Dystroglycan is a transmembrane protein that links the extracellular matrix to the intracellular cytoskeleton. Dystroglycan contributes to early development, the maintenance of skeletal muscle membrane integrity, the structure and function of the central nervous system, myelination and nodal architecture of peripheral nerves, and epithelial morphogenesis. In humans, the loss of dystroglycan function (reduced ligand-binding activity to extracellular matrix proteins with LG domains) caused by aberrant post-translational modification causes several forms of congenital muscular dystrophy called secondary dystroglycanopathies. Previously we showed that molecular recognition of dystroglycan by LARGE is a key determinant in the biosynthetic pathway to produce mature and functional dystroglycan. Both the N-terminal domain and part of the mucin-like domain of α-dystroglycan are essential for high-affinity laminin-receptor function.

The N-terminal domain of α-dystroglycan interacts with LARGE, defining an enzyme–substrate association necessary to initiate functional glycosylation within the mucin-like domain of α-dystroglycan. However, the mechanistics details leading to this specific α-dystroglycan modification are not fully understood. We now report the identity of specific conserved residues that are important determinants for functional dystroglycan glycosylation. Our results provide a molecular basis for post-translational events that have been implicated in the etiology of neuromuscular diseases linked to dystroglycan.

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C.I.2

An update on the congenital muscular dystrophies

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The cogenital muscular dystrophies (CMDs) have seen enormous progress as regards the recognition of nosologic entities, the elucidation of pathophysiology, and therapeutic approaches based on this understanding. This review will focus on the disorders which are not caused by abnormalities of α-dystroglycan. For laminin α2 deficiency the results with the most promising therapeutic potential have been obtained by gene engineering strategies reinforcing the basement membrane-dystroglycan link by agrin or perlecan constructs, or substituting laminin α2 by other laminin chains. The other important group of CMDs, the collagen VI-related Ullrich CMD and Bethlem myopathy, show an increasingly wide spectrum of dominant and recessive mutations of the three col6 genes. Therapeutic advances in this group are based on inhibition of apoptosis or nonsense-mediated mRNA decay. Two new syndromes were mapped to chromosomes 3p23 and 4p16.3. And finally another form of CMD turns out to be a nuclear envelopathy. These advances allow us to postulate distinct pathogenic pathways leading to CMDs as well as to devise tailored therapeutic approaches.

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C.I.3

Overview of congenital myopathies

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The congenital myopathies are defined by distinctive morphologic abnormalities in skeletal muscle. Over the past decade, research has focused on defining and classifying the distinct disease entities, and the identification of disease genes (Table 1). These advances have already translated into improved diagnosis, genetic counselling and increased availability of prenatal diagnosis. The development of tissue culture and animal models of these disorders has led to a better understanding of disease pathogenesis and the development of effective and specific therapies. This presentation will provide an overview of the following areas:

- a summary of some current research into inherited myopathies using tissue culture and animal models of disease.
- the development and testing of novel therapies in animal models.
- potential therapies for the future.

Table 1

Congenital myopathies with identified gene loci

Disorder	Inheritance	Gene/protein
Nemaline myopathy	AD, AR	α-Tropomyosin slow
	AD, AR	Skeletal α-actin
	AD	β-Tropomyosin
	AR	Nebulin
	AR	Troponin T1
	AR	Cofilin
Central core disease	AD, AR	Ryanodine receptor
Myotubular myopathy	X linked	Myotubularin
Centronuclear myopathy	AD	Dynamin 2
	AR	?
Multiminicore disease	AD, AR	Ryanodine receptor
	AR	Selenoprotein N
Myosin storage myopathy	AD	Slow myosin heavy chain
Sarcotubular myopathy	AR	TRIM 32
Congenital fibre type disproportion	AD	Skeletal α-actin
	AD	α-Tropomyosin slow
	AD	β-Tropomyosin
	AR	Selenoprotein N

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C.I.4

Myofibrillar myopathies

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The term myofibrillar myopathy (MFM) is the morphologic denominator of a group of dominant disorders associated with myofibrillar degradation that begins at the Z-disk, accumulation of the arising degradation products, congophilia of some of these products, and appearance of multiple proteins in abnormal fiber regions. The most frequently and strongly expressed proteins are myotilin, desmin, αB-crystallin, and dystrophin. The abnormal muscle fibers are best identified in trichrome-stained frozen sections that harbor pleomorphic amorphous, granular, or hyaline structures, and vacuoles containing membranous material. In a cohort of 70 MFM patients investigated at the Mayo Clinic, the disease typically presented with slowly progressive distal and/or proximal weakness. Cardiomyopathy was present in 17% and evidence for neuropathy in 51%. The EMG was typically myopathic and associated with abnormal electrical irritability, including myotonic discharges. Mutation analysis in different laboratories to date revealed mutations in different Z-disk associated proteins. In our cohort, 16%, 10%, 9%, 3%, and 3% of the patients harbored mutations in ZASP, myotilin, desmin, αB-crystallin, and filamin C, respectively. Because Z-disk changes are present in many muscle diseases, we suggest the following minimal criteria for diagnosis of MFM: (1) pleomorphic abnormal fiber regions with characteristic tinctorial properties in trichrome-stained sections. (2) Vacuolar change in some fibers in most cases. (3) Immunolocalization of multiple proteins in the pleomorphic fiber regions. (4) Congophilia of some hyaline deposits.

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