The nuclear envelope LEM-domain protein emerin

Emerin, a conserved LEM-domain protein, is among the few nuclear membrane proteins for which extensive basic knowledge—biochemistry, partners, functions, localizations, posttranslational regulation, roles in development and links to human disease—is available. This review summarizes emerin and its emerging roles in nuclear “lamina” structure, chromatin tethering, gene regulation, mitosis, nuclear assembly, development, signaling and mechano-transduction. We also highlight many open questions, exploration of which will be critical to understand how this intriguing nuclear membrane protein and its “family” influence the genome.

Emerin is a Conserved LEM-Domain Protein

The LEM-domain is a ~40-residue helix-loop-helix fold conserved both in eukaryotes and in prokaryotic DNA/RNA-binding proteins. With one exception (Lap2 proteins have a second LEM-domain that binds DNA), eukaryotic LEM-domains have one known function: they directly bind a conserved chromatin protein named barrier-to-autointegration factor (BAF). Atomic structures have been solved for the emerin LEM-domain (residues 1–47) either alone, or in complex with BAF. These proteins and genes have acquired many names; for clarity this review will employ the “generally used” protein names indicated in Table I. LEM-domain proteins are conserved in both multicellular and single-celled members of the Opisthokont lineage of eukaryotes, which includes fungi and multicellular animals (“metazoans”). For example the nematode worm C. elegans genome encodes three proteins orthologous to human emerin, Lem2 and Ank1-1. The evolution of the LEM-domain has been thoughtfully discussed. In metazoans, at least, the LEM-domain appears to have a fundamental role in tethering chromatin to the NE. The fusion yeast S. pombe, which lacks lamins and BAF, encodes two LEM-domain proteins orthologous to Lem2 and Man1. Lem2 and Man1 enriches with Swi6 (orthologous to human heterochromatin protein 1 [Hp1]) near telomeres. Overexpression of the LEM- (“Heh”-) domain of either Man1 or Lem2 causes chromatin to compact near the spindle pole body, consistent with the competitive release of telomeres (not centromeres) from sites of attachment at the NE. The conservation of LEM-domain proteins in yeast, apparently independently of both BAF and lamins, suggests LEM-domain proteins are intrinsically important for genome organization and nuclear structure.

Emerin Contributes to Nuclear “Lamina” Structure and Function in Multicellular Animals

Emerin and several other LEM-domain proteins (e.g., Lap2B, Lem2, Man1) are integral membrane proteins that localize predominantly at the NE inner membrane. These LEM-domain proteins bind directly to lamins (nuclear intermediate filament proteins) and BAF, together forming a major component of NE-associated nucleoskeletal structure known as the nuclear “lamina” (Fig. 1). The structural inter-dependence of this “nucleos” of components was revealed by downregulating either lamin or BAF-1, or both Emr-1 and Lem-2, in C. elegans embryos—if any one component was missing, the other two failed to co-assemble, with severe consequences for mitotic chromosome segregation and postmitotic development, signaling and mechano-transduction.
nuclear assembly.\textsuperscript{30,31} In mammalian cells certain LEM-domain proteins localize intriguingly, and dynamically, during mitosis. Lap2α (which is soluble, not membrane anchored) and BAF co-localize on telomeres during anaphase, and during telophase form localized nuclear assemblies.\textsuperscript{33} These “core” structures on chromatin at specific regions of nuclear envelope assembly near the spindle pole.\textsuperscript{29} These “core” structures transiently recruit and concentrate BAF, emerin and A-type lamin(s), and are distinct from neighboring “non-core” regions enriched in lamin B2, LBR and B-type lamins.\textsuperscript{33,34} “Core” regions are NPC-free, whereas “non-core” regions are NPC-rich.\textsuperscript{29} The mitotic roles of emerin and other LEM-domain proteins in mammals are major open questions. Further exploration is needed both to define these mitotic roles, which may be shared by multiple LEM-domain proteins (Table 1), and to determine their impact on genome activity, since mitosis appears to be crucial for LEM-domain proteins to establish functional (repressive) contact with silent chromatin.\textsuperscript{33}

