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Muscle matters in Kennedy's disease

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Abstract

Polyglutamine expansion in the androgen receptor causes Kennedy's disease. Two recent reports raise the possibility that targeting expression of the mutant protein in skeletal muscle, instead of the nervous system, may mitigate manifestations of this disorder.

Kennedy's disease (spinal and bulbar muscular atrophy, SBMA) is a neuromuscular disorder characterized by slowly progressive muscle weakness and atrophy, with degeneration of primary motor neurons in the spinal cord and brainstem of affected individuals (Sobue et al., 1989). The disease is X-linked and caused by expansion of a CAG repeat in the first exon of the androgen receptor (AR) gene, which leads to an expanded polyglutamine tract in the AR protein (La Spada et al., 1991).

Traditionally, SBMA has been viewed as a cell autonomous, primary motor neuron disease. The neuronal death in SBMA and other polyglutamine diseases is at least in part due to a toxic gain-of-function in the mutant protein. In addition to the toxic effects of the AR, loss of normal receptor function also contributes to the disease phenotype, with some patients having symptoms such as breast enlargement and reduced fertility. Therefore, an approach aimed at reducing mutant protein levels without exacerbating the effects androgen deficiency holds great promise as a potential treatment for SBMA.

A number of different treatments have been shown to protect against expanded polyglutamine AR toxicity in SBMA animal models, nevertheless they have thus far failed to result in effective treatment in human clinical trials (Fischbeck, 2012). This failure can be partly attributed to pitfalls in preclinical research, such as lack of blinding and starting treatment before the onset of disease manifestations, which is difficult to do in clinical trials.

The development of therapeutics would also benefit from an improved understanding of the mechanism of motor neuron degeneration in SBMA. Non-neuronal cells such as glial cells

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and muscle likely play a critical role in the pathogenesis of other motor neuron diseases. Appreciation of this role not only gives a better insight into the disease mechanism, but also opens new treatment options, which is particularly desirable for these disorders. For example, cells outside the central nervous system (CNS) may play a primary role in spinal muscular atrophy (SMA). Peripheral targeting of antisense oligonucleotides (ASOs) to restore expression of survival motor neuron protein, deficiency of which causes SMA, robustly ameliorates the disease manifestations in SMA mice (Hua et al., 2011). Furthermore, muscle-specific conditional rescue in SMA mice leads to significant improvement in weight, survival, and motor behavior (Martinez et al., 2012).

Reports by Cortes et al. in this issue and Lieberman et al. in Cell Reports (2014) challenge the traditional view of SBMA as a primary motor neuron disease. These studies establish muscle as a site of mutant AR toxicity and suggest targeting mutant protein expression in this tissue as an approach for treating the disorder (Figure 1). Several lines of evidence from previous studies support a primary contribution of skeletal muscle in the disease pathogenesis: (1) muscle biopsies of SBMA patients show features of both denervation and myofiber degeneration (Soraru et al., 2008); (2) knock-in mice expressing polyglutamine-expanded AR develop early findings of myopathy with little or no motor neuron loss (Yu et al., 2006); (3) muscle-specific overexpression of wild type, non-expanded AR in mice is sufficient to produce SBMA-like neuromuscular disease (Monks, 2007); and (4) genetic overexpression of muscle-specific IGF-1 or peripheral IGF-1 administration has been shown to mitigate SBMA symptoms in transgenic mice (Palazzolo et al., 2009; Rinaldi et al., 2012).

