Emerin and the Nuclear Lamina in Muscle and Cardiac Disease

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Abstract—The human genome is contained within the nucleus and is separated from the cytoplasm by the nuclear envelope. Mutations in the nuclear envelope proteins emerin and lamin A cause a number of diseases including premature aging syndromes, muscular dystrophy, and cardiomyopathy. Emerin and lamin A are implicated in regulating muscle- and heart-specific gene expression and nuclear architecture. For example, lamin A regulates the expression and localization of gap junction and intercalated disc components. Additionally, emerin and lamin A are also required to maintain nuclear envelope integrity. Demonstrating the importance of maintaining nuclear integrity in heart disease, atrioventricular node cells lacking lamin A exhibit increased nuclear deformation and apoptosis. This review highlights the present understanding of lamin A and emerin function in regulating nuclear architecture, gene expression, and cell signaling and discusses putative mechanisms for how specific mutations in lamin A and emerin cause cardiac- or muscle-specific disease. (Circ Res. 2008;103:16-23.)

Key Words: lamin ■ emerin ■ LINC ■ LEM domain ■ nuclear envelope ■ nesprin ■ SUN ■ Emery–Dreifuss muscular dystrophy

The nuclear envelope is composed of 2 lipid bilayers, the outer nuclear membrane, which is contiguous with the endoplasmic reticulum, and the inner nuclear membrane. Positioned within the inner nuclear membrane are a variety of integral membrane proteins (Figure 1). Among the first integral inner nuclear membrane proteins identified were members of the LEM domain family of nuclear proteins, which are named for the founding members, LAP2, Emerin and MAN1.1 The LEM domain mediates binding to the chromatin-associated protein barrier-to-autointegration factor (BAF), an essential protein with roles in higher-order chromatin structure, nuclear assembly, and gene regulation.2 Thus, binding of LEM proteins to chromatin-bound BAF is proposed to recruit chromatin to the nuclear envelope.3 In addition to the LEM proteins, there are approximately 80 to 100 uncharacterized integral inner nuclear membrane proteins.3,4

There is a nuclear intermediate filament network composed of lamins A, B, and C that forms a nuclear envelope-associated lattice and gives the nuclear envelope its strength.5–7 Lamin A and C are splicing isoforms encoded by LMNA.5–7 Additionally, the lamin network is required for stable localization and retention of inner nuclear membrane proteins.4 B-type lamins are essential proteins that are expressed in all cells throughout development,4,8 whereas lamins A and C are expressed only in differentiated cells.9,10 The differential expression pattern of A- and B-type lamins suggests A-type lamins may be important for inducing or maintaining the differentiated state.

Nuclear Envelopathies
Mutations in the genes encoding emerin and lamin A/C produce diseases with a broad spectrum of overlapping, but distinct phenotypes that are commonly referred to as “nuclear...
envelopathies.” A database detailing these diseases and the mutations mapped to them can be found at http://www.umd.be. To date, 10 diseases are mapped to EMD and LMNA mutations, which are characterized by progressive skeletal muscle weakening, dilated cardiomyopathy, life-threatening irregular heart rhythms, contractures of major tendons, abnormal fat deposition, and premature aging.11

Autosomal dominant Emery–Dreifuss muscular dystrophy (AD-EDMD) and X-linked EMD (X-EDMD) are caused by mutations in LMNA or EMD, respectively, and are characterized by skeletal muscle wasting, cardiac conduction defects, and dilated cardiomyopathy.11 Presentation of skeletal muscle wasting generally begins within the first decade of life, whereas cardiac phenotypes begin to present within the second decade.11 Recently, 4 mutations in 2 other nuclear envelope proteins, nesprin-1 and -2, were found in EDMD patients.12 Nesprins interact with emerin and lamin A, suggesting that other emerin and lamin A binding partners may be involved in the EDMD disease mechanism. In fact, a large number of EDMD cases (>40%) are not associated with mutations in EMD or LMNA13 and, thus, are most likely caused by mutations in emerin- or lamin A–binding proteins. Limb-girdle muscular dystrophy 1B is also caused by mutations in LMNA and EMD and is now recognized as a variant of EMD.11

