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Pathogenesis and therapy of spinal and bulbar muscular atrophy (SBMA)

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ABSTRACT

Spinal and bulbar muscular atrophy (SBMA) is a late-onset motor neuron disease characterized by slowly progressive muscle weakness and atrophy. During the last two decades, basic and clinical research has provided important insights into the disease phenotype and pathophysiology. The cause of SBMA is the expansion of a trinucleotide CAG repeat encoding a polyglutamine tract within the first exon of the androgen receptor (AR) gene. SBMA exclusively affects adult males, whereas females homozygous for the AR mutation do not manifest neurological symptoms. The ligand-dependent nuclear accumulation of the polyglutamine-expanded AR protein is central to the gender-specific pathogenesis of SBMA, although additional steps, e.g., DNA binding, inter-domain interactions, and post-translational modification of AR, modify toxicity. The interactions with co-regulators are another requisite for the toxic properties of the polyglutamine-expanded AR. It is also shown that the polyglutamine-expanded AR induces diverse molecular events, such as transcriptional dysregulation, axonal transport disruption, and mitochondrial dysfunction, which play causative roles in the neurodegeneration in SBMA. The pathogenic AR-induced myopathy also contributes to the non-cell autonomous degeneration of motor neurons. Pre-clinical studies using animal models show that the pathogenic AR-mediated neurodegeneration is suppressed by androgen inactivation, the efficacy of which has been tested in clinical trials. Pharmacological activation of cellular defense machineries, such as molecular chaperones, ubiquitin–proteasome system, and autophagy, also exerts neuroprotective effects in experimental models of SBMA.

Contents

Abbreviations: SBMA, spinal and bulbar muscular atrophy; AR, androgen receptor; HD, Huntington's disease; AF, transcativation function; CBP, c-AMP response element binding protein-binding protein; NI, nuclear inclusion; N/C, amino- and carboxyl-terminal domains; Hsp, heat shock protein; HAT, histone acetyltransferase; JNK, c-Jun N-terminal kinase; LHRH, luteinizing hormone-releasing hormone; 17-AAG, 17-allylamino-17-demethoxygeldanamycin; CHIP, C terminus of heat shock cognate protein 70-interacting protein; HDAC, histone deacetylase; ASC-J9, 5-hydroxy-1,7-bis(3,4-dimethoxyphenyl)-1,4,6-heptatrien-3-one.

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1. Introduction

Although most of neurodegenerative diseases were first documented in the late nineteenth century, it was recent advancement in neurobiology that identified the causative molecules and thereby provided insights into the pathogenesis. Continual efforts to understand the disease mechanisms have identified the accumulation of intracellular and extracellular proteins as the molecular basis for various neurodegenerative diseases. Moreover, the creation of animal models that recapitulate human pathology has been driving the translation of biological insights into disease-modifying therapies which inhibit the core pathological events in neurodegeneration. Particularly, a number of promising therapies have been developed for polyglutamine-mediated neurodegenerative disorders on the basis of their monogenic nature of disease.

Over the last two decades, nine polyglutamine diseases have been identified: spinal and bulbar muscular atrophy (SBMA); Huntington's disease (HD); dentatorubral-pallidoluysian atrophy and six forms of spinocerebellar ataxia (Orr and Zoghbi, 2007; La Spada and Taylor, 2010). SBMA, the first polyglutamine disease ever discovered, is an adult-onset, hereditary neurodegenerative disease characterized by slowly progressive muscle weakness due to the degeneration of lower motor neurons and by gender-dependent manifestation of disease phenotypes (Kennedy et al., 1968; Katsuno et al., 2006a; Finsterer, 2010). The cause of SBMA is the expansion of a trinucleotide CAG repeat, which encodes the polyglutamine tract, within the gene encoding *androgen receptor* (*AR*) (La Spada et al., 1991). The androgen-dependent toxicity of polyglutamine-expanded AR protein has been construed as the molecular basis for the selective degeneration of lower motor neurons, and an important target of therapy development. Basic research using animal models suggests candidate agents to treat SBMA, the efficacy of which has been tested in clinical trials (Ranganathan and Fischbeck, 2010). Here we outline the molecular pathogenesis and the therapeutic strategies currently being developed, and discuss the future direction of SBMA research.