**Emerin and Other LEM-domain Proteins Organize and Tether Chromatin at the NE**

Functional overlap is a major theme for LEM-domain proteins. In *C. elegans* the two NE-localized LEM-domain proteins, Emr-1 and Lem-2, have overlapping roles in nuclear structure, mitosis and development,\textsuperscript{35} and are co-essential for viability.\textsuperscript{36} The two fission yeast proteins, Lem2 and Man1, localize to the NE inner membrane and are co-essential for nuclear structure.\textsuperscript{37} In mice, emerin and Lem2 have overlapping roles, along with Man1, in the regulation of MAP kinase signaling during myoblast differentiation.\textsuperscript{38} Emerin can also bind the N-terminal domain of Man1 directly,\textsuperscript{39} but whether or how this affects its functions is unknown. Among 16 proteins that bind emerin directly (discussed extensively below) are three “shared” partners (in addition to laminins and BAF) that also bind at least one other LEM-domain protein. These shared partners are Bfc (BCL-associated transcription factor 1 [BCLAF1]),\textsuperscript{40} germ cell-less (GCL)\textsuperscript{41} and the chromatin-silencing enzyme HDAC3 (histone deacetylase 3). HDAC3 directly binds emerin\textsuperscript{42} and Lap2β. HDAC3 and the transcription factor cKrox co-mediate silent chromatin tethering to Lap2β at the NE; as noted above, these tethering complexes are established during mitosis,\textsuperscript{43} when the nucleoskeleton undergoes complex and dynamic reorganization and then reassembles nucleocytoskeleton.\textsuperscript{44} In all, four LEM-domain proteins—emerin,\textsuperscript{45} Lap2β,\textsuperscript{46} Otefin (in *Drosophila*)\textsuperscript{47} and Lem-2 (in *C. elegans*)—along with A- and B-type lamin filaments\textsuperscript{48,49} mediate chromatin organization and tethering at the NE.\textsuperscript{50} These discoveries are providing unique and unexpected insight into genome biology.\textsuperscript{50}

**Discovery of Emerin: Loss of Function Causes Emery-Dreifuss Muscular Dystrophy**

The emerin gene (originally *STX*, renamed *EMD*) was identified in 1994 by genetic mapping\textsuperscript{1} of a linked recessive Emery-Dreifuss muscular dystrophy (X-EDMD; Emery and Dreifuss, 1966).\textsuperscript{52} EMD is characterized by contractures of major tendons, slowly progressive skeletal muscle wasting and weakness, and dilated cardiomyopathy with potentially lethal ventricular conduction system defects that can cause sudden cardiac arrest.\textsuperscript{53} In rare cases, EMD mutations cause limb-girdle muscular dystrophy or severe cardiac conduction defects.\textsuperscript{54,55} Two years after X-EDMD was genetically mapped came a surprise: emerin was revealed as a NE membrane protein.\textsuperscript{56} Indeed the emerin and lamin “protoclasses” have become a rich source of candidate disease genes. For example EMDMD is also caused by mutations in at least five other genes: *LMNA* (A-type lamins; numerous mutations reported),\textsuperscript{57} SYNE-2 (nesprin-2; one reported mutation),\textsuperscript{58} SYNE-1 (nesprin-1; three reported mutations),\textsuperscript{59} TMEM43 (LUMA; two reported mutations)\textsuperscript{60} or FHL2 (four-and-a-half LIM domains 1; seven reported mutations).\textsuperscript{61} Four of these proteins (FHL-1 is untested) interact

| Gene Symbol | Gene AKA | Gene Aliases | Generally used protein name(s) |
|-------------|----------|--------------|-------------------------------|
| LEMD1       | LEMD1    | LEM1, CT-50  | Lemb1, Lem5                   |
| LEMD2       | LEMD2    | NET20, L4H8C21.1 | Lem2                        |
| LEMD3       | LEMD3    | MAN1         | Man1                         |
| LEMD4       | TMPO     | TP, LAP2, CMD1, LEMD3, PRO00868, MGC61508 | Lamina associated polypeptide 2 (Lap2α, β, γ, δ, ε or ζ) |
| LEMD5       | EMR (Emerin) | LEMD5, STA, EMD | Emerin                     |
| LEMD6       | ANKLE1   | LEM3, LEM6, ANKRD41, FLJ39369 | Ankle1 or Lem3               |
| LEMD7       | ANKLE2   | LEMD7, FLJ22280, FLJ26132, RPA06692 | Ankle2                     |

NCBI, National Center for Biotechnology Information; HGNC, Human Gene Nomenclature Database.
Emerin is a 254-residue type-II integral membrane protein with a proposed 23-residue hydrophobic (transmembrane) domain near the C-terminus, and a tiny (11-residue) luminal domain. Consistent with this domain organization, newly synthesized (presumably soluble) emerin polypeptides in the cytoplasm are inserted into the endoplasmic reticulum (ER) membrane post-translationally, possibly mediated by ATP-dependent TRC40/LAMTOR complexes that mediate the “guided entry of tail-anchored” (GET) pathway. Once inserted, emerin diffuses throughout the contiguous membrane systems of the ER/NE, including the “pore membrane” surrounding each NPC, where the outer and inner NE membranes are connected. Extensive FRAP and FRAP studies showed membrane-anchored emerin easily “slides past” the NPC because its cytoplasmically-exposed domain is small (~25 kD).

