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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.

Keywords

Emerin; Emery-Dreifuss muscular dystrophy; Nuclear envelope; Lamina; Laminopathies; Lamins A/C

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 95–99) 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 mesh-work 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 complexes, suggesting the wide-spectrum of diseases caused by *LMNA* mutation may result

from disruption of lamin A/C binding to a specific set of inner nuclear membrane proteins or disrupting tissue-specific nucleo-cytoplasmic transport.

4. Emerin

The emerin gene (*EMD*) consists of six exons and five introns and is located on the X-chromosome. *EMD* encodes a 254 amino acid protein with a 220 amino acid N-terminal nucleoplasmic domain, a 23 amino acid C-terminal transmembrane domain and an 11 residue luminal domain. Newly synthesized emerin is inserted into the endoplasmic reticulum (ER) post-translationally [60,61] and then diffuses through the ER into the contiguous membranes of the nuclear envelope. Emerin's small size (29 kD) allows it to diffuse freely through the NPC while membrane-anchored [61,62]. Once inside the nucleus, emerin binds A-type lamins. Emerin binding to lamins is required for proper localization to the nuclear envelope, as cells lacking A-type lamins show increased emerin mobility throughout the nuclear envelope and ER [61–64].

Emerin is ubiquitously expressed [30,65,66] and has been implicated in the regulation of gene expression, cell signaling, and nuclear and genomic architecture [38,67,68]. Emerin, along with *Lap2 β* , *emerin* and *MAN1*, is a founding member of the LEM-domain proteins, named for the LEM-domain, which binds to barrier to autointegration factor (BAF) [69,70]. The LEM-domain comprises approximately 40 amino acids (residues ~4 to 44) at emerin's N-terminus and adopts a helix-loop-helix fold that is conserved from prokaryotes to eukaryotes [71] and has evolved *via* surface residue modification to bind BAF [71,72]. The LEM-domain is essential for BAF binding, as alanine substitutions at residues 11, 24, 30 or 34 within the LEM-domain significantly reduce emerin binding to BAF [73]. With the exception of a second DNA-binding LEM-like domain in *Lap2* proteins [71], BAF binding is the only known function of the LEM-domain. LEM-domain proteins are conserved throughout the metazoan lineage [74,75] with LEM-domain proteins implicated in tethering chromatin to the nuclear envelope.

Outside of the LEM-domain [76] and the transmembrane domain (residues 223–246), emerin has no known secondary structure. However, two studies using emerin protein fragments have functionally demarcated several regions of emerin [61,77]. Residues 3–219 mediate the localization of the transmembrane domain of an unrelated protein to the nuclear envelope [61]. Deletion of residues 107–175 cause cytosolic aggregation of emerin [77], suggesting they are required for emerin's nuclear envelope localization. Emerin enrichment at the nuclear envelope was unaffected by deletion of residues 1–106, 2–64 or 175–222 [77]. Nuclear envelope localization of emerin was slightly improved by deletion of residues 67–108 [77]. Residues 107–254 were sufficient for nuclear envelope accumulation [77]. This suggested residues 109–175 were required for nuclear envelope enrichment. However, it did not separate the regions required for localization to the nuclear envelope from those residues required for transport into the nucleus, a prerequisite for nuclear envelope localization. Fragments containing residues 110–147 are sufficient for nuclear import, despite the absence of a canonical nuclear localization sequence [61]. Collectively, these studies showed that residues 110–147 mediate nuclear transport of emerin, while residues 109–175,

which include the lamin A-binding domain, mediate emerlin nuclear envelope localization. Important regions of the emerlin protein are highlighted in Fig. 1.

5. Emerlin function

5.1. Regulation of transcription factor activity

Emerlin binds to a number of transcription regulators, including GCL [78], Btf [79], Lmo7 [80], β -catenin [81], SIKE [82] and BAF [73] and regulates the expression of their target genes. Emerlin also binds the splicing factor YT521-B [83]. Further supporting roles in emerlin regulating gene expression, emerlin was shown to regulate the expression of many muscle and cardiac genes [33,34,38]. Each emerlin-binding transcription factor and how emerlin is thought to regulate their function is discussed below.

