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Molecular pathogenesis of spinal bulbar muscular atrophy (Kennedy's disease) and avenues for treatment

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Structured abstract

Purpose of review: To illustrate the current understanding and avenues for developing treatment in spinal and bulbar muscular atrophy (SBMA), an inherited neuromuscular disorder caused by a CAG trinucleotide repeat expansion in the androgen receptor (AR) gene.

Recent findings: Important advances have been made in characterizing the molecular mechanism of the disease including the disruption of protein homeostasis, intracellular trafficking, and signaling pathways. Biomarkers such as MRI quantification of muscle volume and fat fraction have been used to track disease progression, and will be useful in future clinical studies. Therapies tested and under development have been based on diverse strategies including targeting mutant AR gene expression, stability, and activity, and pathways that mitigate disease toxicity.

Summary: We provide an overview of the recent advances in understanding the SBMA disease mechanism and highlight efforts to translate these insights into safe and effective therapy.

Keywords

spinal and bulbar muscular atrophy; muscle imaging; androgen receptor; motor neuron disease

Introduction

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease [1], is caused by a CAG repeat expansion in the androgen receptor (AR) gene on the X chromosome with a corresponding increase in the length of a polyglutamine tract in the AR protein [2]. Onset usually occurs in the mid 40s, with a range of 18 to 64 years [3]. The disease causes slowly progressive degeneration of the muscle and lower motor neurons in men who consequently develop muscle weakness, atrophy, and fasciculations. Disease progression is slow compared to other motor neuron diseases, with a decline in muscle strength of about 2% per year [4]. Features of disease are due to both gain and loss of AR function resulting in toxicity [5] and androgen insensitivity with gynecomastia and reduced fertility. Disease models have been developed which recapitulate key features of disease, allowing characterization of disease mechanism and enabling preclinical testing of candidate

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Conflicts of interest

There are no conflicts of interest.

therapeutics. There is currently no FDA approved disease-modifying therapy, and further randomized double-blind placebo-controlled trials are needed to evaluate candidate therapeutics.

Proteostasis and trafficking

Alteration of protein homeostasis and trafficking is a problem in many forms of polyglutamine disease [6,7]. In SBMA, defects in autophagic clearance and recycling of cellular proteins have been implicated [8]. Altered autophagy has been demonstrated in AR113Q knock-in mice, mediated by a disruption in transcription factor EB (TFEB) and its downstream target genes [8,9]. Studies in skeletal myoblasts have shown that the mutant AR protein causes reduced expression of important autophagic proteins such as BAG3 and VCP [10]. Overexpression of BAG3, a component of the chaperone assisted selective autophagy (CASA) complex, helped to enhance the clearance of the mutant AR. Pharmacologic activation of autophagy with the TFEB regulator trehalose also increased the clearance of the mutant AR in skeletal myoblasts [10] and in a mouse motor neuron-like hybrid cell line (NSC34) [11].

Arnold et al. used heterokaryon shuttling assays to show that the mutant AR has reduced nuclear export [12]. As a steroid hormone receptor, the AR undergoes nuclear translocation upon ligand activation with testosterone or dihydrotestosterone. Targeting mutant AR to the cytoplasm increases its proteasomal degradation and reduces the amount of aggregated protein. Although altered nucleocytoplasmic transport has been implicated in other neurodegenerative diseases [13,14], a global disruption of nucleocytoplasmic transport was not detected in SBMA.

The formation of fibrillar aggregates is common in many expanded polyglutamine containing proteins [15], however it is unclear how this occurs and how it relates to toxicity. In an analysis of androgen receptor structure, increased length of the polyglutamine tract within the AR has been shown to increase its helical structure [16]. It is possible that this alteration of secondary structure in the AR transactivation domain influences the protein's ability to regulate transcription. The structure of the transactivation domain is intrinsically disordered with only transient interactions with associated interacting complexes [17]. Changes in the secondary structure of this region have been shown to modify AR interaction with co-activators [18]. Using fly and mouse models for SBMA, Badders et al showed that modulation of AR co-regulator binding at the activation function-2 (AF2) domain may have a beneficial effect on disease toxicity [19]. They identified two compounds, tolfenamic acid and MEPB, as compounds that achieve this modulation and improve motor function in the mouse model.

Disrupted signaling pathways

There is increasing evidence in SBMA that disruption of signaling pathways has an important role in the pathogenesis and is a potential target for ameliorating disease. A transcriptomic screen in a mouse model of SBMA identified dysregulation of several genes in motor neurons including Charged Multivesicular Body Protein7 (Chmp7) [20].

Dysregulation of Chmp7 was found to occur in pre-manifesting SBMA mice before increases in LAMP2 and p62, indicating an early disruption of the endosome-lysosome system. Disruption of other important pathways involving p53, DNA repair, Wnt, and mitochondrial function were also detected. As potential contributors to transcriptional dysregulation, it is likely that epigenetic modifications such as histone acetylation or DNA methylation also occur. The DNA methyltransferase Dnmt1 was found to be highly expressed in SBMA mouse and patient motor neurons suggesting an alteration of epigenetic modification [21]. A DNA methylation array found increased promotor methylation of the hairy and enhancer of split 5 (*Hes5*) gene, and overexpression of this gene reduced toxicity in a cell model of SBMA. Treatment of the SBMA mice with RG108, an inhibitor of DNA methylation, mitigated disease toxicity.