Proteins with larger exposed domains (> 60 kD) fail to accumulate at the inner membrane. Alternative mechanisms to reach the inner membrane do not appear to apply for emerin, emerin lacks “FG-repeats” and its predicted nuclear localization signal (residues 35–47). It is not required for nuclear import, as discussed below (Fig. 3). Having reached the inner membrane, evidence suggests emerin is retained and accumulated by binding A-type lamins, for which human emerin has high (40 nM) affinity in vitro.66,69 Energetic forces that drive emerin assembly into the nuclear lamina may include (1) direct posttranslational binding of emerin to specific nuclear lamina proteins, (2) nascent emerin binding to high-affinity partners that in turn recruit other proteins and establish a stable complex at the NE, or (3) a hypothetical mechanism that “hides” the hydrophobic domain and thereby allows nascent emerin to associate with a soluble protein with partners outside the nucleus.66,69

Unconventional destinations (e.g., plasma membrane) might be achieved by binding to high-affinity partners (e.g., nesprin-1 isoforms; Fig. 4B) at the NE outer membrane. Unconventional destinations (e.g., plasma membrane) might be achieved, we speculate, either by (1) direct posttranslational insertion of nascent emerin into alternative membrane(s), (2) diffusion onto ER vesicle membranes and trafficking to the plasma membrane, or (3) a hypothetical mechanism that “hides” the hydrophobic domain and thereby allows nascent emerin to associate with a soluble protein with partners outside the nucleus.66,69

Emerin Biogenesis and Nuclear Envelope Localization

Emerin is expressed in essentially all tissues. This suggests the relative mildness of EDMD disease, which mainly affects striated muscle, may be due to the presence of another LEM-domain protein(s) that “backs up” or compensates for emerin loss, as seen for emerin and Lem2 during mouse myoblast differentiation.65 “Backup” function might also be provided by unidentified isoform(s) of Lap2, since the Lap2 gene (TMEM20; Table 1) is upregulated in EDMD patient muscle, and a mutation in LAP2α is genetically linked to cardiomyopathy.65

Emerin localizes predominantly at the NE in skeletal and cardiac muscle.65,69 Similarly, immuno-gold EM labeling and digitonin

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With each other, and with emerin, suggesting EDMD disease is caused by the disruption of NE-anchored "link the nuclear skeleton and cytoskeleton" (LINC) complexes that include these proteins.57,58 (Fig. 2). In contrast to nesprins, SUN-proteins and lamin A, all of which directly transmit mechanical force,66,67 emerin is required to sense force and activate the downstream mechanosensitive genes IEX-1 and EGR-1.66 The mechanisms by which emerin senses and signals mechanical force are unknown.

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Emerin is expressed in essentially all tissues.62 This suggests the relative mildness of EDMD disease, which mainly affects striated muscle, may be due to the presence of another LEM-domain protein(s) that “backs up” or compensates for emerin. "L" indicates the L-domain proteins, BAF, HDAC3 and Man1. Direct binding to lamins has roles in signaling, mechano-transduction, nuclear architecture, chromatin tethering and gene regulation. Also depicted are enzymes and pathways that directly target or regulate emerin. “O” indicates the OGT (O-linked N-acetylglucosamine) transferase, which transfers a single N-acetylglucosamine residue to Ser6 in emerin.

Figure 1. Nuclear "lamina" structure has three fundamental components: lamins, LEM-domain proteins and BAF (barrier-to-autointegration factor). These components bind each other with nanomolar affinity in vitro (see text). In C. elegans, loss of any one component (lamin or BAF, or two LEM-domain proteins [Emr-1 and Lem-2]) disrupts co-assembly of the other two and hence blocks nuclear reassembly after mitosis.
In two studies, cells that expressed truncated or internally-deleted emerin polypeptides were stained by indirect immunofluorescence to assess potential localization in the cytoplasm/ER ("C/ER") or nucleoplasm ("NP"), or enrichment at the NE, as summarized in Figure 3. Emerin residues 3–219 (comprising almost the entire nucleoplasmic domain) concentrate at the NE inner membrane when fused to the transmembrane and lumenal domains of chicken hepatic lectin (CHL), a type II integral membrane protein normally found in the ER, endosomes and plasma membrane (Fig. 3, Emerin-CHL). Emerin residues 107–175 were required to block emerin aggregation in the cytosol (Fig. 3, Δ107–175). NE enrichment was reportedly unaffected by loss of residues 2–64, residues 1–106 or residues 175–222, and was slightly improved by deleting residues 67–108 (Fig. 3). This study also showed the full C-terminal half of emerin (residues 107–254) was sufficient to enrich at the NE (Fig. 3, GFP-Δ1–106).
Emerin residues 3–205 and 3–147 accumulated in the nucleoplasm, whereas residues 3–109 remained in the cytoplasm; this suggested residues 110–147 either possess a non-canonical NLS, or associate with an NLS-bearing partner ("piggyback" import; Fig. 3).66 Residues 117–170 are indeed sufficient for import (Fig. 3),66 but the mechanism and relevance to membrane-anchored emerin are unknown. Piggyback mechanisms are possible, since mutations in this region (residues 117–170) disrupt binding to HDAC3, actin and lamin A (see below), all of which are imported into the nucleus as soluble proteins. In summary, the mechanisms of emerin enrichment at the NE are not yet understood, and are likely to involve a partner(s) other than lamins (e.g., nuclear protein 4.1R, discussed later).
Direct Partners and a Mutagenesis-Based Map of Functional Regions in Emerin