The primary cause of Hutchinson–Guilford progeria syndrome (HGPS), a premature aging syndrome, is caused by the LMNA mutation C1824T.14 HGPS is characterized by loss of subcutaneous fat, growth retardation, loss of bone density, diminished muscle development, and premature death (≈10 to 15 years of age) by stroke or myocardial infarction.15 The C1824T mutation in LMNA activates a cryptic splice site that results in incomplete processing of lamin A and retention of the farnesyl-group at its C terminus.14 Retention of the farnesyl group results in enhanced nuclear envelope localization of the mutant lamin A protein (LAΔ50) that causes defects in nuclear architecture, DNA damage, and chromatin dynamics.16–18 Interestingly, stem cells expressing LAΔ50 exhibit significant differentiation defects,14,19 suggesting the premature aging phenotype in HGPS may result from stem cell dysfunction.14 Mesenchymal stem cells differentiate to form muscle, tendons, cartilage, skin, and fat, which are the affected tissues in nuclear envelopathies. The mesenchymal stem cell differentiation defect and subsequent tissue deterioration by LAΔ50 expression14 suggests a potential mechanism for how specific mutations in lamin A cause a wide spectrum of phenotypes. Similar mechanisms may also be responsible for increased tissue deterioration (eg, heart and vasculature) that occurs in healthy individuals, because there is an age-dependent increase in LAΔ50 expression in healthy adults.16,20

Mutations in lamin A also cause a number of diseases that lack significant cardiac involvement. Charcot–Marie–Tooth syndrome type 2B (CMT2B1) is a peripheral neuropathy, which is caused by an autosomal recessive mutation in LMNA.21 CMT2B1 patients exhibit motor defects, loss of large nerve fibers, distal amyotrophy, and loss of deep-tendon reflexes.21 Dunnigan-type familial partial lipodystrophy (FPLD) and mandibuloacral dysplasia (MAD) are also caused by LMNA mutations and exhibit fat redistribution from the limbs and trunk to the neck, face, and abdominal region.22–24 MAD is further characterized by skeletal malformations including craniofacial abnormalities and digital osteolytic legions.24

Mouse models have been generated that exhibit some aspects of the nuclear envelopathy phenotypes. For example, mice lacking lamin A/C exhibit dystrophic and cardiomyopathic phenotypes, resulting in death by 6 to 7 weeks of age.25 One-year-old lamin A/C heterozygous mice exhibit increased nuclear deformation and apoptosis in atrioventricular (AV) node cells and reduced sarcomeric contractility and develop AV conduction defects similar to those seen in a subset of patients with LMNA mutations.26 However, lamin A/C heterozygous mice fail to completely mimic AD-EDMD, because they have normal skeletal muscle and heart function until after 1 year of age, which is roughly equivalent to a 34-year-old human. Mice containing the AD-EDMD causing lamin A mutation H222P exhibit decreased locomotion, cardiac fibrosis, dilated cardiomyopathy, and cardiac conduction defects, which result in death by 9 months of age.27 Thus, these mice represent a good model for studying heart and skeletal pathology during EDMD disease progression.

An emerin-null mouse also has been generated and exhibits no overt dystrophic or cardiomyopathic phenotypes28,29 but exhibits minor motor coordination problems and slight AV conduction elongation after 40 weeks of age.28 Emerin-null mice also exhibit delayed muscle regeneration after myotrauma.29 Thus, these mice exhibit subtle phenotypes consistent with X-EDMD. There are several reasons why these mice fail to exhibit a more severe phenotype. First, these mice compensate for the loss of emerin by upregulating downstream muscle regeneration genes to overcome the delayed

**Figure 1.** The nuclear envelope. Shown here is an illustration of the nuclear envelope showing many of the known binding partners for the LEM domain proteins LAP2β, emerin, and MAN1. The LEM domain proteins interact with many nuclear proteins and complexes with a variety of functions, including transcription regulation (eg, GCL) and chromatin remodeling (eg, HDAC3). The LEM domain proteins share a number of binding partners, including lamins, GCL, Btf, and BAF. OM indicates outer nuclear membrane; IM, inner nuclear membrane.
activation of the muscle regeneration transcription program. Furthermore, these mice lead a sedentary lifestyle and are not subjected to the physical and environmental stress consistent with human activity.

A mouse model of dilated cardiomyopathy with conduction system defects was generated by mutating residue 195 of lamin A/C from an asparagine to a lysine. As expected, the mice die by 3 months of age as a result of cardiac arrhythmia and fail to exhibit dystrophic phenotypes. The expression and localization of connexins 40 and 43 are significantly disrupted in these mice. The mice also exhibit disrupted intercalated disc and sarcomeric organization. The regulation of connexin expression and intercalated disc organization by lamin A or C provides a potential molecular mechanism for how specific mutations in lamin A result in heart-specific phenotypes.