5.1.1. Germ cell-less (GCL)—GCL is a transcription repressor that binds the DP3 subunit of the E2F-DP3 heterodimer, thereby inactivating it [84]. GCL binds directly to emerlin *via* regulator binding domain (RBD) 1 and RBD-2 in emerlin [78]. Downregulation of emerlin by RNAi causes mislocalization of GCL from the nuclear envelope to the cytoplasm and increases E2F-mediated gene expression [78]. These results showed that emerlin binding to GCL represses E2F- and DP3-dependent transcription [67]. E2F-DP3-dependent genes are required for entry into S-phase and are repressed by Rb, thereby implicating emerlin in control of cell proliferation. Supporting this hypothesis, increased proliferation was seen in emerlin-null cells [81]. GCL also interacts with the germline specific protein GAGE, which is also highly upregulated in several cancers [85], and GCL and GAGE are co-expressed in both testis and cancer cells [86]. Exogenous GCL recruits endogenous and exogenous GAGE proteins to the nuclear envelope in HeLa cells and three human cancer cell lines [86]. This suggests emerlin or other LEM-domain proteins may influence cancer *via* GCL-binding, however how or to what degree LEM-domain proteins regulate cancer-related pathways remains unknown.

5.1.2. Btf (Bclaf1)—Btf binds directly to emerlin *via* RBD-1 and RBD-2 [78,79]. After apoptotic induction, Btf is released from anti-apoptotic Bcl proteins (Bcl-2 and Bcl-xL) in the cytoplasm [87] and accumulates at the nuclear envelope [79,88]. Btf also localizes to sites of DNA damage marked by histone H2AX [89] where it forms a complex with protein kinase C δ to activate p53 [90]. Btf may also regulate transcription as an mRNA splicing factor [79,91,92] and *via* association with ribonucleoprotein complexes [93]. Btf plays crucial roles in development, as Btf-null mice have polydactyly, immunological problems and premature death due to incomplete lung development [94]. Given Btf's proposed role in splicing and evidence that emerlin binds to the splicing regulator YT521-B [83], emerlin is also predicted to regulate mRNA splice site choice.

5.1.3. Lmo7—Lim-domain-only 7 (Lmo7) is an emerlin-binding transcription factor that shuttles between the cell surface and nucleus [80]. Nuclear localization of Lmo7 requires emerlin, as emerlin downregulation inhibited Lmo7 nuclear localization [80,95]. Emerlin binding to Lmo7 inhibits Lmo7 transcriptional activation of its target genes, including emerlin, suggesting emerlin binding to Lmo7 acts in a negative feedback loop to regulate emerlin expression [80].

Lmo7 is highly expressed in heart and skeletal muscle, suggesting its interaction with emerin may be relevant to the EDMD disease mechanism [96,97]. Lmo7 binds and activates the promoters of critical myogenic differentiation genes, including *Pax3*, *MyoD* and *Myf5* [98]. Expression of these genes is downregulated after myotube formation, which coincides with increased emerin expression. Emerin inhibits Lmo7 activation of *Pax3*, *MyoD* and *Myf5* by binding to Lmo7 and inhibiting Lmo7 binding to the *Pax3*, *MyoD* and *Myf5* promoters [98]. Increased emerin expression coincides with increased Lmo7 localization to the nuclear envelope and cytoplasm, suggesting emerin may inhibit Lmo7 binding to these promoters by stimulating Lmo7 egress from the nucleus [98]. After myogenic differentiation, Lmo7 is primarily localized to the cytoplasm, where it has been shown to interact with focal adhesion proteins. Lmo7 association with focal adhesions is regulated by p130Cas [99]. Thus in addition to regulating important myogenic differentiation genes early during differentiation and skeletal muscle regeneration, Lmo7 is predicted to play important roles in mature muscle and tendons, as well as during muscle cell adaptation to mechanical stress.

Recently the skeletal muscle and cardiac phenotypes were analyzed in a newly generated Lmo7-null mouse to test if Lmo7-null mice recapitulated phenotypes associated with EDMD and to determine if Lmo7 was important for skeletal muscle structure and function. Lmo7-null mice exhibited growth retardation, had smaller skeletal muscle fibers, had larger skeletal muscle nuclei, failed a number of neuromuscular tests and had decreased cardiac function (Mull and Holaska, unpublished results). Lmo7-null mice also had lower levels of phosphorylated Rb, ERK and JNK, consistent with altered Rb and MAPK signaling. These phenotypes are similar to other mouse models of EDMD, suggesting the interaction of Lmo7 with emerin is important for the EDMD disease mechanism.