In addition to binding lamin A and BAF (nuclear “lamina” components), human emerin directly binds at least 14 other proteins (Fig. 4). Emerin has no known secondary structure other than its LEM-domain (residues ~4–44) and transmembrane domain (residues 223–246). To identify functional regions, two sets of clustered Ala-substitution mutations were generated in recombinant emerin (“m-series” mutations): one set targeted residues homologous or identical between emerin and LAP2β, postulated to mediate conserved or shared functions (Table 2).13 The second set of mutations targeted residues that differ between emerin and LAP2β, these were predicted to disrupt emerin-specific functions (Table 3).37 Also tested were four human mutations (S54F, Q133H, P183H, deletion of residues 95–99 [Δ95–99]) that were unusual: each is sufficient to cause emerin-null EDMD disease, even though the mutant protein localizes normally and is expressed at normal or near-normal (~60%) levels.18,19 Emerin polypeptides bearing these various mutations have been tested in vitro for binding to as many as eight different partners: BAF, lamin A, GCL, BrF, YTS21-b, Lmo7, HDAC3, F-actin and Man1 (Fig. 5A). This research yielded a functional map based on the locations of mutations that disrupt binding to each partner (Fig. 5B).

Emerin Biochemistry and the Functional Implications of Known Partners

Few NE membrane proteins other than emerin have been studied at the biochemical level. The equilibrium binding affinity of emerin has been measured for eight partners in vitro (Fig. 4B). Human emerin binds with relatively high (4–500 nM) affinity to each of seven partners (nesprin-1, GCL, lamin A, BrF, Lmo7, BAF and F-actin) and with lower affinity to HDAC3 (7.3 μM; Fig. 4B). Competition studies showed BAF and GCL compete with each other for binding to emerin, whereas GCL and lamin A can co-bind emerin.20 Six distinct emerin-containing multi-protein complexes were purified from HeLa cell nuclei, suggesting emerin might scaffold a variety of multi-protein complexes at the NE.21 We are still far from understanding these complexes or their functions. However studies of proteins that bind emerin, particularly lamin A, BAF, HDAC3 and GCL, discussed below, are beginning to illuminate daily “life” (protein-protein interactions) at the nuclear envelope.

Emerin binds structural components of both the NE (e.g., SUN1, SUN2, nesprins)22,23 and the nucleoskeleton (lamins, actin)22,24 (Fig. 4).Emerin also directly binds signaling transcription factors including β-catenin and Lmo2 (Fig. 4).22,25 These various partners suggest emerin might integrate a variety of mechanical and signaling “inputs,” and by unknown mechanisms convert these inputs into situation- or tissue-appropriate changes in gene activity. Indeed genes that are normally activated in response to mechanical force, fail to activate in emerin-deficient cells.26 Selected partners and their functional implications for emerin and “life at the NE” are summarized below.

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Table 2. Summary of mutations in “conserved” emerin residues identical or homologous in Lap2β

| Name | Wildtype | Mutated |
|------|----------|---------|
| m11  | 11EL     | 11AA    |
| M24  | 24GPV    | 24AAA   |
| M10  | 10TR     | 30AA    |
| M34  | 34YDK    | 34AAA   |
| S54F | 54S      | 54F     |
| m70  | 70ADOMY  | 70AAAA  |
| m76  | 76LPPKEDL| 76PAXADA|
| m112 | 112GPRAVDQVT| 112AA5RVAWAAA|
| m141 | 141SS5SEECKDR| 141ASA5ECKX44|
| m164 | 164THYBPV| 164AA5MPA|
| m179 | 179LS    | 179AA   |
| m196 | 196SS    | 196AA   |
| m207 | 207PP    | 207AA   |
| m214 | 214GAGL  | 214AAGA |

*Sufficient to cause Emery-Dreifuss muscular dystrophy.