Cortes et al. explore the contribution of muscle to SBMA pathogenesis with a new conditional mouse model of SBMA, BAC fxAR121Q, which expresses a full-length human AR transgene with 121 CAG repeats under the control of the endogenous AR promoter. The first exon of the human AR transgene is flanked by loxP sites, which allows removal of the transcription start site by Cre recombinase enzyme. In the absence of Cre, fxAR121Q mice show mutant AR transgene expression comparable to endogenous mouse AR in mRNA, protein, and tissue distribution. Male mice develop progressive muscle weakness, weight loss, and reduced survival, similar to other transgenic SBMA mouse models. Introduction of Cre recombinase under the control of a ubiquitous promoter (CMV-Cre) in fxAR121Q mice completely abrogated mutant AR transgene expression in all tissues. Double transgenic fxAR121Q/CMV-Cre mice were indistinguishable from non-transgenic littermates and never developed SBMA manifestations, demonstrating complete mitigation of mutant AR toxicity through Cre-mediated recombination events in this model. Next, the authors introduced tissue-specific Cre expression driven by a human skeletal actin (HSA-Cre) promoter. fxAR121Q/HSA-Cre mice showed selective suppression of the AR transgene in skeletal muscle. Although AR was still expressed in the spinal cord, and reduced motor neuron soma size and accumulation of mutant AR in nuclear inclusions were unchanged in these mice, muscle-specific abrogation of AR increased survival, suppressed weight loss and weakness, and increased the diameter of motor axons. This study demonstrates a primary role of skeletal muscle in SBMA pathogenesis in these mice and justifies AR gene silencing in muscle tissues as a potential disease-modifying strategy in patients.

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By targeted reduction of mutant AR using ASO technology, Lieberman et al. (2014) took this approach one step closer to the clinic. The authors developed and characterized ASOs selective for human or mouse AR, which suppressed AR mRNA in a dose-dependent fashion in cultured cells. Next, ASOs were tested for their effects on SBMA manifestations in two mouse models: AR113Q knock-in mice that have a CAG repeat expansion in the endogenous mouse AR locus, and the fxAR121Q mice described by Cortes et al. ASOs were delivered subcutaneously, before or at the time of disease onset, and found to markedly suppress AR expression in skeletal muscle but not spinal cord in both mouse models. ASO treatment rescued weight loss, muscle weakness, abnormal gene expression, and lethality in the mice, without altering testosterone levels. Notably, AR suppression by ASOs was maintained up to ten weeks after cessation of treatment. Lowering AR expression in the spinal cord, achieved through intraventricular delivery of ASO, surprisingly did not modify disease manifestations in the fxAR121Q mice, indicating that the main problem in these mice is not in the CNS, and that the best way to correct it is with peripheral rather than central treatment.

While it remains to be seen whether AR suppression reverses SBMA pathology at more advanced disease stages, the findings by Cortes et al and Lieberman et al. have important implications. The data presented confirms previous reports, which place muscle next to motor neurons as an important contributor to SBMA pathogenesis (Monks et al., 2007; Soraru et al., 2008). Moreover, the two studies show that mutant AR accumulation in motor neurons may not be sufficient for polyglutamine toxicity in SBMA models, and they indicate that targeting mutant AR in muscle can ameliorate the functional defects associated with SBMA.

Targeting the periphery for treatment has practical advantages over delivery to the CNS. This approach would also limit the side effects related to AR reduction in the CNS, such as decreased libido, which are known adverse effects of the androgen reduction therapy. Also, skeletal muscle is readily accessible; unlike the spinal cord it can be biopsied for pharmacodynamic measures of drug effect.

Based on the two reports presented here, it is tempting to think of SBMA as a muscle disease rather than a motor neuron disease. However, a confounding factor in the fxAR121Q model may be retained expression of endogenous mouse AR, which has previously been shown to modulate mutant AR toxicity *in vivo* (Thomas et al., 2006). It should be noted that in humans the AR gene is located on the X chromosome, and affected individuals, who are male, have only the one mutated copy. While this genetic context is better recapitulated in the AR113Q knock-in model, these mice have a relatively mild muscle phenotype and, similarly to fxAR121Q mice, motor neuron loss has not been reported. In the knock-in mice, the primary cause of death is urinary retention (Yu et al., 2006), which is not a problem in SBMA patients.

There is clear evidence that loss of normal receptor function also contributes to the disease phenotype. A possibility remains that a decrease in AR protein may further exacerbate symptoms of androgen insensitivity and compromise remaining muscle strength as well as perceived well-being in a clinical setting. Functional reduction of AR via ligand removal has

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been tried in SBMA patients with mixed results. Pharmacological manipulation of the AR ligand testosterone, either through chemical castration or alphareductase inhibition, did not significantly improve primary clinical outcomes in randomized, placebo-controlled studies (Katsuno et al., 2010; Fernandez-Rhodes et al., 2011).