5.1.4. β -catenin—Emerin directly binds to the Wnt signaling transcription factor β -catenin through its adenomatous polyposis coli (APC)-like domain [81]. Emerin inhibits β -catenin activity by preventing its accumulation in the nucleus. Emerin-null cells show increased expression and nuclear accumulation of activated β -catenin [81,100], leading to upregulation of β -catenin target genes and increased cell proliferation [81]. Increased β -catenin protein levels were linked with reduced protein degradation in emerin-null fibroblasts undergoing adipogenic conversion [100]. Interestingly, siRNA-mediated knockdown of β -catenin also led to decreased mRNA expression and nuclear accumulation of emerin [100], suggesting emerin and β -catenin regulate one another's expression, localization and activity. Wnt signaling is essential for myogenic progenitor cell maintenance [101] and differentiation [102], suggesting the interaction between emerin and β -catenin is important for regulating myogenic differentiation and skeletal muscle regeneration.

5.1.5. Barrier-to-autointegration factor (BAF/Banf1)—BAF is a highly conserved 89 amino acid protein essential for post-mitotic nuclear assembly [69], cell viability [70] and cell cycle progression [103,104]. BAF plays a critical role during mitosis to orchestrate reformation of the nuclear envelope. In anaphase, BAF is targeted to chromosomes at “core” regions near the spindle attachment sites of telophase chromosomes. Upon its recruitment, BAF recruits lamin A and emerin to these core regions during nuclear envelope reassembly

[105–107]. Although BAF is ubiquitously expressed, BAF appears to have tissue-specific roles, since *Caenorhabditis elegans* lacking BAF affect tissue-specific functions, including gonadal cell migration, vulva formation, muscle maintenance and germ-line survival and maturation [69]. Thus it will be important to determine how BAF deletion causes tissue-specific defects.

BAF is a core element of the nuclear lamina, directly binding all LEM-domain proteins. BAF also binds directly to histones H3 and H4 and selected linker histones, such as H1.1 [108], where BAF functions to condense DNA *via* looping [109]. BAF interacts with the homeobox transcription factor CRX and represses its activity [110], suggesting BAF also directly regulates transcriptional activity and gene expression. BAF overexpression has diverse influences on post-translational histone modifications and significantly influences the levels of both silencing and active histone marks [111]. Thus the regulation of gene expression by BAF may result from its regulation of chromatin architecture. It will be interesting to determine how BAF may regulate chromatin architecture at defined genomic loci in a tissue-specific manner.

BAF is present in two different emerlin-containing complexes, one of which forms a regulatory complex containing histone deacetylases 1 and 3 [82], suggesting emerlin and BAF may interact to repress chromatin at the nuclear envelope. BAF forms higher-order complexes with Lap2(3 and DNA [112], suggesting that Lap2 β binding to BAF-DNA complexes may also recruit chromatin to the nuclear envelope. Mutations in BAF that are proposed to decrease protein stability and that lead to decreased BAF protein expression cause Nestor-Guillermo progeria syndrome (NGPS) [113,114], which results in mislocalization of emerlin to the cytoplasm [113]. Emerlin binding to BAF is required for proper nuclear reassembly after mitosis [107], suggesting emerlin mislocalization or absence may contribute to the NGPS phenotype.

Emerlin and BAF may also be important for regulating DNA repair. Evidence of emerlin and BAF association with DNA repair proteins (Cul4a and DDB2) subsequent to UV light exposure suggests emerlin may also be important for the DNA damage response [108]. In *C. elegans*, BAF, along with LEM-domain proteins, serves an essential function in chromatin attachment to the inner nuclear membrane, and emerlin-null *C. elegans* are hypersensitive to DNA damage [115]. Additionally, mutant lamin A or emerlin-deficient HeLa cells show reduced levels of phosphorylated histone H2AX in response to treatment with DNA crosslinking agent [116,117], suggesting proper emerlin function may be required for genomic stability.