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Table 3. Summary of mutations in emerin-specific residues not conserved in Lap2β

| Name | Wildtype | Mutated |
|------|----------|---------|
| Δ45-99 | 95Y  | 95YEEEY Deleted |
| Q133H | 133Q | 133H |
| m122 | 122T5 | 122AA |
| m145 | 145EE | 145AA |
| m31 | 151ER | 151AA |
| m65 | 167YDC | 167AAA |
| m73 | 175SSL | 175AA |
| P183H | 183P | 183H or 183T |
| m192 | 1925S5S55S5 | 1925A5AAA |
| m198 | 1985LSL5SR | 1984AAAA |
| m206 | 2064RRPE | 2064APA |

*Sufficient to cause Emery-Dreifuss muscular dystrophy.

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Lamin A

Lamins A and C (lamins A/C) are major alternatively-spliced products of the LMNA gene that polymerize to form A-type nuclear intermediate filaments that concentrate near the inner nuclear membrane and are a major component of the nucleo-skeleton.1 A-type lamins have roles in chromatin tethering, epigenetic regulation, DNA damage repair, mechanotransduction, replication and development.1,2,3 Lamina A has 28 reported direct and indirect partners besides emerin including Lem2,57 Man14 and BAF.37,97 A-type lamins are regulated by phosphorylation, SUMOylation, O-GlcNAcylation and other modifications (see ref. 97). Over 350 missense mutations in the LMNA gene have been linked to over...
Figure 5. Functional map based on emerin missense mutations that disrupt binding to specific partners. (A) Summary of binding results for each named partner, tested for binding to each “m-series” (stuttered Ala substitutions) or EDMD-causing mutations in emerin (mutations specified in Tables 2 and 3). Scoring: normal binding (+), weakened binding (± and gray), and undetectable binding (black box). nt, not tested. (B) Results from (A) mapped schematically to the emerin polypeptide. APC-L, APC-like domain. TM, transmembrane domain. (C) Schematic diagram of known phosphorylation sites in emerin (see Fig. 6). Hexagons, O-GlcNAc sites; circles, phospho-Ser/Thr; squares, phospho-Tyr; white, asynchronous cultures; black, mitotic cultures and conditions. Black with outline, sites identified in both asynchronous and mitotic cells. Double-underlined region has at least two O-GlcNAc sites and potentially other modifications that are uncharacterized due to the large size of the corresponding tryptic peptide and poor recovery by mass spectrometry.
13 human diseases including EDMD, lipodystrophy, atypical Werner syndrome and Hutchinson-Gilford progeria syndrome (HGPS). 89 Emerin missense mutations that disrupt binding to lamin A (Fig. 5A and B) are located centrally in emerin (residues 70–164), and affect residues that are identical or conserved in Lap2β (Table 2).11

**Barrier-to-Autointegration Factor**

The conserved LEM-domain of emerin (and other LEM-domain proteins) confers direct binding to an essential chromatin protein named Barrier-to-Autointegration Factor (BAF). 106,107 BAF is an 89-residue (10 kD) protein that is highly conserved in multicellular eukaryotes. 99 A homozygous missense mutation (A12T) in human LEM-protein, Ankle1, expressed at highest levels in hematopoietic tissue (Table 1).11 A loss of function mutation of the *C. elegans* ortholog, Lem3, which (like Ankle1) is a nuclease, causes deficiencies in chromosome segregation and anaphase bridge progression.118 Interestingly *C. elegans* that lacked either emerin (erm-1 null) or Lem2 (lem-2 null) were also hypersensitive to DNA damage.114 Together these studies show BAF and LEM-domain proteins (including *C. elegans* emerin) have critical role(s) in the DNA damage response and genome integrity. There are hints that human emerin might also influence the DNA damage response, since emerin and BAF co-associate with the DNA repair proteins CUL4A and DDB2 within minutes after cell exposure to UV (UV) light.111 HeLa cells that overexpress laminopathy-causing mutations in GFP-lamin A,112 and HeLa cells downregulated for emerin, both show reduced phosphorylation of H2AX (“γ-H2AX” response) after treatment with inter-strand DNA crosslinking agents such as camptothecin (Berk and Wilson, unpublished results).

