Journal of Student Research (2017) Volume 6, Issue 1: pp, 14-18
Review Article

# The Genes, Proteins, and the Cell Biological Processes Underlying Emery-Dreifuss Muscular Dystrophy

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Emery-Dreifuss Muscular Dystrophy (EDMD) is a type of muscular dystrophy characterized by contractures, or shortening of muscles or joints in the elbows and Achilles tendons, muscle wasting and weakness as well as cardiomyopathy. There are two main forms of inherited EDMD, X-linked recessive and autosomal dominant. There is also a rarer form of autosomal recessive inheritance with only a few cases ever reported. The X-linked form of EDMD is caused by mutation of the *STA* gene that encodes the protein emerin, while the autosomal dominant form is caused by a missense mutation on the *LMNA* gene, which encodes lamin A/C proteins. Both emerin and lamin A/C are nuclear envelope proteins that interact with other proteins to create a connective network that attaches the nuclear lamina to the cytoskeleton. These nuclear envelope proteins interact via accessory proteins to chromatin and also thereby stimulate gene expression. The exact mechanism of how mutations in these genes lead to muscular dystrophy is not well understood. The "structural hypothesis," states that the absence of these envelope proteins result in a weakened cell and would eventually end in nuclear disruption. The "gene regulatory hypothesis" states that emerin and lamin may be transcription factors whose absence results in tissue-specific effects. This review addresses these hypotheses, describes what is known about the cell and molecular biology underlying EDMD and considers recent as advances in therapeutics.

**Keywords:** Emery-Dreifuss Mascular Dystrophy

## Symptoms

Emery-Dreifuss Muscular Dystrophy (EDMD) is a progressive neuromuscular disorder caused by mutations in genes coding for nuclear envelope proteins. It is one of nine known muscular dystrophies and was first observed in a family in Virginia in the 1960s. It is now thought to affect 1 in every 100,000 people (Jimenez- Escrig et al., 2012). The first symptoms include contractures, or shortening of a muscle or joint, that causes increased weakness in the Achilles tendons, cervical muscles and elbows as well as limited movement of the neck and spine (Emery, 2002). Later symptoms include progressive muscle wasting and weakness, happening in the proximal muscles of the arms and distal muscles in the legs (Emery, 1989). End-stage symptoms include, cardiomyopathy, which could range from sinus bradycardia, prolongation of the PR interval, or the time between atrial and ventricular depolarization, to heart attack (Emery, 2002). Initial symptoms usually surface during childhood or early adolescence with most patients experiencing cardiac involvement by at least age 30 (Helbling-Leclerc et al., 2002).

## The Genes and Proteins of EDMD

There are two main forms Emery-Dreifuss Muscular Dystrophy inheritance, X-linked recessive and autosomal dominant (AD-EDMD) (Bonne et al., 200). There is also an autosomal recessive form of EDMD but it is extremely rare with only a few cases ever reported (Jimenez- Escrig et al., 2012). Historically, there was thought to be only one form of X-linked EDMD, named EMD, caused by a mutation in the *STA* gene, which encodes for the serine-rich protein made of 254 amino acids named emerin, but a recent study (2009) showed that there is indeed another X-linked form of EDMD caused by a mutation in the *FHL1* gene, which encodes for a family of gene regulatory protiens (Ognibene et al., 1999 & Gueneau et al., 2009). The autosomal dominant form of EDMD is due to a mutation in the *LMNA* gene, which encodes for A-type lamins (Bonne et al., 2000).

Through amino acid sequence homology and peripheral nuclear localization, emerin has been suggested to be a member of the nuclear lamina-associated protein (LAP) family that is localized at the nuclear rim (Ognibene et al., 1999). Emerin is expressed in skeletal and cardiac muscles as well as many other tissues (Yates et al., 2009). It has been shown to be localized to the inner nuclear membrane through its hydrophobic C-terminal domain and to be very strongly connected to the nuclear lamina (Ognibene et al., 1999). This integral membrane protein stretches out into the nucleoplasmic space and associates with other envelope membrane proteins to maintain the integrity of nuclear structure (Bera et al., 2014).