2. Clinical and histopathological features of SBMA

More than a hundred years have elapsed since the first description of SBMA from Hiroshi Kawahara, who described the clinical and hereditary characteristics of two Japanese brothers with progressive bulbar palsy (Kawahara, 1897). This work was followed by several reports on similar cases with or without X-linked pattern of inheritance (Katsuno et al., 2006a). The details of clinical, genetical, and pathological features of this disorder were first documented by Kennedy et al. in 1968. The causative gene of SBMA was located on the proximal arm of chromosome X by Fischbeck et al. (1986), that was followed by the identification of the trinucleotide CAG repeat expansion in the *AR* gene in 1991 (La Spada et al., 1991). This was the first discovery of polyglutamine-mediated neurodegenerative diseases, and led to the development of cellular and animal models. SBMA is also known as Kennedy's disease. Other names for this disease include bulbospinal neuronopathy, X-linked spinal muscular atrophy, bulbospinal muscular atrophy, spinobulbar muscular atrophy, spinal bulbar muscle atrophy, and bulbar and spinal muscular atrophy.

SBMA chiefly affects adult males. The prevalence of this disease is estimated to be 1–2 per 100,000, whereas patients may have been misdiagnosed as other neuromuscular diseases such as amyotrophic lateral sclerosis (Fischbeck, 1997; Parboosingh et al., 1997; Guidetti et al., 2001). Although patients of various ethnic backgrounds have been reported around the world, a high prevalence of SBMA has been reported in some isolated areas such as Vasa region of Finland (Udd et al., 1998; Finsterer, 2010).

The major symptoms of SBMA are weakness, atrophy, and fasciculations of bulbar, facial, and limb muscles, which are attributable to degeneration of lower motor neurons in the spinal cord and brainstem (Kennedy et al., 1968; Harding et al., 1982). In extremities, involvement is usually predominant in proximal musculature, and is occasionally asymmetric. The onset of weakness is usually between 30 and 60 years of age, but is often preceded by nonspecific symptoms such as postural tremor and muscle cramps (Sperfeld et al., 2002; Atsuta et al., 2006; Rhodes et al., 2009; Hanajima et al., 2009). The initial site of weakness is lower limbs in more than half of patients (Atsuta et al., 2006; Rhodes et al., 2009). Typically, affected individuals require a wheelchair 15–20 years after the onset of weakness (Atsuta et al., 2006; Chahin and Sorenson, 2009). Fasciculations are not apparent at rest, but become conspicuous upon voluntary muscle movement. These contraction fasciculations are especially noticeable in the face, neck, and tongue. Neuromuscular symptoms are often worsened by coldness and by fatigue after exercise. Bilateral facial and masseter muscle weakness, poor uvula and soft palatal movements, and atrophy of the tongue with fasciculations are often encountered (Fig. 1A). Speech has a nasal quality in most cases due to reduced velopharyngeal closure. Patients occasionally experience laryngospasm, a sudden sensation of dyspnea (Sperfeld et al., 2005). Advanced cases often develop dysphagia, eventually resulting in aspiration or choking. Muscle tone is usually hypotonic, and no pyramidal signs are detected. The deep tendon reflex is diminished or absent with no pathological reflex. Sensory involvement is largely restricted to a sense of vibration, which is affected distally in the legs (Sobue et al., 1989). Cerebellar symptoms are absent, while dysautonomia and mild cognitive impairment have been reported in a limited number of patients (Mirowska-Guzel et al., 2009; Rocchi et al., 2011).

Patients occasionally demonstrate signs of androgen insensitivity such as gynecomastia, testicular atrophy, dyserection, and decreased fertility, some of which are detected before the onset of motor symptoms (Fig. 1B) (Nagashima et al., 1988; Sperfeld et al., 2002; Battaglia et al., 2003). Abdominal obesity is common, whereas male pattern baldness is rare in patients with SBMA (Sinclair et al., 2007). Profound facial fasciculations, bulbar signs, gynecomastia, and sensory disturbances are the main clinical features distinguishing SBMA from other motor neuron diseases, although genetic analysis is indispensable for diagnosis.

Electromyogram shows neurogenic abnormalities, and distal motor latencies are often prolonged in nerve conduction studies (Guidetti et al., 1996; Suzuki et al., 2008; Higashihara et al., 2011). Motor unit number estimation, a quantitative measure of spinal