**HDAC3**

Emerin associates with all core components of the nuclear co-repressor (NCOR) complex, which represses genes by stably binding chromatin. One NCOR component is HDAC3, which deacetylates specific Lys residues in the histone H4 tail to promote NCOR interaction with chromatin. Emerin also binds HDAC3 directly.79 In the mutation-based functional map of emerin, HDAC3 is sensitive to diverse mutations (Fig. 5A and B), and is the only known partner that is disrupted by all four "special” EDMD-causing mutations.108 Furthermore emerin association increases the enzyme activity (Vmax) of HDAC3 by 2.5-fold in vitro, suggesting emerin enhances HDAC3-dependent gene silencing.115 This finding is consistent with an epigenetic phenotype (globally increased H4K5 acetylation) seen in emerin-downregulated cells and emerin-null mouse fibroblasts.79 Thus HDAC3-emerin association may be fundamentally important for tissue-specific gene repression. The LEM-domain protein Lap2β also binds HDAC3 directly,79 and influences the levels of histone H4 acetylation.110 Notably Lap2β interaction with HDAC3 is required for the NE tethering of Lamina Associated Domains (LADs) of DNA, specifically LADs enriched in cKrox binding sites (GAGA sequence).32 These findings support overlapping roles for emerin and Lap2β in tissue-specific gene silencing and tethering at the NE.

**Btf and GCL**

Less is known about two other "shared” partners, Btf and GCL. Btf (BCLAF1), which binds emerin120 and Man1,121 is a poorly understood, multifunctional protein with roles in DNA damage response,121 apoptosis,118,119,122 transcriptional regulation,118 and development.115 In response to DNA damage, Btf localizes to sites of damage120 and can interact with protein kinase Cδ to form a complex that activates the p53 promoter.115 Most Btf is sequestered in the cytoplasm by anti-apoptotic proteins Bcl-2 and Bcl-xL, but then accumulates at the NE after apoptosis is induced.120,121 Other work suggests Btf is an mRNA splicing factor.109,118-121,123 That associates with ribonucleoprotein complexes.122-123 The phenotypes of Btf-null mice include polydactyly, deficient ex vivo T cell activation, and postnatal death due to improper lung development.123 Emerin also has poorly understood roles in regulating mRNA splice site selection by another partner, named YT521B.124 Why Btf associates with emerin is unknown, but one
forms. However it is uncertain which if any nesprin isoforms which are partly or fully included within most related iso-

ular motor, nuclear myosin Ic, directly in vitro even when myosin misregulated in emerin-deficient muscle.

human fibroblasts. Interestingly GCL also associates with, trol. One study reported increased proliferation in emerin-null

nuclear lamina nucleoskeleton, and help maintain a uniform the core integral membrane components of LINC complexes. Emerin binds directly to SUN-domain proteins and nesprins, and its LEM-domain brethren share other part-

niers is unknown, due to gaps in knowledge about most other LEM-domain proteins.

SUN-Domain Proteins and Nesprins

Emerin binds directly to SUN-domain proteins and nesprins, the core integral membrane components of LINC complexes, LINC complexes transmit mechanical force across the NE to the nuclear lamina nucleoskeleton, and help maintain a uniform distance between the inner and outer membranes of the NE (for a review, see ref 2). Emerin binding to nesprins was studied using relatively short isoforms, nesprin-1α and nesprin-2β, which are partly or fully included within most related iso-

forms. However it is uncertain which if any nesprin isoforms localize at the NE inner membrane. By contrast SUN-domain proteins localize almost exclusively at the NE inner membrane. Emerin binds the nucleoplasmic domains of SUN1 (SUN1 resi-

dues 223–302) and SUN2 (specific residues unmapped). Much more work is needed to understand how LINC complexes contact lamin and emerin.

F-actin and Nuclear Myosin 1c

Emerin directly binds (and caps) the pointed end of actin fila-

ments, stabilizing F-actin in vitro. Emerin also binds the molec-

ular motor, nuclear myosin Ic, directly in vitro even when myosin is “burning” ATP. These results suggest emerin might anchor "cortical" actin-myosin networks near the NE. Emerin also asso-

iates (at least indirectly; direct binding not tested) with the mul-
tifunctional structural protein 4.1R in vitro, which directly binds actin and spectrin to form a ternary complex, and is required for mitotic spindle function and nuclear assembly. The nuclear localizations of emerin and 4.1R are mutually dependent: loss of 4.1R decreases emerin retention at the INM and vice-versa, and loss of either protein increases accumulation of β-catenin in the nucleus. The nuclear skeletal roles of actin, myosin, spectrin and 4.1R are major understudied areas of cell biology.

