Preface

Special issue on the muscular dystrophies: Molecular basis and therapeutic strategies

The muscular dystrophies are a heterogeneous group of inherited diseases characterized by progressive skeletal muscle weakness and wasting, although a number of other tissues may be affected. It is not surprising that experimental studies aimed at revealing the molecular basis of various muscular dystrophies have led to important insights into the functional organization of muscle cells, including the discoveries of dystrophin and the dystroglycan and sarcoglycan complexes. Perhaps more surprising is that research on these disorders has revealed novel insights into nuclear envelope structure and function and the impact of microsatellite expansions and macrosatellite contractions on gene expression.

The objectives of this special issue are to review current pathogenic mechanisms underlying the muscular dystrophies and to discuss current and future therapeutic approaches. The first section, which focuses on pathogenic mechanisms involved in the muscular dystrophies, begins with a comprehensive review of dystrophin (Duchenne/Becker) and its multiple interactions with other sarcolemma-associated proteins (Ervasti). Another X-linked disease, Emery–Dreifuss muscular dystrophy (EDMD), is caused by mutations in the EMD gene that encodes the inner nuclear membrane protein emerin. Interestingly, autosomal dominant EDMD is caused by specific mutations in the LMNA gene, and Roux and Burke discuss the fascinating question of how mutations in emerin and lamin A/C lead to X-linked and autosomal EDMD, respectively. Wasting of proximal shoulder and pelvic girdle muscles is characteristic of the limb-girdle muscular dystrophies (LGMDs), and LMNA mutations are also associated with an autosomal dominant form of this disease, LGMD 1B. Although additional LGMDs are caused by mutations in a number of sarcolemma-associated proteins (dysferlin, α-/β-/γ-/δ-sarcoglycans, caveolin 3), Kramarova and colleagues discuss how recessive mutations in CAPN3, which encodes the cytosolic protease calpain 3, results in LGMD 2A. In contrast to the LGMDs, the distal dystrophies, which begin with muscle weakness in the hands, forearms, lower legs, or feet, are attributable to mutations in genes encoding several sarcomeric proteins, including myosin, titin, desmin, and dysferlin (Udd). Next, Lisi and Cohn shift the focus to the congenital muscular dystrophies (CDMs). Although these developmental diseases are caused by mutations in components of the extracellular matrix (laminin α2, collagen VI), sarcolemma (integrin α7), and endoplasmic reticulum (selenoprotein-1), an increasing number of CDMs have been linked to genes that regulate the glycosyla-

tion status of α-dystroglycan (LARGE, POMT1, POMT2, FCMD, FKRP). The last three articles in this section review an interesting set of muscle disorders caused by changes in microsatellite and macrosatellite repeat number. Abu-Baker and Rouleau provide an overview of PABPN1 (GCC)n expansions, intranuclear PABPN1 protein aggregates, and their potential roles in oculopharyngeal muscular dystrophy; van der Maarel and coauthors discuss how D4Z4 macrosatellite contractions lead to facioscapulohumeral muscular dystrophy; and Cho and Tapscott focus on research showing that RNA-based mechanisms appear to play a predominant role in myotonic dystrophy. In the second section, the preceding articles on pathogenic mechanisms are complemented by additional reviews on genetic models. Guyon and colleagues discuss the isolation of zebrafish muscle mutants and their use to evaluate pathogenic mechanisms and potential therapies for muscular dystrophy. Phenotypic variability is a common clinical feature of muscular dystrophy, and mouse model studies designed to evaluate the influence of genetic background and modifiers are reviewed by Heydeman and colleagues.

The final two sections focus on current treatments and potential new therapies. The third section includes articles on existing treatment strategies for Duchenne muscular dystrophy (DMD) (Wagner et al.) and a review of modern diagnostic tools for the LGMDs (Bushby et al.). Odom and coauthors begin the final section by reviewing recent progress on the use of viral-mediated, particularly adeno-associated virus, gene therapy to ameliorate dystrophic muscle changes. This special issue concludes with reviews of alternative therapeutic strategies, including non-viral (plasmid-mediated gene delivery, antisense oligonucleotide induced exon skipping, oligonucleotide-mediated gene editing) (Rando) and stem cell (Price et al.) approaches.

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