The autosomal dominant form is the second most common form of inheritance caused by a missense mutation in the *LMNA* gene (Bera et al., 2014). The lamins encoded by *LMNA* are type V intermediate filament proteins that are present in the nuclear envolope as fibrous lamina (Bera et al., 2014). These intermediate filament proteins are originally assembled into the basic coiled-coil structure but are later packaged into the higher order structures of lamins A and C by parallel stacking interactions (Bera et al., 2014). These lamins participate in structural support for the nuclear envelope and also provide an attachment site for other nuclear proteins (Bera et al., 2014).

Only about 40% of Emery-Dreifuss Muscular Dystrophy cases are caused by mutations to the *STA* and *LMNA* genes (Meinke et al., 2014). Recent studies have linked the presence of mutations in the *FHL1* gene as another mode of EDMD inheritance (Gueneau at el., 2009). The *FHL1* gene is made up of eight exons with the first two believed to be non-coding regions (Gueneau et al., 2009). The other exons, when alternatively spliced, encode three protein isoforms, FHL1A, FHL1B and FHL1C (Gueneau et al., 2009). The most abundant isoform expressed is FHL1A and is found in striated

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muscles with the two other lesser-abundant isoforms expressed in striated muscles as well as in the brain and testes (Gueneau et al., 2009). FHL1 proteins act as transcriptional regulators of genes that increase myofiber size (Sabatelli et al., 2014). The FHL1A protein localizes in the myrofribrillar sarcomeres as well as in the sarcolemma and is involved in cell adhesion and myoblast differentiation (Sabatelli et al., 2014). Mutations in the distal exons (5 to 8) of the *FHL1* gene affect each of the FHL1 isoforms differently but all result in a large decrease in FHL1 expression in sarcomeres and a delay in muscle differentiation of myoblasts in EDMD patients (Gueneau et al., 2009).

Emerin and lamin A/C interact with each other to create a network that connects the nuclear lamina to the cytoskelton, a system named the linker of nucleoskeleton and cytoskeleton (LINC) complex (Meinke et al., 2014). Emerin, lamins and and their partner biding proteins, SUN1 and SUN2 as well as nesprin-1 and nesprin-2, all interact to form this complex (Meinke et al., 2014). Without each protein, this complex fails to form properly, thus resulting in disturbances to normal muscle functions that have been linked to EDMD phenotype (Meinke et al., 2014).

Together, mutations in the *STA*, *LMNA*, and *FHL1* genes do not account for all cases of EDMD, suggesting that other contributing genes have yet to be discovered (Meinke et al., 2014).

**Slight differences in symptoms when comparing different forms of EDMD**

Although the X-linked and autosomoal dominant forms of EDMD both lead to the three main symptoms described above, the severity and first appearance of symptoms differ somewhat (Puckelwartz et al., 2011). In X-linked EDMD, joint contractures are typically the first symptom to manifest, while in AD-EDMD that symptom may not emerge until after the onset of muscle weakness (Puckelwartz et al., 2011). Patients with AD-EDMD typically have more severe and progressive wasting of the biceps brachii and more difficulty walking compared to those with X-linked types of EDMD (Bonne et al., 2000). Mutations of the *LMNA* gene associated with AD-EDMD correlate with a larger range of symptom severity as compared to mutations in other EDMD-associated genes (Bonne et al., 2000). The X-linked form of EDMD caused by a mutation of the *FHL1* gene can vary in its phenotypic severity (D'Arcy et al., 2014). *FHL1* mutations that affect all three protein isoforms result in the most severe symptoms associated with X-linked EDMD (D'Arcy et al., 2014).