**Nuclear Architecture and Mechanotransduction**

Emerin and lamin A are expressed in all differentiated cell types, yet these diseases specifically affect only a subset of tissues. Thus, it was proposed that emerin and lamin A have roles in tissue-specific gene expression, cell signaling, or nuclear structure. Structural models are consistent with nuclear defects seen in cells lacking emerin or lamin A, and further supported by evidence that emerin is a pointed-end F-actin capping protein that interacts with actin-containing structural complexes in HeLa cells (Figure 2).

Illustrating the importance of maintaining proper nuclear envelope architecture for cardiac function, the AV node is nuclear myosin I (NMI), which is an alternatively translated isoform of myosin-1C that contains 16 extra residues at the N terminus. Emerin forms complexes with NMI, αII-spectrin, and actin in HeLa nuclei, suggesting emerin provides structural functions at the inner nuclear membrane by linking actin—NMI—spectrin complexes to the nuclear lamina (Figure 2). The structural functions of emerin are predicted to be analogous to the plasma membrane-associated actin cortical network, which consists of integral membrane proteins, anchoring proteins, spectrin filaments, actin, and junctional complexes.

NMI is also involved in other aspects of nuclear architecture and function. For example, NMI binds directly to the large subunit of RNA polymerase II and is required for transcription in vitro. NMI and actin are also implicated in regulating the movement of transcription machinery or chromatin during transcription. Given the roles of NMI in nuclear architecture and gene expression, the interaction of emerin with NMI is predicted to have multiple consequences. First, emerin and NMI, together, may directly influence nuclear architecture or transcription activity or both. Alternatively, because NMI is a barbed-end-directed motor, emerin may load NMI onto the pointed end of actin filaments and promote the movement of myosin and unknown cargo, such as chromatin or transcription machinery, into the nucleoplasm. Supporting this model, activation of a reporter gene locus moves from the nuclear envelope to the nuclear interior in an actin- and NMI-dependent manner.

The LINC (links nucleoskeleton and cytoskeleton) complex is composed of nesprin proteins at the outer nuclear membrane and SUN domain proteins at the inner nuclear membrane. Nesprins interact with actin filaments, intermediate filaments, or microtubules in the cytoplasm and SUN domain proteins at the nuclear envelope. The SUN domain proteins bind directly to lamins and interact, either directly or indirectly, with inner nuclear membrane proteins. Components of the LINC complex were initially described in Caenorhabditis elegans and are composed of ANC-1, a nesprin-1 homolog, and UNC-84, a founding member of the SUN domain proteins. Similar to its mammalian counterparts, ANC-1 localization is dependent on the SUN domain of UNC-84. UNC-83, another nesprin-related protein, also binds directly to the SUN domain of UNC-84, which is required for proper outer nuclear membrane localization of UNC-83.

The nesprin family is composed of nesprin-1, -2, and -3. The full-length isoforms are predicted to encode proteins of 1014, 796, and 110 kDa, respectively, but the existence of the full-length nesprin-1 isoform has not been documented. Additionally, multiple nesprin isoforms have been documented, including nesprin-1α, nesprin-1β, nesprin-1γ, nesprin-2α, nesprin-2β, nesprin-2γ, nesprin-3α, and nesprin-3β. The largest nesprin-1 and -2 isoforms contain...
N-terminal actin-binding domains, C-terminal KASH and transmembrane domains, and spectrin repeat domains, which are predicted to form helical conformations that extend up to 500 nm from the nuclear envelope. The KASH and transmembrane domains of nesprin-1 and -2 mediate their localization to the nuclear envelope, whereas the N-terminal actin-binding domain mediates their attachment to the actin cytoskeleton. Nesprin-1 and -2 are stabilized at the nuclear envelope by interaction of their KASH domains with SUN domain proteins at the inner nuclear membrane.