In addition to gene level dysregulation, alteration of signaling pathways also occurs at the protein level. Using phosphorylation protein arrays from spinal cord and skeletal muscle from mice that were pre-onset, early manifesting, and at advanced stages of disease, changes in the Src signaling pathway were detected in both tissues at all time points evaluated [22]. Treatment of SBMA cells and mice with inhibitors of Src signaling resulted in improved cellular viability, and body weight and grip strength in animals treated at 8 weeks of age. The transcriptional regulator myocyte enhancer factor 2 (MEF2) was found to be reduced in the skeletal muscle of AR113Q knock-in SBMA mice by RNAseq analysis [23]. Reduction in MEF2 expression was found to be dependent on both androgen activity and polyglutamine length, and also detected in mice expressing mutant polyglutamine-expanded huntingtin. Expression of a constitutively active form of MEF2 in the SBMA mouse muscle resulted in an increase in muscle fiber size and increased expression of MEF2 target genes. This and other evidence suggests that skeletal muscle may be a therapeutic target in SBMA patients. SBMA mouse muscle has been found to have disruption of neurotrophic factors such as brain derived growth factor (BDNF), suggesting a potential therapeutic role for growth factor support [24]. The alteration in SBMA mouse muscle is associated with glycolytic-to-oxidative fiber-type switching and mitochondrial dysfunction, and dependence on the age at which mutant AR is expressed [25]. The accumulation of toxic effects at early stages of the disease may indicate a need for intervention in patients at an early age.

Biomarkers for evaluating therapeutics

The insights gained in studying cellular and animal models of SBMA are yielding therapeutic targets that can proceed to clinical investigation. Evaluation of candidate therapeutic options in SBMA patients is dependent on appropriate biomarkers to gauge therapeutic efficacy [26]. One of the strategies that has emerged for quantifying disease severity and progression is MRI imaging of limb muscles. Dixon MRI was used to detect changes in muscle fat content in SBMA patients in a recent natural history study over a time period of 18 months [27]. The average muscle fat content increase over this time period was 2%. Other outcome measures in this study which changed over 18 months include muscle strength in knee extensors, handgrip strength, 6-minute walk distance, and serum creatinine levels. In a separate study of 40 SBMA patients, decreases in creatinine levels were found to occur over 10 years before disease onset [28]. The pattern of muscle involvement is important and targeting a specific region during limb imaging may be necessary. Although

the pattern of muscle involvement is diffuse overall, leg muscles are more vulnerable, and thigh and calf flexors are more involved than extensors [29]. Muscle fat content was found to correlate with muscle function, disease severity, and creatinine levels. In a separate study of 21 SBMA patients, 21 ALS patients, and 16 healthy controls, significant fat infiltration was detected in the bulbar and limb muscles from SBMA subjects [30]. Fat infiltration correlated with disease severity, and STIR imaging detected more hyperintensity in the lower limb muscles of ALS patients. In addition to muscle imaging, analysis of facial nerve atrophy [31] and liver fat content [32,33] are other imaging biomarkers for use in future studies.

Another measurement which has been investigated as a potential biomarker is neurofilament (NF) protein abundance. NF proteins are expressed in neurons and can be detected in the blood and cerebrospinal fluid (CSF) upon axonal injury and degeneration [34]. Plasma phosphorylated neurofilament heavy chain (pNF-H) has been found to be elevated in infants with spinal muscular atrophy and correlates with markers of disease severity [35]. The levels of neurofilament light chain (NFL) and pNF-H were found to be significantly higher in the CSF from patients with motor neuron disease compared to controls and those with Parkinson's or Alzheimer's disease [36]. In a study of 93 SBMA, 53 ALS, and 73 healthy controls, the plasma levels of NFL were normal in SBMA compared to controls and did not change over a time period of 12 and 24 months in a smaller cohort of SBMA subjects [37]. Plasma levels of pNF-H were similarly unchanged in 46 SBMA subjects compared to 50 healthy controls [38]. An evaluation of NF protein levels in the CSF from SBMA patients has not yet been done, however studies in other disease cohorts have found a correlation between plasma and CSF pNF-H levels [39].

Other clinical measures to be considered include the calculation of specific muscle force and contractility through the combined assessment of stationary dynamometry measurement of muscle force with quantitative MRI imaging [40]. The specific muscle force decreases in all muscle groups with age, as does the contractility in knee extensors, ankle plantar- and dorsiflexors, and elbow flexors. Measurement of bulbar strength may also be considered, including analysis of speech and evidence of velopharyngeal dysfunction associated with lifting of the soft palate. Nasalance score measurements using a Nasometer II device to assess nasality were abnormal in SBMA subjects, and correlated with other measures of bulbar function [41]. Additional tools to evaluate bulbar function may include the 6-K-scale assessment of V, VII, IX, X, and XII cranial nerve and ansa cervicalis function [42]. Measurements using neuropsychological evaluations have not detected abnormalities in SBMA patients [43].

