus" syndrome appears, typically beginning between the ages of 20 and 50 years (Coutinho and Andrade, 1978; Paulson, 1998 Oct 10 [updated 2011 March 17]). Cerebellar ataxia, progressive external ophthalmoplegia, dysarthria, dysphagia, pyramidal signs, dystonia, rigidity, and distal muscle atrophies are common features of MJD. The highly variable clinical presentation led to a description of four distinct clinical subtypes of MJD (Coutinho and Andrade, 1978; Lima and Coutinho, 1980; Paulson, 2007; Riess et al., 2008; Rosenberg, 1992). Type 1 begins early in life, often before age 20, may progress more quickly and is characterized by prominent pyramidal signs (rigidity and spasticity) and extrapyramidal features (bradykinesia and dystonia) as well as ataxia. Type 2, the most common type, has an intermediate