5.2. Signaling

Emerlin-null mice have a relatively mild phenotype, with delayed muscle regeneration, motor coordination defects and mild atrioventricular conduction defects [34,118]. The absence of emerlin in mice and humans leads to the misexpression of a number of skeletal muscle and cardiac genes that are regulated by MyoD and Rb [33,34,119]. A large number of canonical myogenic signaling genes, including members of the Wnt, TGF β , Notch and IGF pathways, are misexpressed in emerlin-null mouse myogenic progenitors [38]. Loss of emerlin also disrupts gene expression in the JNK, MAPK, NF- κ B and integrin signaling

pathways in humans and mice [119–121]. Despite an increasingly clear role in the regulation of cell signaling, many open questions remain as to how disruption of these key signaling pathways caused by loss of, or mutations in, emerin contributes to the EDMD phenotype. Promisingly, treatment with an ERK inhibitor prevented dilated cardiomyopathy in an EDMD2 mouse model [122]. Further investigations into the mechanisms by which disrupting specific signaling pathways cause muscle regeneration and cardiac conduction defects and whether pharmacologic and non-pharmacologic agents can rescue these defects are essential for developing EDMD treatments.

5.3. Nuclear structure

There is evidence emerin plays important roles in maintaining nuclear architecture. These include biophysical studies showing that emerin-null cells have decreased elasticity [123] and that the nuclear membrane is more malleable in emerin-null cells [123,124]. At the cellular level, X-EDMD patients have severe nuclear shape abnormalities in approximately 25% of their skeletal muscle, smooth muscle and fibroblast nuclei [21,23]. Cultured lamin A/C- or emerin-null MEFs also show nuclear morphology defects, including increased nuclear deformability, impaired viability under mechanical strain and defective mechanotransduction [124,125]. It is predicted these structural defects contribute to the decreased nuclear elasticity and increased fragility seen in EDMD patient cells [123].

The mechanosensitive transcription factor megakaryoblastic leukemia 1 (MKL1), which is involved in cardiac function and development [126], requires emerin for its nuclear accumulation and activity [127] in response to mechanically induced increases in actin polymerization [128,129]. The roles of these and other proteins in the regulation and function of the nucleoskeleton remain largely unknown [49]. However, it is known that emerin binds to a number of structural proteins that are predicted to be key regulators of nuclear architecture. These are discussed below.

5.3.1. The LINC complex, nesprins and SUN-domain proteins—The linker of nucleoskeleton and cytoskeleton (LINC) complex physically connects the cytoskeleton to the nucleus and transmits mechanical forces from the cytoskeleton across the nuclear envelope to the nucleoskeleton [130,131]. The LINC complex is implicated in diverse cellular processes, including cell division [132], cytoskeletal organization [133] and organelle positioning [134], showing its importance for basic cellular functions. The outer nuclear membrane components of the LINC complex are the nesprins, a large family of spectrin-repeat transmembrane proteins [133,135] that bind the cytoskeleton by binding to actin or microtubules [133,136]. Nesprins interact with C-terminus of inner nuclear membrane SUN-domain proteins in the lumen of the nuclear envelope [137,138]. SUN-domain proteins are essential for the recruitment of nesprins to the outer nuclear membrane [139,140]. The interaction between SUN-domain proteins and nesprins maintains the size of the lumen [49,141] and aids in the positioning of the nucleus in mature myofibers [7].

Application of force to the plasma membrane or cytoskeleton deforms the nucleus and activates mechanosensitive genes [142,143]. LINC complex proteins and lamin A/C directly transmit mechanical force from the plasma membrane and cytoplasm to the nucleus

[125,130]. Emerin and lamin A directly bind nesprins and SUN-domain proteins [141,144,145]. Emerin-null or lamin A/C-null cells have defects in mechanotransduction and show increased nuclear fragility [123,125]. Emerin is also required for the activation of the downstream mechanosensitive genes *IEX-1* and *EGR-1* [124]. Additionally, mutations in the cytoskeletal linker protein desmin have been shown to increase AD-EDMD severity [146]. Collectively, this suggests disruption of the LINC complex and failure to properly transmit force from the plasma membrane and cytoplasm to the nucleus contributes to the EDMD disease phenotype [7,49,147].

5.3.2. Actin—N-WASP and ARP2/3, which stabilize polymeric actin, were shown to localize to the nucleus [148,149]. Additionally, the actin-nucleating factors mDia and JMY are also found in the nucleus [150,151]. F-actin was shown to be present in developing *Xenopus* oocyte nuclei [152,153] and the polymerization of nuclear actin is necessary for transcriptional reprogramming of *OCT4* in somatic cells by *Xenopus* oocytes [154]. Collectively, these results suggest nuclear actin is capable of forming F-actin polymers in eukaryotic nuclei, and that nuclear F-actin is important for gene expression and nuclear function.