Emerin is required for the nuclear accumulation and activ-

ity of the mechanosensitive transcription factor, megakaryo-

blastic leukemia 1 (MKL1). MKL1 localizes predominantly in the cytoplasm, but moves into the nucleus in response to mechanically-induced increases in actin polymerization. In the nucleus, MKL1 and serum response factor (SRF) co-

activate genes encoding cytoskeletal proteins. Lmna and Emd mouse embryonic fibroblasts (MEFs) have reduced MKL1 nuclear localization after mechanical stimulation. Ectopic over-

expression of GFP-emerin in Lmna or Emd MEFs rescues MKL1 nuclear localization. Three emerin mutants incapable of binding actin (clustered Ala-substitutions m151 or m164, and "special" EDMD-causing mutation Q135H) failed to rescue MKL1 nuclear accumulation, suggesting emerin associa-

tion with actin is required. However other functions of emerin may also contribute to the nuclear accumulation of MKL1: the emerin m151 and Q135H mutations also disrupt binding to the LINC-domain protein Man1 (see Table 3; Fig. 5A) and have not yet been tested for binding to lamin A, and the m164 mutation also disrupts binding to lamin A (Table 2; Fig. 5A): Whether MKL1 binds emerin directly is unknown.
defects with age.151,152 This unfortunately has limited their use as an EDMD model.

In EMDD patient muscle and emerin-null mice, loss of emerin misregulates certain muscle-specific and heart-relevant genes regulated by Rh and MyoD.153-156 MyoD-dependent genes are crucial for muscle development and repair. Some genes misregulated in EMDD (including CREBRE, SNAP25, and RBL2), and the emerin gene itself, depend for their transcriptional activation on Lmo7.157,158 In regenerating emerin-null mouse muscle and cells, Rb remains inappropriately hyper-phosphorylated, and cells that should arrest during differentiation instead continue proliferating.159 The mechanisms by which Rh–MyoD-regulated pathways depend on emerin are unknown, but might involve loss of emerin-dependent gene tethering at the NE. Rh/MyoD-regulated pathways are also required in muscle stem (“satellite”) cells, which express emerin and have long-term roles in muscle homeostasis, repair and regeneration.160 Loss of emerin in satellite cells is proposed to reduce their capacity to repair and regenerate muscle tissue,161 due in part to increased nuclear fragility162 and reduced mechano-transduction.163

Loss of emerin also affects genes regulated by the JNK, MAPK, NF-κB, integrin, Wnt and TGFβ signaling pathways.164 The nuclear localization and activity of ERK1/2 (a MAPK) increases in emerin-null mouse hearts.165 Thus emerin is proposed to block or attenuate the nuclear accumulation of at least one (Y167).167 The Src-regulated sites are critical for BAF phosphorylation, since the triple Y to F substitution (at Y59, Y74 and Y95) impairs emerin phosphorylation by the virus-encoded kinase US3 and cellular PKCα as a mechanism for the virus to directly bud and exit at the NE.179,183 Emerin is also hyperphosphorylated by the Kaposi sarcoma associated herpesvirus.180 The MAPK pathway kinase ERK2 phosphorylates emerin directly both in vitro, and during nuclear egress of vesicular stomatitis virus G-protein-pseudotyped virus.181 This virus-induced hyper-phosphorylation causes emerin to mislocalize and might represent a viral strategy to hijack the host RNP-egress pathway.179,180

Emerin is phosphorylated at 26 sites (including tyrosines) during mitosis,142,143,176 with up to 83–94% stoichiometry.152,153

Emerin is also phosphorylated during interphase at 30 reported sites (Figs. 5C and 6). Only a few kinases, and one phosphatase, that target emerin have been identified,162,166,167,179 as summarized in Table 4. Emerin is phosphorylated on Ser49 and at least one other residue by PKA.163 Emerin is also targeted by the metabolically important kinase GSK3β at unknown site(s) in vitro.164

A new pathway was reported in postsynaptic neurons, wherein nascent RNPs exit the nucleus directly through the NE; this pathway involves PKC-dependent hyperphosphorylation of lamin A.168 This pathway is proposed to be exploited in cells infected with Herpes simplex virus type 1, where emerin is targeted by the virus-encoded kinase US3 and cellular PKCα as a mechanism for the virus to directly bud and exit at the NE.179,183 Emerin is also hyperphosphorylated by the Kaposi sarcoma associated herpesvirus.180 The MAPK pathway kinase ERK2 phosphorylates emerin directly both in vitro, and during nuclear egress of vesicular stomatitis virus G-protein-pseudotyped human and feline immunodeficiency viruses.182 This virus-induced hyper-phosphorylation causes emerin to mislocalize and might represent a viral strategy to hijack the host RNP-egress pathway.179,180

