CLINICAL INVESTIGATION

Skeletal muscle as an emerging therapeutic target in spinal and bulbar muscular atrophy

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Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is an adult onset neuromuscular disease characterized by the selective degeneration of motor neurons in the brainstem and the anterior horns of the spinal cord [1]. Patients develop progressive muscle weakness and atrophy, which leads to a slow deterioration of the ability to move. Tongue and facial muscles are also involved. The cause of SBMA is the expansion of a polymorphic CAG repeat sequence, which encodes a polyglutamine tract (polyQ), in the first exon of the androgen receptor (AR) gene on chromosome X [2]. In healthy subjects, the number of CAG repeats ranges from 12 to 36, whereas in SBMA patients the size of the repeat is increased from 38 to 62. AR belongs to the steroid/thyroid receptor family. Upon binding of its ligands, testosterone or dihydrotestosterone (DHT), AR translocates from the cytoplasm to the nucleus where it regulates the expression of a subset of genes. In SBMA, expanded polyQ repeat in the AR leads to nuclear accumulation of the receptor and this either disrupts AR functions or triggers toxic mechanisms for the cell [3]. As the binding of androgens to polyQ-AR is required to initiate the disease process, males are affected while females show only subclinical symptoms even if homozygous for the mutation [4]. This suggests ablation of androgens as a potential therapeutic strategy. However, this approach, while working well in animal models of the disease, did not give the expected results in human patients. Therefore, after more than 20 years since the discovery of the genetic cause, there is not yet an effective therapy for SBMA.

SBMA is believed to be primarily a motor neuron disease. However, evidence has been provided that demonstrates that damage caused by the interaction between androgens and polyQ-AR in skeletal muscle cells may also have a primary role in disease pathogenesis. In support of this idea is the observation that SBMA patients show myogenic changes, such as fiber splitting, fibers with central nuclei, together with the neurogenic atrophy [5]. In primary skeletal muscle cell cultures obtained from SBMA patient biopsies, we observed an androgen-dependent impairment of myogenesis leading to hypotrophic myotubes with excessive levels of polyQ-AR in the nucleus [6]. Interestingly, SBMA patients have high levels of serum creatine kinase, sometime even before the onset of clinical manifestations [5,7]. Signs of muscle denervation and myopathy have also been described in transgenic and knock in mouse models of SBMA [8,9]. Importantly, in the knock in SBMA mice, muscle atrophy precedes spinal cord pathology, suggesting a predominant role for muscle in this mouse model. Overexpression of normal AR solely in muscle results in a phenotype that resembles SBMA, further leading to argue a role for muscle in SBMA pathogenesis [10].

We have proposed that modulation of PI3K/Akt pathway in skeletal muscle may represent a promising avenue to cure

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SBMA. Indeed, activation of Akt leads to AR phosphorylation, which reduces hormone binding and AR toxicity in cell culture models of SBMA [11]. IGF-1 is a mediator of muscle hypertrophy through the activation of PI3K/Akt pathway [12]. Akt activation has anabolic effects in muscle, where it induces new protein synthesis and inhibits protein degradation [13]. Augmentation of IGF-1 signaling by overexpression of a muscle-specific IGF-1 isoform selectively in SBMA muscle ameliorates disease manifestations in a transgenic mouse model of the disease [9]. Moreover, SBMA mice showed improved motor performance and increased survival even when treated with IGF-1 after disease onset [14]. Notably, the IGF-1 effect on disease course was accompanied by Akt activation and phosphorylation of AR. Another stimulus that leads to activation of the PI3K/Akt pathway in muscle is β2-adrenoreceptor stimulation. Although it remains to be established whether β-adrenergic activation may exert protective effects in SBMA by acting on PI3K/Akt pathway, we recently carried out a pilot trial providing evidence that clenbuterol, a β2-agonist, is effective in improving motor function in SBMA patients with no relevant adverse events [15].

Regardless the modulation of PI3K/Akt pathway, all these observations suggest that muscle-directed therapies may represent *per se* a reliable strategy to cure SBMA. Muscle exerts a trophic effect to motor neurons by releasing survival and growth factors that are retrogradely transported and modulate crucial cell pathways in motor neurons. Interestingly, the expression of neurotrophins and growth factors is altered either in mouse models of SBMA [16] or in the muscle of SBMA patients [17]. On the other hand, any treatment aimed at improving muscle function is certainly welcome in SBMA since muscle weakness is the leading cause of disability in motor neuron disorders. Accordingly, a trial with CK-2017357, an orally bioavailable fast skeletal muscle troponin activator, is currently ongoing in patients with amyotrophic lateral sclerosis [18]. Finally, muscle-directed treatments are prone to an easier monitoring, for example by serial sampling of the tissue, during patient follow up in clinical trials. This could definitely be relevant if one takes into account the slow progression of the disease. Past clinical trials designed for 1- or 2-year treatment in SBMA could not be as effective as expected because they were not long enough to exert a positive outcome. Conversely, the availability of the target tissue may offer sensitive and specific biomarkers to evaluate the efficacy of the treatment in less time. Taking these considerations together, development of muscle-directed therapy for SBMA may be an avenue that should be pursued to delay or arrest disease onset and progression.

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