Nuclear actin has numerous functions, including regulating chromatin architecture, cellular stress responses, transcription and nuclear export [155,156]. It also has predicted roles in regulating nuclear architecture through interactions with nuclear pore-linked filaments (PLFs) [157]. Emerin binds actin and caps the pointed end of actin filaments to stabilize F-actin *in vitro* [158]. Emerin also binds nuclear myosin Ic and the nuclear-specific spectrin isoform α II [82]. Emerin co-purifies *in vivo* with nuclear protein 4.1R, which binds both spectrin and actin [159]. 4.1R is also required for mitotic spindle formation and nuclear assembly [160,161] and emerin and 4.1R localization is mutually dependent, as the loss of either protein leads to a loss of inner nuclear membrane retention of the other protein; this mislocalization leads to increased nuclear accumulation of β -catenin [81,162]. Thus emerin is predicted to play a role in anchoring cortical nuclear actin-myosin networks near the nuclear envelope, which is also predicted to provide structural rigidity to the nuclear envelope.

5.4. Chromatin architecture

Emerin-null cells have less repressed chromatin [163–165] and fibroblasts [163] and skeletal muscle [23] from EDMD patients has altered genomic organization. Emerin-null myogenic progenitors contain chromatin modifications indicative of relaxed chromatin architecture [166]. These data are consistent with emerin regulating chromatin repression, but the molecular mechanisms remain unclear. Nuclear lamina components mediate the establishment or maintenance of repressive chromatin at the nuclear envelope [35,167–173]. Positioning of active genes to the nuclear periphery results in their repression [168,172]. Association of genomic loci with the nuclear periphery requires nuclear envelope disassembly and reassembly [168,174]; dissociation of genomic loci from the nuclear periphery is independent of nuclear envelope disassembly and reassembly. BAF and the nuclear lamina were shown to localize to specific regions of chromatin at the end of mitosis

during nuclear envelope reformation [107], suggesting their recruitment to chromatin may serve to recruit repressed loci to the nuclear envelope during nuclear envelope reassembly.

Global mapping of chromatin interactions with B-type lamins or emerin showed approximately 40% of the drosophila and human genomes contact the nuclear envelope in large (0.1–10 Mb; median size 553 kb in humans; [169], largest 180 kb in drosophila; [170]) discrete regions named lamin-associated domains (LADs) [169,170]. LADs consist of largely heterochromatic regions [169,170] and are characterized by low gene density, repetitive DNA and repressive chromatin marks [175,176]. Chromosome territories in primary human fibroblasts are altered in response to serum withdrawal [177] and LAD organization also changes during cellular differentiation [176]. Specifically, LADs were monitored during murine embryonic stem cell (ESC) differentiation into neural precursor cells (NPCs) and astrocytes (ACs). LADs had broadly overlapping genomic coverage (73–87% similar) in different cell types [176]. Interestingly, genomic regions containing genes that are activated during differentiation (*e.g.* brain development) lost association with the nuclear lamina during differentiation, while others that are repressed during differentiation (*e.g.* cell cycle) were recruited to the nuclear lamina [176]. The changes in association with the nuclear lamina were correlated with changes in the expression of genes within these loci during development [176], suggesting changes in association of these loci with the nuclear lamina are important for cellular identity.

Interestingly, there is evidence for two classes of LADs, constitutive LADs (cLADs), which are always associated with the lamina, and facultative LADs (fLADs), which vary by cell type [178]. Interestingly, cLADs are high in A/T content, but only ESC fLADs have high A/T content [178], suggesting some of the interactions between the genome and the nuclear envelope is sequence-dependent. Ectopic insertion of sequences from the lamina-associated *IgH* and *Cyp3a25* loci was sufficient to reposition nucleoplasmic chromatin to the nuclear envelope after mitosis [174]. These lamina-associated sequences (LASs) repressed transcription of a co-integrated reporter gene, suggesting that LASs are sufficient to repress a subset of lamin-associated genes [174]. LASs co-localized with lamin B during nuclear envelope reassembly, suggesting a possible mechanism for targeting repressed loci to the nuclear envelope [174]. Additionally, an extended GAGA motif (at least ten repeats) was shown to be necessary and sufficient to localize genomic loci to the nuclear lamina and silence genes within these loci. This association with the nuclear lamina occurs *via* the binding of cKrox to the extended GAGA sequence, which then associates with Lap2 β [174]. Single cell analyses that track the fate of endogenous LADs across mitosis, however, suggest LAD sequences are not sufficient for the post-mitotic nucleation of the nuclear envelope [179]. Thus, to what extent the repression of chromatin at the nuclear envelope is sequence dependent remains an open question.

