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EDITORIAL

Myopathy: Recent Progress, Current Therapies, and Future Directions

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In this issue of *Neurotherapeutics*, a collection of articles highlights recent advances in the classification, diagnosis, and, most importantly, treatment of numerous muscle diseases. Although individual myopathies can be rare, muscle diseases as a whole are common and can be broadly divided into inherited and acquired myopathies. The inherited myopathies include the muscular dystrophies, congenital myopathies, glycogen storage disorders, fatty acid oxidation disorders, ion channel disorders, and mitochondrial myopathies, whereas the acquired myopathies include various types of autoimmune myopathies, infectious myopathies, endocrine myopathies, and toxic myopathies, as well as inclusion body myositis.

It has been 30 years since the successful cloning of the gene encoding dystrophin [1]. Dystrophin mutations cause Duchenne muscular dystrophy, the most common inherited muscle disease affecting children. The genetic bases of hundreds of other inherited muscle diseases have since been elucidated and additional genes and mutations are identified each year. These discoveries have improved our understanding of skeletal muscle physiology and pathophysiology. Moreover, insights into the genetic basis of inherited myopathies promise to stimulate the development of effective curative therapies for these disorders. Nevertheless, in most cases, current therapeutic strategies still consist mostly of supportive care and/or treatments aimed at minimizing symptoms.

Shieh leads off this issue by reviewing strategies to treat Duchenne muscular dystrophy [2]. In addition to the two FDA-approved treatments for this disease, corticosteroids and the exon-skipping agent eteplirsen, consideration is given to other agents currently under investigation that may improve or slow the progression of weakness by reducing inflammation, promoting muscle regeneration, reducing fibrosis, facilitating mitochondrial function, or restoring functional dystrophin protein expression.

Next, Chu and Moran tackle the limb–girdle muscular dystrophies, a collection of 34 distinct genetic diseases characterized by reduced or absent expression of specific muscle proteins [3]. Again, despite lack of treatment, small gene therapy clinical trials performed in patients with several of these diseases show promise and suggest that expression of absent muscle proteins can be successfully and safely restored.

An exciting and relatively recent development in myology has been the discovery that aberrant expression of DUX4 is the underlying pathology in facioscapulohumeral muscular dystrophy. Hamel and Tawil discuss how disrupting DUX4 expression or blocking its downstream effects could alleviate weakness in patients with this common form of muscular dystrophy [4].

The myotonic dystrophies (types 1 and 2) are among the more common inherited muscle disorders; these are multisystem diseases that can affect not only skeletal muscle, but cardiac muscle, the central nervous system, and other organ systems. LoRusso et al. provide an update on current strategies for managing patients with myotonic dystrophy, including the use of mexiletine to improve clinical myotonia, which can otherwise significantly impair muscle function [5].

Mutations in the ryanodine receptor type 1 (RYR1), a large gene (> 159 kilobase pairs) with over 700 known pathogenic mutations, can cause a variety of congenital myopathies including central core disease, multi minicore disease, core–rod myopathy, centronuclear myopathy, and congenital fiber-type

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disproportion. Lawal et al. describe how this pathophysiologic diversity has led investigators to focus therapeutic efforts on targeting downstream mechanisms, such as oxidative stress [6]. This includes a recently completed trial of *N*-acetylcysteine, a precursor to the antioxidant glutathione.

Interestingly, centronuclear myopathies can be caused by mutations in *RYR1* and other genes, including the gene encoding dynamin 2, a GTPase that mediates membrane fission during multiple cellular processes (such as endocytosis and organelle division/fusion). In this issue, Zhao et al. describe how mutated dynamin 2 becomes functionally hyperactive and thus impairs multiple cellular pathways including T-tubule biogenesis, actin dynamics, and autophagy [7]. Although siRNA has been used to knockdown dynamin 2 expression and restore muscle function in an animal model of central nuclear myopathy, therapies to treat the human disease remain to be developed.

In contrast to mutations in *RYR1*, which give rise to a diversity of clinical manifestations, patients with mutations in the *GNE* gene have a more homogeneous phenotype: bilateral foot drop in young adulthood that progresses to affect more widespread muscle groups as patients age. The *GNE* gene encodes a bifunctional enzyme, UDP-*N*-acetylglucosamine (GlcNAc) 2-epimerase/*N*-acetylmannosamine (ManNAc) kinase, that catalyzes the rate-limiting step in the biosynthesis of sialic acid. As Carrillo et al. explain here, muscle damage in patients with GNE myopathy may be a consequence of the resulting hyposialylation of muscle glycans, which are important for numerous cellular functions. In the absence of current treatments, the authors discuss various potential strategies aimed to provide precursors of the sialic acid biosynthetic pathway or to restore enzymatic activity by gene or cell therapy approaches [8].