The nesprin-1α isoform, which is preferentially expressed in skeletal muscle and heart, contains the KASH and transmembrane domains but lacks the actin-binding domain. Nesprin-1α localizes to the inner nuclear membrane, forms antiparallel homodimers, and binds directly to emerin and lamin A, suggesting that the N terminus of nesprin-1α is nucleoplasmic (Figure 2). Nesprin-1α is highly expressed in neuromuscular junction nuclei and is upregulated during myotube differentiation. Interestingly, expression of a dominant negative form of nesprin-1, which encodes the C-terminal 344 residues including the KASH domain, significantly mislocalizes neuromuscular junction nuclei. Thus, the localization of neuromuscular junction nuclei is dependent on the interaction of nesprin-1 with SUN domain proteins. Furthermore, mice lacking nesprin-1 have defective neuromuscular junction nuclear positioning. However, it is unclear whether the nesprin-1 KASH domain deletion in these mice results in a bona fide nesprin-1-null mouse or whether the nesprin-1α KASH protein is made and acts dominant negatively.

The SUN domain is a conserved domain initially discovered in C elegans UNC-84 because it shared significant homology with the Schizosaccharomyces pombe protein Sad1. There are 4 mammalian SUN domain genes, which encode SUN1, SUN2, SUN3, and SPAG4. SUN1 and SUN2 contain 3 putative transmembrane domains and a hydrophobic domain of unknown function. SUN1 and SUN2 localize to the inner nuclear membrane with the C-terminal SUN domain in the periplasmic space between the inner and outer nuclear membranes. The N terminus of SUN1 and SUN2 interacts with A-type lamins and the coiled-coiled domains are predicted to form homo- and heterodimers of SUN1 and SUN2. The inner nuclear membrane localization of SUN2 is disrupted in lamin A/C-null fibroblasts, but SUN1 localization is normal. Instead, SUN1 localization to the nuclear envelope requires nesprin-1 and -2. Thus, lamin A/C and nesprin proteins are required to localize SUN domain proteins and stabilize the LINC complex.

The interaction between the SUN domain and nesprin proteins at the nuclear envelope is predicted to transduce mechanical signals from the plasma membrane to the nucleus and regulate nuclear architecture and emerin- and lamin-dependent gene expression. Support this hypothesis, fibroblasts lacking lamin A/C or emerin exhibit defective mechanotransduction, increased nuclear deformability, and impaired viability when subjected to mechanical strain. On mechanical stimulation, wild-type cells significantly induce the expression of 2 mechanoresponsive genes, egr-1 and iex-1. egr-1 encodes an antiapoptotic cardiomyocyte-protective protein, and egr-1 encodes a transcription factor associated with reduced stress-induced heart damage. Increased apoptosis and attenuation of egr-1 and iex-1 induction occurs in cells lacking lamin A/C or emerin that are submitted to mechanical strain, demonstrating that emerin and A-type lamins perform important roles in mechanotransduction. Thus, defective mechanotransduction may contribute to the pathology of nuclear envelopopathies with cardiac involvement, because iex-1 and egr-1 are important for cardioprotection.

Transcription Factor Scaffolding

GCL

The first transcription regulator shown to bind emerin was germ cell-less (GCL), a transcription repressor conserved from C elegans to humans. GCL is concentrated at the nuclear envelope and binds directly to emerin with high affinity. GCL represses E2F-DP–dependent gene expression by binding directly to the DP3 subunit of E2F-DP heterodimers. Emerin downregulation causes mislocalization of GCL from the nuclear envelope and a concomitant increase in E2F-DP reporter activity, suggesting that GCL binding to emerin recruits E2F-DP heterodimer–chromatin complexes to the nuclear envelope and represses transcription. GCL contacts 2 surfaces on emerin, regulator binding domain (RBD)-1 (residues 34 to 83) and RBD-2 (residues 175 to 217). All transcription regulators identified to date require residues within the RBDs for emerin binding.

Biochemical analysis of emerin complexes shows that emerin can only form complexes with either lamin A and GCL, or lamin A and BAFF, because BAFF competes with GCL for emerin binding. Thus, BAFF is proposed to regulate GCL activity, as well as the activity of other emerin-binding transcription regulators that bind RBD-1 and -2. Posttranslational modifications of 1 or more of these proteins, including emerin, are also predicted to regulate the formation of BAFF–emerin–lamin A or GCL–emerin–lamin A complexes in vivo.