How LADs are established or maintained at the nuclear envelope remains a mystery, but more clues are beginning to emerge. It was previously shown that emerin interacts with core components of the Nuclear Co-Repressor (NCoR) complex [82], a repressive chromatin complex containing histone deacetylase 3 (HDAC3). Recently, it was shown that emerin directly interacts with and regulates the activity of HDAC3, which increases its enzymatic activity 2.5-fold *in vitro* [166]. Notably, HDAC3 binding is disrupted in the four “special”

EDMD-causing emerin mutations [166], suggesting the functional interaction between emerin and HDAC3 is important for the EDMD disease mechanism. Interaction between emerin and HDAC3 is essential for proper spatiotemporal regulation of the expression of the essential myogenic genes *Myf5*, *MyoD*, and *Pax7* in differentiating murine myogenic precursor cells [48], implicating the interaction between emerin and NCoR in the formation of repressive chromatin at the nuclear envelope during differentiation. Localization of these genes and their inactivation at the nuclear envelope required both emerin and HDAC3; in emerin-null cells direct activation of HDAC3 catalytic activity rescued both their expression and subnuclear localization [48], suggesting HDAC3 catalytic activity is essential for the formation of repressive chromatin at the nuclear envelope. A global increase in H4K5 acetylation, the preferred target of the NCoR complex, is seen in emerin-deficient cells. Increased H4K5 acetylation is also detected on genes that are aberrantly upregulated in differentiating emerin-null myogenic progenitors [48], suggesting the interaction between emerin and HDAC3 may be important for regulating the coordinated spatiotemporal expression of myogenic gene expression by regulating chromatin dynamics at their promoters. Thus, there are at least two known mechanisms for establishing or maintaining repressive chromatin at the nuclear envelope.

5.5. Summary of emerin functions

Emerin is involved in a diverse array of biological processes. These include the direct and indirect regulation of transcription factor activity and localization; intra- and intercellular signaling; nucleo-cytoskeletal mechanotransduction and nuclear structure; and chromatin condensation, organization, and epigenetic modification. Emerin's functions, including many of the pathways and proteins involved, are summarized in Fig. 2.

6. Post-translational modification and regulation of emerin

Human emerin contains nearly 40 known phosphorylation sites [180–198] (visualized in [116]). Emerin is phosphorylated during interphase and mitosis, but the proteins and pathways that mediate phosphorylation on these sites, and the functional consequences of these modifications, remain poorly understood.

During interphase emerin is phosphorylated at nearly 30 sites [194–196,199]. Known modifiers include the serine/threonine kinases protein kinase A (PKA; [184]), GSK3 β [200], PKC δ [201], and ERK2/MAPK [202]. Emerin is also phosphorylated on multiple tyrosines by Src (Y59, Y74, Y95) [188], Abl (Y167) [188] and Her2 [188,203]. Notably, mutation of Src phosphorylation sites on emerin (simultaneous Y to F substitution at residues 59, 74 and 95) decreases emerin binding to BAF by 70%, showing emerin phosphorylation is critical for BAF binding [188]. The ERK branch of MAP kinase signaling is upregulated in emerin- and lamin-deficient hearts [119,120]. ERK2 directly phosphorylates emerin *in vivo* during lentiviral infection [202] and virally induced hyper-phosphorylation causes altered distribution of emerin at the inner nuclear membrane and mislocalization of emerin to the outer nuclear membrane [201,204]. Emerin dephosphorylation occurs *in vivo* and protein phosphatase 1 activity weakens the interaction of emerin with nuclear actin [205]. Lambda phosphatase, a serine/threonine kinase, however, increased the interaction between emerin

and actin [205], suggesting emerin-actin dynamics are regulated by distinct post-translational modifications in emerin.