Patients with mutations in genes encoding enzymes responsible for glycogenolysis or glycogen synthesis can present with exercise-induced muscle symptoms, such as cramping or rhabdomyolysis, or with muscle atrophy and weakness. Although enzyme replacement strategies are not yet available for most glycogen storage disorders, supportive care can prevent adverse outcomes, and Tarnopolsky's review emphasizes the role of preventing crises through modulation of activity and diet [9].

Enzyme replacement therapy is now available for patients with Pompe disease, a lysosomal storage disorder affecting cardiac and skeletal muscle caused by mutations in the gene coding for acid alpha-glucosidase (GAA). As presented by Kohler et al. in this issue, enzyme replacement does alter the natural history of Pompe disease, with the most pronounced positive effects noted in cardiac muscle [10]. Unfortunately, enzyme replacement therapy does not improve skeletal muscle outcomes to the same degree, and thus additional treatment modalities still need to be developed for patients with this lysosomal storage disease.

Mutations in nuclear DNA or mitochondrial DNA (mtDNA) can disrupt the function of mitochondrial proteins resulting in an impairment of oxidative phosphorylation that may cause damage not only to skeletal muscle, but to other organs as well. Although no curative therapies are yet available, Ahmed et al. discuss strategies for the symptomatic management of these diseases [11]. A recent success in the field has been the availability of new reproductive options that may prevent the transmission of disease-causing mutations from mother to offspring. This process had to overcome stringent ethical considerations. Mitochondrial donation involves transfer of nuclear DNA from an affected egg into an enucleated egg from a healthy donor which retains normal mtDNA. Although this technique is limited to mtDNA disorders, it results in an embryo with DNA which originated from "three parents": nuclear DNA derived mostly from both parents and wild-type mitochondrial DNA derived from the healthy donor [12].

Alterations in the electrical excitability of the muscle cell membrane underlie the episodic and fluctuating symptoms experienced by patients with mutations in genes encoding muscle sodium, chloride, calcium, or potassium channels. Although no FDA-approved disease-modifying treatments are available for these channelopathies, Phillips and Trivedi discuss various off-label strategies for managing the symptoms that can otherwise functionally disable patients [13]. They include the use of lamotrigine, a sodium channel blocker that was recently shown to reduce clinical myotonia in a double-blind, placebo-controlled trial.

McGrath et al. move the discussion from genetic muscle disease to the acquired autoimmune myopathies, a heterogeneous family of diseases that includes dermatomyositis, immune-mediated necrotizing myopathy, the antisynthetase syndrome, and overlap-myositis [14]. Most patients with one of these diseases have inflammatory infiltrates on muscle biopsy and respond to immunosuppressive agents. In their review, the authors provide a strategic approach to treating patients with autoimmune myopathy, with an emphasis on escalating therapy in patients who do not respond to steroids and avoiding the potential side-effects of immunosuppressive therapies.

Although muscle biopsies from those with inclusion body myositis also have prominent cellular infiltrates, these patients do not usually improve with immunosuppressive therapy. To help explain this, Naddaf et al. present recent work showing that many patients with inclusion body myositis have circulating populations of abnormal T cells that also infiltrate skeletal muscle; these T cells may be especially resistant to current immunosuppressive therapies [15]. In addition, degenerative pathways leading to the abnormal accumulation of cellular proteins may play a role in inclusion body myositis pathogenesis and help explain the refractory nature of this disease. The authors discuss a number of potential treatment strategies to prevent aberrant protein accumulation, promote muscle growth, and/or suppress the inflammatory response.

Ultimately, they argue, effective treatment of inclusion body myositis may need to target both the degenerative and inflammatory pathways.

Taylor and Thompson round out this issue with a discussion of statin–associated muscle symptoms, which range from mild muscle pain to rhabdomyolysis [16]. Although it remains unclear what proportion of statin-treated patients have muscle symptoms that can be attributed to the statin, this remains a common problem in clinical practice. In their article, the authors provide a particularly helpful algorithm for managing these patients, with an emphasis on eliminating contributing factors (such as hypothyroidism and vitamin D insufficiency), reducing the statin dose, or switching to another type of statin. Fortunately for patients who remain intolerant of statins, new agents such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can also be used to effectively lower lipid levels.

This issue provides an updated view on the current developments and avenues of investigation being pursued in clinical myology, in addition to practical methods of medical management. Although disease-modifying therapies remain elusive for many of these conditions, there is reason to remain enthusiastic about recent progress that has been made in unraveling the pathology underlying many of them. We remain hopeful that they will result in effective therapies in the foreseeable future.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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