Further work using in vitro culture and animal models is needed to answer remaining questions. What aspects of muscle dysfunction promote the disease process? How does the muscle pathology in SBMA contribute to motor neuron degeneration in SBMA? Will amelioration of the disease by targeting muscle uncover other CNS manifestations? Answering these questions will help in translating this potential treatment option into effective treatment in patients.

In summary, the reports by Cortes et al. and Lieberman et al. emphasize the role of skeletal muscle as an important contributor to SBMA pathogenesis and underscore the importance of exploring approaches targeting peripheral tissues for treatment. Clearly, in this disease the muscle matters.

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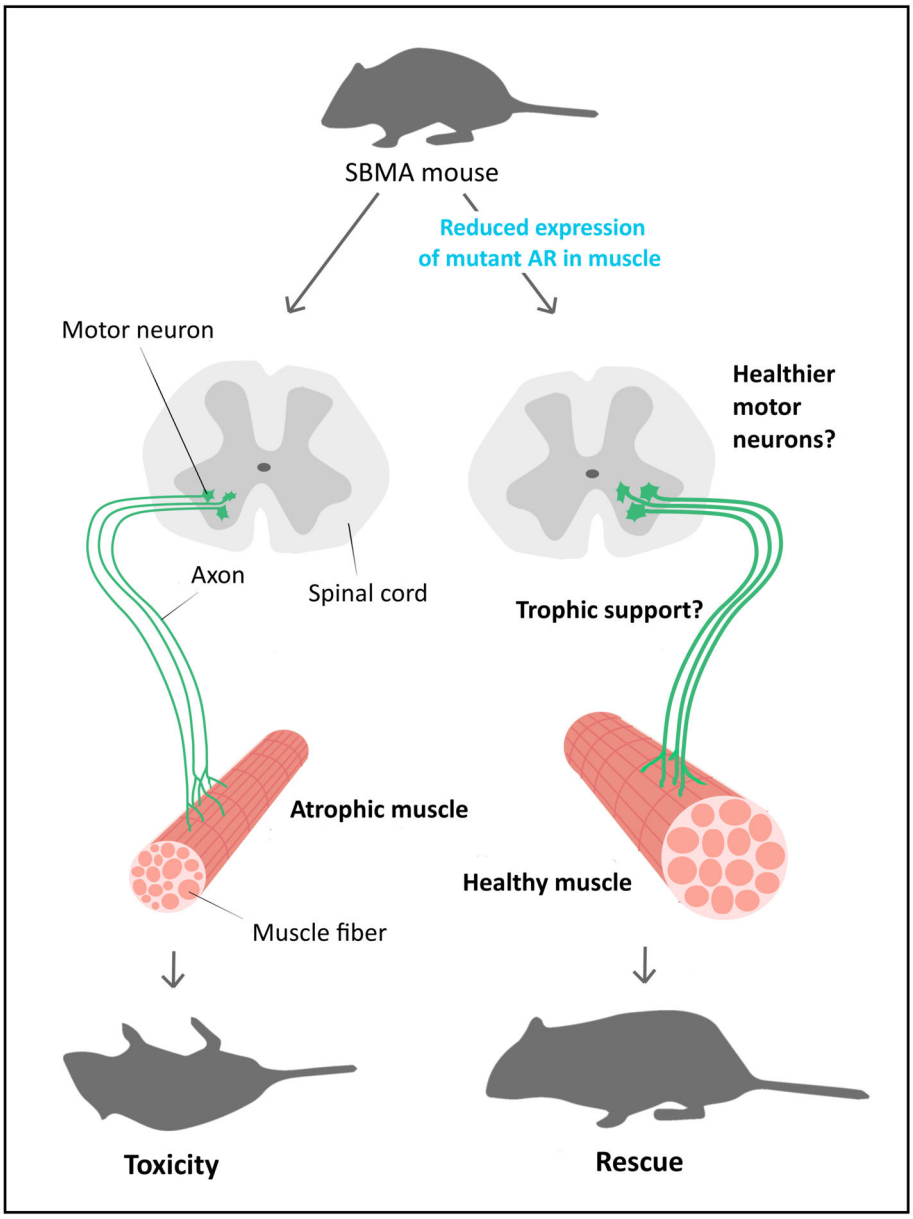

Figure 1.

Reducing mutant AR expression in muscle has beneficial effects in SBMA mouse models.