During mitosis, nuclear envelope proteins, including emerin and lamins, are hyperphosphorylated prior to nuclear disassembly [60,193]. The phosphatase PTP1B accumulates at the nuclear envelope when sumoylated prior to mitosis, and PTP1B levels are inversely correlated with emerin tyrosine phosphorylation [206]. Cdk1 accumulates in the nucleus prior to mitosis, phosphorylating lamin filaments on S22 and S392, residues flanking the lamin rod domain [207], which is sufficient to depolymerize lamins *in vitro* [208]. These phosphorylation events are essential for cell cycle progression, and mutation in these residues arrests the cell cycle by preventing nuclear envelope breakdown and lamina disassembly [209]. Collectively, this shows proper regulation of phosphorylation at the nuclear envelope is essential for cellular function. Direct regulation of emerin or nuclear lamina components by phosphorylation are predicted to be important for regulating gene expressing and nuclear architecture during development and tissue homeostasis. Thus it is predicted disruption of emerin phosphorylation is important for the EDMD disease mechanism.

Recently, it was shown that emerin is modified by the addition of *O*-linked β -N-acetylglucosamine (*O*-GlcNAc) [210]. *O*-GlcNAcylation acts as a nutrient and stress sensor [211,212] and has roles in the modulation of transcription [213], epigenetic regulation [214] and cell signaling [215]. *O*-GlcNAc is a highly dynamic post-translational modification with extensive crosstalk with phosphorylation and can compete with or enhance phosphorylation of its target proteins, depending on the protein or residue that is *O*-GlcNAcylated [215]. Emerin is *O*-GlcNAc-modified at 8 sites. 5 were identified unambiguously (S53, S54, S87, S171, S173), with at least 3 additional sites present (S57 or S58 and 2 sites from residues 175-203) [210]. Of note is Ser54, which is mutated (S54F) in EDMD [29,32]. Modification of Ser173 by *O*-GlcNAcylation or phosphorylation has opposite effects on BAF binding; S173-*O*-GlcNAc increases emerin binding to BAF, but S173 phosphorylation reduces emerin binding to BAF [210]. Differential post-translational modifications of emerin also affect binding to other emerin-binding partners, since *O*-GlcNAcylated emerin shows increased interactions with lamin B and chromatin (*e.g.* histone H3), while phosphorylated emerin shows increased binding to lamin A [210]. Thus differential post-translational modification of emerin is predicted to establish niches within the lamina that associate with distinct emerin-binding proteins. Additionally, emerin *O*-GlcNAcylation may serve to regulate the interaction between BAF and emerin in response to extracellular nutrient status, since *O*-GlcNAcylation has a role in nutrient sensing [215].

7. Overlapping functions of emerin and LEM-domain proteins

LEM-domain proteins are functionally redundant for a number of essential cellular functions. In *C. elegans* this includes the maintenance of nuclear structure, mitosis, and development [216]. Depletion of either emerin or Lem2 in *C. elegans* has no significantly deleterious effects. However, deletion of both emerin and Lem2 is embryonic lethal [217]. The fission yeast LEM-domain proteins Lem2 and Man1 are co-essential for nuclear

envelope structure and integrity [218]. Lem2 and Man1 were also shown to be functionally redundant in regulating MAPK signaling during myoblast differentiation [36].

Lap2 β is 41% similar to emerin in its transmembrane and LEM-domains [5]. Missense mutations in emerin that disrupt lamin A-binding (located in residues 70-164) cover a region that is highly conserved in Lap2 β [73]. Lap2 β and emerin are also similar along their nucleoplasmic regions [73] and they bind similar proteins. Lap2 β also performs some similar functions to emerin, including tethering and organizing chromatin at the nuclear envelope [168,174], and the regulation of gene repression *via* binding to GCL [219]. Two studies have produced a functional map of emerin regions that are shared with Lap2 β [73] or are unique to emerin [78] (both visualized in [116]). Lap2 β binds B-type lamins [220], BAF [112,221] and the transcriptional regulator GCL [219]. Similar to emerin [48,166], Lap2 β binds HDAC3 [219] and Lap2 β overexpression induces H4 deacetylation [222]. Lap2 β binding to HDAC3 is required for NE envelope localization of LADs containing the GAGA-rich cKrox binding site [174]. Collectively these findings provide evidence for functionally redundant roles for Lap2 β and emerin in the regulation of tissue-specific gene expression at the NE.

