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Review

Emerin in health and disease

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ABSTRACT

Emery-Dreifuss muscular dystrophy (EDMD) is caused by mutations in the genes encoding emerin, lamins A and C and FHL1. Additional EDMD-like syndromes are caused by mutations in nesprins and LUMA. This review will specifically focus on emerin function and the current thinking for how loss or mutations in emerin cause EDMD. Emerin is a well-conserved, ubiquitously expressed protein of the inner nuclear membrane. Emerin has been shown to have diverse functions, including the regulation of gene expression, cell signaling, nuclear structure and chromatin architecture. This review will focus on the relationships between these functions and the EDMD disease phenotype. Additionally it will highlight open questions concerning emerin's roles in cell and nuclear biology and disease.

Contents

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1. Mutations in emerin and lamins A and C cause Emery-Dreifuss muscular dystrophy

There are two forms of Emery-Dreifuss muscular dystrophy (EDMD), X-linked (X-EDMD or EDMD1) and autosomal EDMD (AD-EDMD or EDMD2), which can occur in a dominant or very rare recessive form [1,2]. The incidence of X-EDMD is estimated at 1 in 100,000, while the incidence of AD-EDMD is unknown [3]. EDMD is characterized by skeletal muscle wasting, contracture of major tendons and cardiac conduction defects [4]. Emery and Dreifuss first identified EDMD in 1966 as a new form of muscular dystrophy. It was shown nearly three decades later that X-EDMD was caused by mutations in the gene encoding the inner nuclear membrane protein emerin (*EMD*, then known as *STA*; [5]). Five years later AD-EDMD was linked to mutations in the *LMNA* gene, which encodes lamins A and C [6]. EDMD-like syndromes can also be caused by mutations in several other genes, including *SYNE-1* and *SYNE-2* [7], *TMEM43* [8] and *FHL1* [9]. EDMD was the first disease in a broad range of human diseases known as laminopathies, defined as diseases caused by mutations in lamins, emerin and other lamin-binding proteins [10,11]. These diseases have a spectrum of both distinct and overlapping phenotypes, including life-threatening irregular heart rhythms, progressive skeletal muscle wasting, contractures of major tendons, abnormal fat deposition and premature aging [10,12,13].

EDMD presents clinically with a triad of symptoms including (1) early contractures of major tendons and post cervical muscles (notably, this is often prior to any muscle weakness), (2) progressive muscle wasting, beginning in the humeroperoneal regions, and (3) cardiac diseases, including a combination of cardiac arrhythmias, conduction defects and cardiomyopathy [4]. Symptoms usually appear in the first decade of life and progress slowly thereafter [14]. Moderately increased serum creatine kinase levels may be seen, however not at the levels seen in Becker or Duchenne muscular dystrophy [15,16]. Muscle wasting spreads to limb girdle musculature in the second decade of life [14], coinciding with onset of cardiac disease [17]. To prevent sudden death, early detection of cardiac conduction defects is essential, with pacemakers and other treatments for heart failure acting as life-saving medical interventions in many cases [4,18]. Other treatments include orthopedic surgeries to relieve symptoms of contracture, use of mechanical ambulatory assistance and, in later stages, the use of respiratory aids [4,19].

Skeletal muscle pathology shows evidence of myopathy, including variation in muscle fiber size, centralized muscle fiber nuclei, fibrosis and necrosis [20]. Electron microscopy also revealed alterations in nuclear architecture [21–24]. The heterogeneity of these dystrophic changes causes them to be unreliable for diagnosing EDMD and muscle biopsy is rarely used diagnostically. Instead, immunodetection of emerin or FHL1 is performed to aid in diagnosis of X-EDMD. Immunodetection may also aid in the diagnosis of EDMD2. However, immunodetection is often unreliable because EDMD2 is a dominant disease in which wildtype lamins and the mutant proteins are often both expressed; in one study approximately 50% of EDMD2 patients exhibited reduced lamin A/C protein expression [25], though a larger cohort is necessary to confirm this finding. Thus, gene sequencing and deletion or duplication analysis is often used to assist in the diagnosis of EDMD and identify mutations in *EMD* (61% of X-EDMD), *FHL1* (10% of X-EDMD), and *LMNA* (45% of EDMD2) [15,19,26–28].