To confirm the diagnosis of an inherited form of Emery-Dreifuss Muscular Dystrophy, family history of mutations in the *STA*, *FHL1* and *LMNA* genes can be helpful in determining which gene to test (Puckelwartz et al., 2011). However without this distinguishing information, immunodetection of emerin, FHL1, and lamin A and C in males can be used to distinguish between AD-EDMD and X-linked-EDMD (Puckelwartz et al., 2011). Female patients very rarely manifest X-linked EDMD; therefore women and girls are usually tested for AD-EDMD before consideration of an X-linked mode of inheritance (Puckelwartz et al., 2011).

**Affected cellular processes**

Mutations in both the *STA* and *LMNA* genes affect the structure and function of nuclear envelope proteins (Bonne et al., 2000). In normally functioning cells, emerin and lamin filaments, specifically type-A lamins, bind and interact at the inner nuclear membrane to form a stable nuclear envelope (Holaska et al., 2004). Lamins also play a role in chromatin regulation by monitoring heterochromatin through interactions with chromatin binding factors such as histones, heterochromatin proteins, and bridging proteins such as BAF and LAP2α (Gotzmann & Foisner, 2000). The interactions between lamin A/C and chromatin are complex and require the association of other nuclear membrane proteins such as emerin and SUN proteins (Gotzmann & Foisner, 2000). Emerin is a part of the LEM-domain family that also includes other lamin-associated proteins such as LAP2β, MAN1 and LAP2α (Holaska et al., 2004). Emerin binds via its LEM-domain to a BAF (barrier-to-autointegration factor) that affects chromatin structure, nuclear assembly and gene regulation (Holaska et al., 2004). MAN1 is a lamina-associated protein in the inner nuclear membrane and has been shown to play a role in emerin-mediated chromatin organization (Gotzmann & Foisner, 2000). Emerin also binds to Btf, a transcriptional repressor that promotes apoptosis when overexpressed (Lammerding et al., 2005). Emerin has been found to be cleaved during cell death in differentiating mice myoblasts and is thus suggested to have an anti-apoptoptic effect by inhibiting Bft activity (Lammerding et al., 2005).

Emerin and lamin function is dependent on structural anchoring partners such as nesprin-1 and nesprin-2 (Holaska et al., 2004). Nesprin-1 and nesprin-2 are essential for binding both emerin and type A lamins, creating a network that links the nucleoskeleton to the inner nuclear membrane (INM), the outer nuclear membrane (ONM), membrane organelles, the sarcomere and to the actin cytoskeleton (Zhang et al., 2007). In addition, Lamin A/C, prelamin A (precursor to lamin A), emerin, SUN1 and LAP2α are all necessary for muscle cell differentiation as they create a web of cellular structure and chromatin regulation necessary for inducing transcriptional programs required for cell survival (Camozzi et al., 2014). Taken together, these findings suggest that muscle cell-specific chromatin modulation by emerin and lamin A/C, and associated proteins, could underlie the muscle cell-specific symptoms of EDMD (Camozzi et al., 2014).

**Emery-Dreifuss Muscular Dystrophy Mechanisms**

The mechanism by which the FHL1 mutations lead to EDMD is not clear, but may be due to destabilization of the LIM domain 2 that results in FHL1 protein misfolding and aggregation (D'Arcy et al., 2014). Many progressive degenerative disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, prion diseases and amyotrophic lateral sclerosis are caused by protein misfolding. It has been suggested that the development of amyloid fibrils is the main cause of these diseases, but the mechanism for this supposed origin has yet to be certainly determined (Bucciantini et al., 2002). While protein misfolding and aggregation is associated with many progressive degenerative disorders and FHL1 aggregation has been shown to be associated with a number of diseases, the association of aggregation with EDMD is unclear. Instead

FHL1 expression may simply be required in EDMD (Wilding et al. 2004).