The functional overlap between emerin and Lap2 β , as well as other inner nuclear membrane proteins that exhibit tissue-specific expression, may explain the tissue-specificity of EDMD. For example, nuclear envelope localized Lap2 is expressed at low levels in skeletal muscle and the heart [223], but is expressed in all other tissues. In emerin-null mice, nuclear envelope localized Lap2 is dramatically upregulated [33,34], suggesting this compensatory upregulation of Lap2 may explain the mild phenotype of emerin-null mice. It will be interesting to determine if human skeletal muscle and cardiac tissue also show compensatory upregulation of nuclear envelope localized Lap2. Based on the more severe phenotype in humans, we predict this would not be the case.

Recent evidence also suggests LAP1 may be functionally redundant with emerin, which may also potentially explain the tissue specificity of EDMD [224]. LAP1 and emerin interact *in vivo* through their nucleoplasmic domains [224] and emerin is mislocalized to distinct foci in 30% of LAP1 null fibroblasts [224]. Deletion of LAP1 from murine skeletal muscle caused a severe muscular dystrophy phenotype and premature death [224]. Mice lacking both emerin and LAP1 had an even more severe dystrophic phenotype [224]. Notably, LAP1 is expressed approximately twice as highly in mice as humans [224], suggesting high LAP1 levels may also protect against the EDMD phenotype in murine models. Taken together, this data suggests LAP1 and emerin function together in skeletal muscle function.

SUN1 may also be a genetic modifier for EDMD, since deletion of SUN1 in lamin A-null mice, a model of AD-EDMD, rescues their phenotype [225]. It will be necessary to test if LAP1 and SUN1 are true modifiers of X-EDMD and functionally interact with emerin.

8. Open questions, future directions, concluding remarks

In the past two decades since the identification of emerin as the cause of X-EDMD, genetic, cellular and biochemical studies have led to significant insights into the myriad functions of the nuclear envelope, but many questions remain unanswered. Partially due to the difficulty

in analyzing emerin's structure, a more complete picture of the regulation of emerin function by post-translational modification is essential. Particularly important will be to comprehensively study the interplay between emerin's post-translational modification and its regulation of genomic organization, gene expression and cell signaling. How mechanotransduction through the LINC complex *via* emerin impacts gene expression and the mechanism by which emerin reduces nuclear accumulation of emerin-binding transcription factors remain areas that are currently understudied.

The tissue specificity of laminopathies remains poorly understood, but further study into the functional overlap between emerin and other components of the lamina may elucidate pathways essential to uncovering pharmacological and cellular interventions for the cardiac conduction defects and skeletal muscle wasting in EDMD. Current attempts to produce a more accurate EDMD mouse model are essential for this endeavor.

Despite tantalizing clues, the mechanisms responsible for the initiation and maintenance of repressed chromatin at the nuclear envelop still remain largely unknown. Further research into emerin's interaction with the NCoR complex, as well as other repressive chromatin modifying complexes, should begin to elucidate the mechanisms by which genes are positioned at the nuclear envelope to silence their expression. Further systems-level genomic analysis of LADs, especially those that show specific association with distinct inner nuclear membrane proteins (*e.g.* emerin), should uncover DNA sequences or epigenetic signatures that specifically interact with distinct inner nuclear membrane proteins that are predicted to drive their interaction with distinct components of the nuclear lamina. Future investigations into the chromatin modifying complexes that associate with distinct inner nuclear membrane proteins to regulate genomic architecture and repositioning of genomic loci during differentiation will yield significant insight into the impact of nuclear lamina regulation of chromatin architecture on regulation of differentiation and development.

One of the inherent difficulties in finding EDMD treatments is the diverse array of cellular functions emerin influences and the large number of partners it may act through. Each emerin-interacting factor is a candidate for the treatment of EDMD, as well as a clue toward understanding emerin function. To ensure progress continues to be made in understanding the mechanisms underlying EDMD and other laminopathies, it is vitally important that basic cell biology and disease-focused research continue to be performed on emerin and other components of the nuclear lamina.

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Fig. 1.

Important regions of the emerlin protein. LEM, Lap2, emerlin, MAN1 domain; RBD, regulator binding domain; NE, nuclear envelope; APC-L, adenomatous polyposis coli-like domain; TM, transmembrane domain.

Fig. 2. (A) Emerin regulates a number of cellular pathways by acting directly or indirectly with key players in these pathways. (B) Schematic representation of selected emerin protein-protein interactions and their effects on transcription and nucleocytoplasmic transport to regulate gene expression.