95% of mutations in the emerin gene that cause X-EDMD result in loss of emerin protein [5,29–31]; FHL1 protein is absent or present at significantly reduced levels in those with FHL1-related X-EDMD [9]. Four "special" mutant forms of emerin exist in patients (S54F, Q133, P183H and Δ95–99) that cause EDMD despite being expressed at normal or near normal levels and correctly localizing to the nuclear envelope [29,32]. Interestingly, missense or deletion mutations in EMD resulting in stable emerin protein expression have presented less severe phenotypes [31], though whether this is due to familial background effects remains unknown. Approximately 64% of patients who produce emerin do not have mutations in *EMD*, *FHL1* or *LMNA*, implicating other, unidentified genes in EDMD [9].

2. Muscle regeneration and EDMD

Impaired regeneration is thought to contribute to the skeletal muscle defects in EDMD. For example, muscle from both EDMD patients and mice lacking emerin show increased expression of muscle regeneration pathway components [33,34], suggesting repression of these genes requires emerin. Further, emerin-downregulated myoblasts have impaired differentiation [35,36]. It was recently shown that signaling pathways important for myogenic differentiation and skeletal muscle regeneration are disrupted in emerin-null myogenic progenitors, including Wnt, IGF-1, TGF-β, and Notch pathways [37–43].

Muscle regeneration is a multi-step process that repairs damaged muscle tissue [44]. Upon injury, myogenic progenitors are activated and begin proliferating [45]. A small fraction of these cells will retain their stem cell gene expression program and replenish the niche. The remaining activated myogenic progenitors, which express the transcription factors Pax3 and Myf5, will differentiate into proliferative myoblasts that express Pax3, Myf5 and MyoD [46,47]. These myoblasts then terminally differentiate to form myocytes, which turn off Pax3 and Myf5 expression and activate expression of myogenin and other myocyte-specific genes [46]. The committed myocytes then fuse with the damaged myofiber to regenerate the muscle. The coordinated temporal expression of these factors is required for muscle regeneration. Coordinated temporal expression of these critical factors and the proper temporal nuclear localization of their gene loci are disrupted during differentiation of emerin-null myogenic progenitors [48], suggesting a mechanism for how loss or mutation of emerin causes impaired skeletal muscle regeneration.

3. The nuclear lamina

The nucleus is separated from the cytosol by the nuclear envelope, a double lipid bilayer composed of the outer nuclear membrane (ONM), which is contiguous with the endoplasmic reticulum, and the inner nuclear membrane (INM) [49,50]. Interspersed within the nuclear envelope are large macromolecular complexes called nuclear pore complexes (NPCs) that allow for bidirectional transport across the nuclear envelope. The intermediate filament proteins lamin A, lamin B and lamin C form a proteinaceous meshwork at the inner nuclear membrane and provide the nucleus with its strength, rigidity and elasticity [51,52]. There are more than 150 inner nuclear membrane proteins (also known as nuclear envelope transmembrane proteins or NETs) that were recently identified by proteomic screens in various cell types [53–55]. The functions of the vast majority of nuclear envelope proteins remain unknown. Similar to emerin, MAN1 and Lap2, many of these newly identified NETs bind lamins and together the inner nuclear membrane proteins and lamins define the nuclear lamina [56,57]. NETs show diverse, tissue-specific expression and serve a number of known functions, including regulating cytoskeletal organization [54], the cell cycle [58], and genomic organization [59].

Loss or mutations in lamins cause a number of tissue specific and organism-wide diseases [51]. Interestingly, loss of lamin expression or point mutations in lamins leads to mislocalization of inner nuclear membrane proteins and clustering of nuclear pore

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