Btf

Another emerin-binding transcription repressor, Btf, was identified in a yeast 2-hybrid screen for emerin-binding proteins. Btf is ubiquitously expressed, with highest expression in skeletal muscle. Btf is sufficient to repress reporter gene activity in vivo and promotes apoptosis when overexpressed in cells. Emerin binds directly to Btf and 2 EDMD-causing mutations in emerin, S54F and Δ95-99, disrupt Btf binding, suggesting that Btf may be relevant to the EDMD disease mechanism. Emerin and Bcl-2 bind to similar regions of Btf, which predicts that emerin-null cells have increased Btf-bound Bcl-2 and exhibit increased apoptosis.

β-Catenin

β-Catenin is an adherens junction component that is activated by the secreted signaling protein Wnt, which binds members of the frizzled family of plasma membrane receptors. Wnt-bound frizzled causes β-catenin phosphorylation and
stabilization and accumulation of active β-catenin in the nucleus. Active β-catenin binds members of the TCF/LEF family of transcription factors in the nucleus and activates transcription.77 Emerin binds directly to β-catenin and attenuates β-catenin activity. Further, emerin-null cells accumulate nuclear β-catenin and have increased β-catenin transcriptional activity,78 suggesting that disruption of the Wnt-signaling pathway may contribute to the muscle- and heart-specific defects seen in EDMD.

Lmo7
Lim domain only 7 (Lmo7) was identified as an emerin-binding protein by affinity chromatography of HeLa nuclear extracts.73 Genomic deletion of LMO7 plus 8 exons of UCHL3 (Lmo7Δ800) causes dystrophic phenotypes in mice,78 suggesting that Lmo7 is an EDMD-relevant emerin-binding protein. Lmo7 actively shuttles between the nucleus, cytoplasm, and cell surface, where it colocalizes with adherens junctions79 and focal adhesions.73 Lmo7 is proposed to be a transcription activator, because Lmo7 activates the expression of emerin and other heart and skeletal muscle genes.73 Thus, the dystrophic muscle phenotype of Lmo7Δ800 mice may be caused, at least in part, by reduced emerin expression and subsequent misregulation of emerin-dependent genes.

Lmo7 regulates a surprisingly large number of genes.73 Forty-six of these genes are muscle or heart genes, suggesting a role for Lmo7 in heart and muscle function. Four (CREBBP, NAP1L1, LAP2, RBL2) of these genes are misregulated in patients and mice lacking emerin.73,80 Emerin binding to Lmo7 inhibits Lmo7 activity,73 supporting a model in which Lmo7 positively regulates EDMD-relevant genes, including emerin, and is feedback-regulated by emerin binding. In this model, if emerin is limiting or occupied by other partners, then Lmo7 will be free to activate gene expression. However, in tissues where emerin is expressed at high levels, including heart and skeletal muscle,81 Lmo7 is predicted to be emerin-bound and Lmo7-mediated gene expression would be attenuated.

Lmo7 is poised to transduce mechanical or chemical signals from the plasma membrane to the nucleus, because it associates with plasma membrane junctional complexes and shuttles between the nucleus and cytoplasm. Thus, it was proposed that Lmo7 may be released from these junctional complexes by mechanical or chemical stimulation, transported into the nucleus, and activate the expression of emerin and other Lmo7-dependent genes.73 This model predicts that Lmo7 may respond to mechanical signals from the adherens junctions of intercalated discs and modulate transcriptional outputs in response to increased cardiomyocyte stress. Similar pathways would presumably be used by skeletal muscle to regulate transcriptional outputs in response to changes in muscle attachment to the extracellular matrix. Thus, loss of emerin is predicted to disrupt mechanical signaling by failing to regulate Lmo7 activity.

Emerin Regulatory Complexes
Emerin forms at least 5 regulatory complexes proposed to function in gene expression, RNA processing, cell signaling, or chromatin dynamics.37 One of the regulatory complexes contains 2 components of the NF-Y complex, which binds the CCAAT box and activates transcription.82,83 The transcription activators SND-1, FUBP, and XAP-5 are also present in this complex,37 supporting the hypothesis that emerin sequesters transcription regulators at the nuclear periphery. Three other putative regulatory complexes, named 24, 25, and 52,37 contain RNA processing proteins, consistent with the proposed role of emerin in regulating splice-site selection.71 In addition to the RNA processing components complex 24 also contains DNA replication components (MCM2, MCM4, MCM6),37 which is consistent with previous data showing that the nuclear envelope regulates DNA replication.84 Complexes 25 and 52 lack the replication components of complex 24 but contain signaling molecules in addition to RNA-processing components.37 The presence of both signaling and RNA-processing components in the same complex suggests that these proteins physically interact at the nuclear envelope.