The exact method for how mutations of the emerin and lamin A/C proteins lead to the phenotypic characteristics of EDMD is unknown but potential disease mechanisms have been suggested (Camozzi et al., 2014). The two hypotheses are the "structural hypothesis" and the "gene regulatory hypothesis" (Lammerding et al., 2005). The structural hypothesis proposes that mutations in the *STA* and *LMNA* genes lead to increased nuclear weakness and eventual nuclear disruption of muscle cells (Lammerding et al., 2005). The gene regulatory hypothesis puts forward the idea that since lamin A/C and emerin bind to many transcriptional regulators, their absence in a cell would result in tissue-specific effects that would eventually manifest as a muscular dystrophy (Lammerding et al., 2005).

A recent study addressed the mechanism of EDMD by examining the difference between wild-type, emerin-deficient and lamin A-deficient mice embryo fibroblasts (Lammerding et al., 2005). The study found that emerin-deficient cells had a milder phenotype and increased nuclear function compared to the lamin A-deficient cells (Lammerding et al., 2005). Because emerin deficiency did not affect nuclear stiffness and fragility, it was instead thought to impact nuclear envelope organization on a smaller scale (Lammerding et al., 2005). Additionally, the mechanotransduction response genes, egr-1 and iex-1, were impaired in emerin-deficient mouse cells, which resulted in an increase of apopostosis in response to mechanical stress (Lammerding et al., 2005). These data suggested that the emerin-associated pathologies primarily result from an impaired signaling response rather than a stress-induced injury of the nuclear membrane (Lammerding et al., 2005).

To better understand the lamin-associated form of EDMD, the role of lamins as wide-scale supervisors of chromatin regulation were considered as a possible mode in which interruption of normal cellular function can occur (Camozzi et al., 2014). Mutations affecting this process resulted in the detachment of heterochromatin from the nuclear lamina as well as the loss of heterochromatin domains of nuclei in fibroblasts and mature muscle fibers (Camozzi et al., 2014). Along with the loss the heterochromatin domains, nuclei of affected muscle cells appear elongated which has been suggested to be caused by nuclei that have failed to position correctly during muscle cell differentiation, thus causing a formation of clustered nuclei (Camozzi et al., 2014). Nuclei affected by the lamin A/C mutation also show irregular distribution of the nuclear matrix as well as loss of chromatin from the nuclear envelope (Lammerding et al., 2005). These altered nuclei have been linked to disrupted sarcomere structure and shown to result in an EDMD-like phenotype (Camozzi et al., 2014).

Unlike lamin- deficient EDMD, which can result from many types of mutations to the *LMNA* gene, X-linked EDMD is primarily caused by nonsense-mutations of the *STA* gene that result in cellular deficiency of emerin (Gotzmann & Foisner, 2000). There have only been few cases in which *STA* missense mutation have caused a decrease in emerin expression (Gotzmann & Foisner, 2000). However, in all reported cases, emerin mutations result in the mislocalization of this protein to the ER (Gotzmann & Foisner, 2000). This mislocation has also been described in mutations of the emerin-associated proteins, nesprin-1 and nesprin-2 (Gotzmann & Foisner, 2000). Mutations in nesprin-1 and nesprin-2 encoding genes, *SYNE1* and *SYNE2* respectively, cause nuclear morphology defects and interrupt the binding interactions of nuclear envelope proteins that help keep a cell properly structured through the mislocation of emerin, (Zhang et al., 2007). Mutations in the *LMNA* gene often also result in the mislocalization of emerin to the ER, and because of this, it has been suggested that the results of lamin A/C mutations encompass the phenotypic outcome of emerin-deficieny EDMD in addition to their own (Lammerding et al., 2005). In *C. elegans* lacking emerin expression, histone deacetylases were expressed at a lower rate, thus suggesting that the enzymes involved in epigenetic modifications of histones could be contributing to EDMD pathogenesis (Camozzi et al., 2014).

