

Structural and Molecular Basis of Skeletal Muscle Diseases

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Preface

Over the past 10 years, the impact of modern microscopic pathology and molecular genetics on the diagnostic accuracy and understanding of the pathogenesis of muscle disease has been enormous. The resourceful and skilled application of the modern techniques of molecular genetics has been revolutionary. The initial and best example was the discovery of the gene whose mutation is the cause of Duchenne muscular dystrophy (DMD). This discovery bore fruit. It made possible the routine use of mutational analysis of patients for a precise diagnosis; in particular to distinguish Duchenne from Becker muscular dystrophies. Furthermore, it permitted a more refined and reliable method of carrier detection and prenatal diagnosis for these disorders.

The identification of the protein product of this gene allows us to use microscopic or immunoblot display of dystrophin for diagnostic purposes. Furthermore, it permitted at least 4 additional developments. Firstly, it led to the discoveries of several other molecules at the surface membrane of muscle fibers whose functional partnership is essential for the integrity of the muscle cell. Mutations of the genes encoding these molecules themselves can cause different forms of muscular dystrophies. Secondly, the discovery of dystrophin led to a better understanding of many aspects of the physiology and biochemistry of the muscle fiber surface membrane and made DMD a biologically highly informative experiment of nature. Thirdly, the molecular understanding of dystrophin deficiency and its deleterious consequences promise the development of truly effective therapy. Lastly, the example of the success of the discovery of dystrophin was heralding the molecular age of myology. It spurred feverish activities in molecular research, the fruits of which are represented by the discoveries of the molecular background of scores of other inherited muscle diseases.

Along with these momentous developments in molecular genetics, the microscopic pathology of skeletal muscle has also enjoyed a parallel surge of sophistication and practical informativeness. This is exemplified by increasing availability of highly specific and powerful antibodies for the qualitative and quantitative display of protein products of most of the genes whose mutation can cause muscle disease. Thus, the immunocytochemical profile obtained can be correlated with traditional microscopic pathological alterations at the light and electron microscopic level providing a powerful tool for a better understanding of the pathophysiology of muscle fiber damage or destruction in a given disease. It will also enable us to monitor directly the efficacy and safety of therapeutic interventions. In selected cases, microscopic techniques permit direct demonstration of genetic alterations (ie, fluorescent in situ hybridization or other forms of in situ hybridization) or even the study of the expression of specific genes by in situ reverse transcriptase polymerase chain reaction (RT-PCR).

The foregoing developments also pose challenges in designing modern educational formats, which are the most suitable to present current comprehensive knowledge of muscle disease for pathologists, clinicians and researchers. The Editors of this volume also faced that dilemma. One option was to follow the traditional categories of muscle disease and with each entity highlight the relevant state of knowledge of the molecular and microscopic features and correlate it with clinical phenotype and treatment options. Most current texts of myology have been written along these lines.

The other approach is less traditional and would take advantage of the vastly improved knowledge of the pathogenesis of muscle disease. By this approach, we would group diseases according to common basic etiological and/or pathogenic features. We recognize the fact

that there are still quite a few muscle diseases in which the lack of precise pathogenic knowledge does not permit the latter approach. However, the number of these diseases is fast decreasing. Another problem with this approach is that it necessitated the creation of a "miscellaneous" category for some muscular dystrophies where the molecular defects do not have a common denominator other than being "dystrophygenic."

Furthermore, there are disorders, which on pathogenic basis, could be equally grouped in 2 categories, eg, the *congenital myasthenic syndromes*, which could be listed either under *ion channel disorders* or *neuromuscular transmission defects*. Other examples are *nemaline myopathies* and *central core disease* that could belong to either *developmental disorders* or *myofibrillar disorders*. Nevertheless, we decided to organize the categories of muscle diseases according to the "pathogenic" approach. We have not allowed the molecular and pathological facts to hang in a void, so the authors have provided a brief initial clinical correlation for each disease. Subsequently, they presented and illustrated the essential up-to-date knowledge of molecular and microscopic facts, which are indispensable for the formulation of the pathogenesis, which is the key point for each entity. In allowing this routine, we tried to remain thoroughly factual, but we did not refrain from attractive hypotheses when they were applicable.