Emerin also interacts with a chromatin-modifying complex called the nuclear corepressor (NCoR) complex.37 The emerin-containing NCoR complex can be efficiently purified from HeLa cell nuclei, and the core components of the NCoR complex (HDAC3, TBL1, TBLR1, NCoR) efficiently coimmunoprecipitate with emerin.37 Based on these findings, it was proposed that emerin may tether silencing complexes, including the NCoR complex, to the inner nuclear membrane and initiate or maintain repressed chromatin at the nuclear envelope. Other nuclear envelope proteins are also predicted to tether repressed chromatin at the nuclear periphery. For example, heterochromatin protein 1 (HP1), which specifically binds silenced chromatin containing lysine 9-methylated histone 3,85,86 binds the lamin B receptor,87 and LAP2β binds HDAC3 and regulates its activity.88 The interactions of emerin with these regulatory complexes are likely to be important for regulating heart- and muscle-specific signaling, chromatin architecture, and gene expression. Furthermore, misregulation of these tissue-specific functions in cells lacking emerin or lamin A may contribute to the mechanisms underlying nuclear envelopathies.

Regulation of Emerin Function
The interactions of emerin with individual binding partners and complex components are likely to be regulated by posttranslational modification of emerin, because 12 emerin residues are known to be phosphorylated.89-93 Emerin phosphorylation is predicted to regulate its interactions with BAF, Lmo7, GCL, Btf, β-catenin, and architectural and regulatory complexes. Additionally, emerin-binding partners (eg, BAF) are also posttranslationally modified,94 which is predicted to enhance or inhibit emerin binding and influence the composition of emerin complexes, because certain partners (eg, BAF and lamin A or GCL and lamin A) can bind emerin in vitro, whereas others (eg, BAF and GCL) compete with each other for emerin binding.67 Hence, a posttranslational modification of emerin that favors BAF binding would be predicted to disrupt transcription factor binding.

The regulation of emerin function by phosphorylation is predicted to be important for the EDMD disease mechanism. For example, 1 of the phosphorylation sites (Y95) lies within
a deleted region of emerin (Δ95-99) seen in some EDMD patients.59,60 Emerin Δ95-99 protein is stable and localizes properly to the inner nuclear membrane,59 suggesting this deleted region is critical for emerin function. Thus, phosphorylation of Y95 is predicted to regulate the interaction of emerin with partners important for the EDMD phenotype. Emerin residue Y59 is just downstream of another mutation (S54F) seen in a subset of patients with EDMD,61 suggesting that phosphorylation of Y59 may also regulate emerin functions important for the EDMD pathogenesis. For example, phosphorylation of Y59 is predicted to inhibit transcription regulator (GCL, Btf, Lmo7) binding to emerin,67,72,73 and, thus, increase expression of their respective target genes.69,73 Inhibition of transcription regulator binding to emerin by phosphorylation of Y59 may also increase the availability of “free” emerin to bind BAF or architectural components (lamin A, actin), because they are predicted to be unaffected by phosphorylation of Y59. The regulation of emerin binding to its various partners is predicted to be important for regulating tissue-specific emerin functions; however, the molecular mechanisms underlying how tissue-specific defects are caused by disrupting Y59 or Y95 phosphorylation are not yet known.

Concluding Remarks

The use of integrated approaches that combine mouse models of nuclear envelopopathies with cell-based and biochemical assays has been instrumental in beginning to determine the molecular mechanisms underlying how nuclear envelope proteins function in a variety of integral cellular processes, including chromatin dynamics, nuclear architecture, and transcription regulation. The next step is to determine how emerin and lamin A regulate muscle- and heart-specific gene expression and nuclear architecture, which will be integral for understanding the disease mechanisms underlying nuclear envelopopathies. Elucidating the molecular mechanism of site-specific emerin phosphorylation and its effects on emerin complex formation and binding to transcription regulators and architectural proteins will also be necessary for understanding the regulation of tissue-specific emerin functions and its role in EDMD pathogenesis. Studying the mechanism of tissue-specific regulation of gene expression and nuclear architecture by emerin and lamin A will undoubtedly identify novel targets for drug development.

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None.

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Holaska Emerin and Signal Transduction 21
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