**Treatments**

A study done in 2007 aimed to address myoblast differentiation using the C2C12 mouse cell line (Favreau et al., 2008). The formation of muscle cells, or myogenesis, is regulated by myogenic basic helx-loop-helix transcription factors such as MyoD and the myocyte enhancing binding factor MEF2 and their interactions with histone deacetylases, histone acetyl transferases and the chromatin remodeling complex SWI/SNF (Favreau et al., 2008). The mutation of lamin A at arginine 453 (R453W) of AD-EDMD prevents the differentiation of myoblast to myocyte in C2C12 mouse cells (Favreau et al., 2008). This inability to differentiate was shown to be the result of incomplete cell cycle arrest and low expression of myogenic factors (Favreau et al., 2008). One reason for the poorly differentiating myoblasts was the expression of cell proliferation inducers such as CD1 and Rb hyperphosphorlation at a time when these proteins should have been inactive (Favreau et al., 2008). The second reason was the repression of both CD1 and hyperphosphorlayted Rb at the time when cell cycle arrest promoting proteins such as CD3, p21 and hypophosphorylated Rb were active (Favreau et al., 2008).

Myoblast differentiation of these cells was significantly increased by treatment with PD98059 (an inhibitor of the MEK-ERK differentiation inhibition pathway) and IGF-II (an activator of PI3, which is an enzyme that encourages cell proliferation and differentiation) (Favreau et al., 2008). It is thought that a similar treatment for patients could allow myogenesis to occur and could thereby improve the muscular and cardiac symptoms caused by AD-EDMD (Favreau et al., 2008).

The most life-threatening aspect of EDMD is cardiac complication, which generally surfaces in every patient before age 30 (Helbling-Leclerc et al., 2002). Without the implantation of a pacemaker, patients are at risk of sudden heart block (Helbling-Leclerc et al., 2002). It is well known that the angiotensin-converting enzyme inhibitor (ACEI) along with β-blockers improve cardiac functions in adult patients with chronic heart failure; however, it was unknown if this therapy could help patients with cardiac difficulties due to muscular dystrophy syndromes (Kajimoto et al., 2006). In a study testing the affects of ACEI and β-blockers on patients with muscular dystrophy, it was shown that those given only ACEI did not see an increase in ventricular function

(Kajimoto et al., 2006). It was noted that the combinatory therapy of both ACEI and the β-blocker carveldiol was more effective at improving left ventricular function as well as plasma VNP (Ventricular Natriuretic Peptide) levels (Kajimoto et al., 2006).

**New Research Findings**

Only about 50% of patients who present with the characteristics of Emery-Dreifuss Muscular Dystrophy contain mutations that have been pinpointed to a particular gene, thus implying the presence of other causative genes (Gueneau et al., 2009). A 2011 research study found that missense mutations in the *TMEM43* gene that caused alteration of its expressed protein, LUMA, an inner nuclear membrane protein (Liang et al., 2011). LUMA interacts with lamins and emerins and is suggested to have an important role in cellular function although this biological process is still mostly unknown (Liang et al., 2011). LUMA is made up of large hydrophilic and 4 transmembrane domains, with mutations in the hydrophilic domain suggested to interfere with the nuclear envelope integrity as well as protein-to-protein interactions (Liang et al., 2011).

In an even more recent study, researchers examined EDMD patients who did not exhibit mutations within the *LMNA*, *STA* or *FHL1* gene and searched for the presence of mutations in other genes (Meinke et al., 2014). This study revealed *SUN1* and *SUN2* as causative genes in some cases of EDMD (Meinke et al., 2014). Patients with mutations in *SUN1* or *SUN2* exhibited impaired rearward nuclear organization of their fibroblasts, resulting in a defective nuclear cytoskeleton coupling (Meinke et al., 2014). These data underscore the importance of nuclear-cytoskeleton coupling, specifically nuclear microtubule association and its role in EDMD (Meinke et al., 2014).

**Concluding Remarks**

In the fifty-five years since EDMD was first described, much has been learned regarding the affected genes as well as the mechanism(s) of disease action. Despite this progress, additional genes continue to be identified, and there are likely more to be discovered in the future. Every new causative gene identified and characterized adds a new layer of complexity onto the disease mechanism(s). Nonetheless, treatment targeting pathways known to be involved are currently being developed, and seem to hold a great deal of promise for EDMD patients.

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