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Review

Nuclear envelope defects in muscular dystrophy

Kyle J. Roux, Brian Burke *

Department of Anatomy and Cell Biology, The University of Florida College of Medicine, 1600 SW Archer Road, Gainesville, FL 32606, USA

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Abstract

Muscular dystrophies are a heterogeneous group of disorders linked to defects in 20–30 different genes. Mutations in the genes encoding a pair of nuclear envelope proteins, emerin and lamin A/C, have been shown to cause the X-linked and autosomal forms respectively of Emery–Dreifuss muscular dystrophy. A third form of muscular dystrophy, limb girdle muscular dystrophy 1b, has also been linked to mutations in the lamin A/C gene. Given that these two genes are ubiquitously expressed, a major goal is to determine how they can be associated with tissue specific diseases. Recent results suggest that lamin A/C and emerin contribute to the maintenance of nuclear envelope structure and at the same time may modulate the expression patterns of certain mechanosensitive and stress induced genes. Both emerin and lamin A/C may play an important role in the response of cells to mechanical stress and in this way may help to maintain muscle cell integrity.

Keywords: Muscular dystrophy; Nuclear envelope; Nuclear lamia; Laminopathy; Emerin

1. Introduction

Muscular dystrophies (MDs) represent a diverse group of several dozen inherited disorders [1]. While their common feature is always progressive weakness and degeneration of skeletal muscle, these various disorders may differ, quite considerably, with respect to location of affected tissues, disease progression and severity. Disparity in affected muscles can easily be appreciated when comparing facioscapulohumeral MD 1A (FSHMD1A OMIM #158900) to limb girdle MD 1A (LGMD1A OMIM #159000). In the former, the muscle groups affected are in the face, shoulder girdle and lower legs. In the latter, proximal weakness of the hip girdle is observed which only later progresses to the shoulder girdle. Other forms of muscular dystrophy, for example Emery–Dreifuss MD (EDMD OMIM #310300), may feature degeneration of cardiac muscle in addition to skeletal muscle. Finally, certain forms of muscular dystrophy such as EDMD may appear early in life whereas others such as LGMD1A display an adult onset. Mutations in at least 20–30 genes [2,3] have been associated with MD. Proteins encoded by these genes can be grouped according to their subcellular localization. While this review will focus primarily on MD-linked nuclear proteins, functional parallels between protein groups will be explored.

2. Cytoskeletal and extracellular matrix related muscular dystrophies

The most common form of MD is Duchenne MD (DMD OMIM #310200) [1]. This is an X-linked disorder with an early onset of about 3–5 years of age. The affected gene in DMD encodes dystrophin, an extremely large (~400 kDa) protein related to alpha actinin and spectrin. In muscle cells, dystrophin functions to link the actin cytoskeleton to the plasma membrane and extracellular matrix (ECM) [2,3]. The N-terminus of dystrophin interacts directly with cytoskeletal actin filaments, but not actin filaments of the contractile apparatus. Distal regions of the molecule bind a complex of plasma membrane proteins containing, among others, members of the dystroglycan and sarcoglycan families of glycoproteins. Alpha-dystroglycan in turn binds to alpha2-laminin on the extracellular face of the plasma membrane providing a link to the ECM. Perhaps not surprisingly, mutations in the genes encoding dystroglycans, sarcoglycans and laminin have all been linked to various forms of muscular dystrophy [2,3]. In addition, forms of MD such as Fukuyama congenital muscular dystrophy appear to involve proteins that are implicated in the intracellular processing of

* Corresponding author. Tel.: +1 352 392 0040; fax: +1 352 392 3305.
E-mail addresses: bburke@ufl.edu, kroux@ufl.edu (B. Burke).

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newly synthesized dystroglycans and sarcoglycans [4,5]. What all of these proteins have in common is their contribution to the integrity of a structural network, with signaling properties, that connects the muscle cell cytoskeleton to the ECM through the plasma membrane. Other MD-associated genes encode cytosolic proteins like calpain-3 and sarcomeric proteins such as titin. The latter functions both as a molecular ruler in sarcomere assembly as well as an elastic component of the contractile apparatus. In this way titin makes a direct contribution to muscle cell functionality.

3. Nuclear envelope related muscular dystrophies

In recent years an additional group of MDs have been linked to defects in nuclear envelope proteins [1]. The prototype of these is Emery–Dreifuss MD. EDMD displays two inheritance patterns, X-linked (EDMD OMIM #310300) and autosomal (EDMD2 OMIM #181350). Both forms of the disease display similar physical symptoms featuring degeneration of muscles of the upper arms, shoulder girdle and lower legs, and contractures of the Achilles tendons as well as of tendons of the elbows and neck. These contractures have a childhood onset and are one of the early signs of the disease. EDMD also features a very significant cardiac involvement with both cardiac muscle degeneration and associated conduction system block. The latter frequently requires the implantation of a pacemaker in early adulthood and may ultimately necessitate a heart transplant.