Targeting the androgen receptor

One approach to treating SBMA has been androgen reduction, which is beneficial in mouse models [5]. Two randomized double-blinded studies of leuprorelin acetate, a luteinizing hormone-releasing hormone (LH-RH) agonist that decreases testosterone release from the testes, did not show significant evidence of efficacy in primary outcome measures [44,45]. In the first study of 50 SBMA subjects, no effect on the primary outcome measure of motor function was detected as measured by the ALS Functional Rating Scale (ALSFRS), although

an improvement in functional scores and swallowing parameters was seen in those subjects who participated in an open-label extension for an additional 96 weeks [44]. In a second study of leuprorelin in 199 subjects, no significant effect on swallow function was detected after 48 weeks of treatment [45]. In a pooled analysis of two randomized double-blinded studies, no effect of leuprorelin was detected on the primary outcome measure of longitudinal change of pharyngeal barium residue over 48 weeks [46]. Evidence of some benefit with leuprorelin was found in a non-randomized study of 36 patients treated for up to 84 months in which a difference in the ALSFRS-R, Limb Norris Score, and Norris Bulbar Score was detected [47].

A gene targeting strategy for reducing the toxicity of the mutant AR uses antisense oligonucleotides (ASOs) to decrease levels of AR mRNA. ASOs are synthetic single-stranded nucleic acids that can target specific RNA transcripts. An ASO approach is under development for other polyglutamine disorders including Huntington's disease and spinocerebellar ataxias [48,49]. ASOs have also been used as customized treatment for "N-of-1" patients with rare inherited diseases [50]. A strategy to target the mutant AR transcript in SBMA may thus be useful. ASOs targeting the AR in AR113Q knockin and BAC fxAR121 mouse models were able to rescue deficits in muscle function and extend lifespan [51]. The ASO was administered subcutaneously and resulted in selective reduction of AR levels in the periphery but not the CNS suggesting the potential utility of peripheral AR targeting. In a separate study, the effects of a single intracerebroventricular administration of ASO targeting the AR were studied in a transgenic mouse model overexpressing AR97Q [52]. The treated mice had good suppression of mutant gene expression in the CNS, delayed disease onset, and improved body weight and survival. Clinical trials of ASOs in SBMA patients will be needed to validate target engagement and evaluate their effect on clinically relevant measures.

Another approach being considered is with the curcumin analogs ASC-J9 and ASC-JM17, which improve protein degradation, mitigate oxidative stress, and reduce toxicity in cell, fly, and mouse models of SBMA [53,54]. Selective androgen receptor modulators (SARMs) offer advantages by allowing AR anabolic effects and potentially interfering with toxic gain of function biology [55]. AR modulators identified in a screen by Badders et al. [19] were found to modulate interactions of the activation function-2 (AF2) domain of AR in SBMA mice and flies to improve muscle function while preserving the normal beneficial effects of androgens. The utility of exercise in SBMA also warrants additional investigation, as 8 weeks of high-intensity exercises were reported to yield improvement in maximum oxygen capacity, workload, and fitness in 8 patients [56]. High-intensity exercises should be further investigated to evaluate efficacy in a larger cohort of SBMA patients.

Conclusion

Advances in our understanding of cellular toxicity, biomarkers for tracking disease, and clinical trial experience have brought SBMA researchers closer to safe and effective disease-modifying treatment. Our insights into the disease mechanism and the disruption of protein turnover, trafficking, and cell signalling pathways point toward therapeutic targets that can

be validated in preclinical studies. The availability of multiple model systems is helpful for testing new agents with good therapeutic potential.

In taking the next step to determine whether a candidate intervention is efficacious in patients, it is important to have biomarkers that are predictive of clinical benefit. These should have good test-retest reliability and be accessible to centers participating in future clinical trials. An important emerging biomarker in SBMA is MRI quantification of muscle volume and fat content [27, 57]. In a recent clinical trial of an insulin-like growth factor-1 mimetic, a significant difference in the change of thigh muscle volume was detected in the interventional group compared to placebo over a 12-week time frame in a relatively small number of patients [57].

There have been several well designed clinical trials in SBMA, and further therapeutics development is currently underway. The strategies include targeting AR expression and stability, modulation of AR activity, and pathways that may mitigate disease toxicity. The diversity of approaches and improvement in our ability to evaluate therapeutic efficacy are encouraging progress in the development of safe and effective treatment for SBMA.

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Key points

1. The molecular pathogenesis of SBMA likely involves disruption of multiple processes including transcriptional regulation, protein homeostasis, intracellular trafficking, mitochondrial function, and cellular signaling.
2. MRI measurements of thigh muscle volume and fat fraction are useful markers of disease progression.
3. Therapeutic strategies under development target mutant AR expression, stability and activity, and pathways that may mitigate disease toxicity.