We trust that the new system of organization of clinical myology will not confuse the readers but it will emphasise the tremendous impact of microscopic pathology and molecular science in the field.

George Karpati

Contents

Preface	vi	8. Disorders of catabolic mechanisms	133
1. General pathological, immunopathological, and genetic background of skeletal muscle disorders	1	Lysosomal disorders	
2. Diseases associated with sarcolemmal and extracellular matrix defects	5	Alpha glucosidase deficiency syndromes	134
Dystrophinopathies	6	LAMP-2 deficiency	142
Sarcoglycanopathies	24	X-linked myopathy with excessive autophagy	145
Dysferlinopathies	29	Proteolytic disturbances	
Caveolinopathies	33	Defects of non-lysosomal proteolysis: Calpain3 deficiency	148
Laminin α 2 (merosin) gene mutations	37	9. Neuromuscular transmission defects	155
Collagen VI gene mutations. Bethlem myopathy/Limb-girdle muscular dystrophy	41	Myasthenia gravis	156
Heparin sulfate proteoglycan (perlecan) deficiency		The Lambert-Eaton myasthenic syndrome	166
Schwartz-Jampel syndrome	43	Congenital myasthenic syndromes	170
Muscular dystrophy caused by α 7 integrin deficiency	45	10. Myopathies affecting fuel and energy metabolism	181
3. Diseases associated with myonuclear abnormalities	47	Selected disorders of carbohydrate metabolism	182
Defects of nuclear membrane related proteins (emerin, lamins A/C)	48	Defects of fatty acid metabolism	189
Abnormalities in nuclear positioning (centronuclear myopathies)	57	Oxidative phosphorylation defects	202
4. Myofibrillar and internal cytoskeletal proteins	61	Myoadenylate deaminase deficiency	214
Actinopathies	62	11. Dysimmune and infectious myopathies	217
Core Diseases		Dysimmune myopathies. Definition of entities and experimental models of myositis	218
Central core disease	65	Polymyositis and dermatomyositis	221
Multi-minicore disease	68	Inclusion body myositis	228
Desmin-related myopathies	70	Viral myositis	231
Nemaline myopathies	74	Bacterial myositis	236
Plectin deficiency	78	Fungal, protozoal, and other parasitic infections	238
Telethonin deficiency	81	12. Toxic and iatrogenic disorders	245
Myotilinopathy	82	13. Effects of chronic denervation and disuse on muscle	251
Myosin heavy chain depletion syndrome	83	Effects of denervation on muscle	252
Autosomal dominant myosin heavy chain IIa myopathy	85	Effects of disuse on muscle	257
5. Diseases associated with ion channel and ion transporter defects	89	14. Endocrine disorders and myotrophic molecules	259
Myotonia and paramyotonia	90	15. Miscellaneous myopathies	265
Dyskalemic episodic weakness	95	Cancer-related muscle disease	266
Malignant hyperthermia and central core disease associated with defects in Ca ²⁺ channels of the sarcotubular system	99	Effects of ageing on skeletal muscles and their clinical significance	270
Brody disease associated with defects in a Ca ²⁺ pump	103	Hereditary inclusion body myopathies	274
6. Myopathies based on complex molecular defects	107	Marinesco-Sjögren syndrome	277
Repeat expansion diseases		Osteomalacia myopathy	279
The myotonic dystrophies	108	Vitamin E deficiency	282
PABPN1 dysfunction in oculopharyngeal muscular dystrophy	115	Amyloid myopathy	284
Large telomeric deletion disease, Facioscapulohumeral dystrophy	119	Rare myopathies of childhood	287
7. Developmental disorders of skeletal muscle	123	16. Neuromuscular resources on the Internet	291
X-linked myotubular myopathy	124	17. The principles of therapies and prevention based on cellular and molecular mechanisms of muscle disease	295
Congenital fibre type disproportion	130	Contributors	305
		Acknowledgments	309
		Index	310