In 1994, the X-linked form of EDMD was mapped to a gene encoding emerin, a 29 kDa membrane protein (named after Professor Alan Emery, who originally described the disease [6]) [7]. Emerin immediately provided two surprises. First, it turned out to be a nuclear envelope membrane protein and second it was not specific to muscle [8,9]. Instead it is expressed in virtually all human-cell types. Subsequent discussion will delve further into the etiology of both X-linked and autosomal EDMD, as well as other associated disorders, in an attempt to elucidate how defects in ubiquitously expressed proteins might give rise to tissue specific diseases. Finally, recent findings will be examined which might functionally connect nuclear envelope components with dystrophin and dystrophin associated proteins (dytroglycans and sarcoglycans etc.) that are linked to Duchenne, Becker and related forms of MD.

4. The nuclear envelope

The nuclear envelope (NE) is a selective barrier that forms the interface between the nucleus and the cytoplasm, and as such plays a central role in defining the biochemical identities of each compartment [10,11]. In addition to its barrier function, it is becoming increasingly clear that the NE is a key determinant of nuclear architecture and may strongly influence cytoplasmic organization. The NE contains several discrete structural elements, the most prominent of which are the inner and outer nuclear membranes (Fig. 1). In mammalian somatic cells these two membranes are separated by a uniform gap of about 30–50 nm referred to as the perinuclear space (PNS). The INM and ONM are connected at annular junctions which create aqueous channels between the nucleoplasm and cytoplasm. These channels are occupied by nuclear pore complexes (NPCs), massive multi-protein assemblies that regulate the trafficking of macromolecules across the NE. A mammalian somatic cell nucleus typically contains several thousand NPCs.

In addition to its continuities with the INM at the periphery of each NPC, the ONM also displays multiple connections to the peripheral endoplasmic reticulum (ER) to which it is functionally related. Evidently the INM, ONM and ER form a single continuous membrane system. Similarly, the PNS constitutes a perinuclear extension of the ER lumen, and contains both secretory proteins and soluble ER resident proteins, including ER chaperones.

The final major structural feature of the NE is the nuclear lamina [12]. This is a relatively thin (20–50 nm) protein meshwork that is closely associated with both the nuclear face of the INM and the underlying chromatin. The key components of the nuclear lamina are a group of proteins known as A- and B-type lamins. The lamin proteins are members of the more extensive cytoplasmic intermediate filament (IF) family and like all IF proteins contain a central coiled-coil domain flanked by non-helical head and tail domains. In contrast to their cytoplasmic counterparts, each of the lamins contains a nuclear localization sequence (NLS) within the C-terminal non-helical domain required for efficient nuclear import of newly synthesized lamin proteins. Both A- and B-type lamins are known to interact with membrane proteins of the INM [12] as well as with chromatin [13,14]. In this way, the nuclear lamina may provide anchoring sites at the nuclear periphery for higher order chromatin domains in addition to stabilizing and organizing the NE. While the bulk of the lamins appear to reside at the nuclear periphery, nucleoplasmic lamins have also been observed [15–17] with proposed roles in several aspects of nuclear metabolism, including DNA replication [18–21].

In mammalian cells there are two major A-type lamins, A and C, encoded by a single gene, *LMNA* [22]. These two proteins are identical for the first 566 amino acid residues. Both proteins possess unique C-terminal extensions. In the case of lamin C this consists of a sequence of six amino acids. The unique region of lamin A is considerably larger at 98 amino acids. Two other A-type lamins have been described. The first of these, lamin AΔ10 [23], lacks a 30 amino acid sequence within the unique lamin A specific region that is encoded by exon 10 (*LMNA* contains 12 exons). While it is found in somatic cells, its abundance and distribution has yet to be well defined. Lamin C2 [24] is male germ cell-specific and essentially consists of a truncated form of lamin C that contains an alternative N-terminus modified by myristoylation.

Mammalian somatic cells also contain two B-type lamins, lamins B1 and B2 [25], encoded by separate genes (*LMNB1* and *LMNB2*) [26,27]. A third B-type lamin, lamin B3, derived from the *LMNB2* primary transcript by alternative splicing is male germ cell-specific [28]. While B-type lamins as a class are expressed in all nucleated cell types, the expression of A-type lamins is developmentally regulated [29,30]. As a general rule, A-type lamins are found in most adult differentiated cell types but are absent from both early embryonic cells and adult stem