Emerin is nearly 10-fold Tyr hyper-phosphorylated in NIH3T3 cells that overexpress Her2.182 At least two nonreceptor Tyr kinases target emerin directly. Src specifically phospho-tyrosylate at least three residues (Y99, Y74, Y95) and Abl targets at least one (Y167).183 The Src-regulated sites are critical for BAF binding, since the triple Y to F substitution (at Y99, Y74 and Y95) decreases BAF binding by 70% in vivo.184 All three sites are phosphorylated during interphase (Fig. 6).184 Emerin is also...
ubiquitinylated at K88,18,19,20 but the specific context and conse-
quENCES of this modification, like phosphorylation, are unknown. These diverse modifications, especially Tyr-phosphorylation and O-GlcNAcylation (discussed below), suggest emerin is regu-
lated by tissue-specific signaling, potentially as a mechanism for "cross-talk" regulation of gene expression at the NE.

One potential therapy for EDMD, being developed by Worman and colleagues, is based on their discovery that MAP kinase signaling is overactive in emerin-deficient mouse hearts; presymptomatic treatment with an ERK kinase inhibi-
tor prevented dilated cardiomyopathy in an autosomal-dominant Lmna mouse model.188 Additional pharmacological strat-
egies to treat EDMD may emerge from a better understanding of the kinases and other enzymes that regulate emerin itself or other (potentially "compensating") LEM-domain proteins.

Emerin is Sweet: Regulation by O-Linked β-N-Acetylglucosamine Transferase

Emerin is directly regulated by O-GlcNAc transferase ("OGT"; UDP-N-acetylglucosamine-peptide β-N-acetylglucosaminyl-
transferase), an essential enzyme that attaches a single β-N-
acetylglucosamine sugar to Ser/Thr residues of target proteins.21,22 The OGT-null condition in mice is lethal at embryonic stage E4.5, and in embryonic stem cells.23 Similarly, mice null for OGA (β-N-acetylglucosaminidase), the enzyme that removes O-GlcNAc, have delayed development and die at birth, with severe defects in mitosis.24-25 OGT is a pleiotropic enzyme with crit-
ical roles in the cellular stress response,26-29 mitosis,30 epigenetic regulation31 and transcriptional regulation.32 O-GlcNAcylation is highly dynamic, influences target proteins at many different levels and can compete or cooperate with phosphorylation to regu-
late specific sites.33 Emerin is highly O-GlcNAcylated in mam-
malian cells; in vitro studies identified five sites (Ser53, Ser54, Ser87, Ser871 and Ser873) and revealed at least three additional sites.34 Two sites (Ser53 and Ser54) are each individually criti-
cal for overall emerin O-GlcNAcylation not only in cells but also in vitro, suggesting potential control of emerin conforma-
tion. A third site (Ser173) is proposed to function as a molecular "switch". O-GlcNAcylation at Ser173 promotes emerin binding to BAF, whereas Ser173 phosphorylation promotes emerin hyper-
phosphorylation and reduces BAF association in cells.35 All five identified O-GlcNAc sites in emerin are phosphorylated during mitosis (Fig. 5C), suggesting OGT and mitotic kinases might compete for control of emerin.

Concluding Remarks

Basic biochemical, cellular and genetic studies of emerin have yielded unprecedented insight into the structure and function of the nuclear envelope and nuclear lamina networks, and the fundamental roles of the conserved LEM-domain protein fam-
dily. Perhaps most surprising, and frustrating in terms of EDMD disease therapy, is the sheer variety of functions to which emerin contributes—from mitosis and chromosome segregation, to silent chromatin tethering, mechano-transduction and signal-
ing. However emerin's roles in signaling have encouragingly suggested the first potential pharmacological treatment for EDMD. Further biochemical studies and human gene map-
ing studies will continue to complement each other; proteins that bind emerin represent candidate EDMD genes, and each mapped EDMD gene is a vital clue to understanding both human laminopathy disease and NE-dependent mechanisms of signaling and genome control. Given the many open questions in this young field, we wish to emphasize the dual importance of continuing both directly EDMD-relevant, and basic curios-
ity-driven, research. Both strategies are crucial to understand emerin and its fellow LEM-domain proteins, and uncover their overlapping vs. unique roles in human physiology that might lead to new therapies.

Table 4. Enzymes that target emerin

| Ser/Thr kinases | Identified sites | Assay |
|-----------------|-----------------|-------|
| PKA             | 549             | in vitro, MS |
| PKC             | n.d.            | in vivo, inhibitors |
| ERK2/MAPK       | n.d.            | in vivo, inhibitors, in vitro |
| GSK3β           | n.d.            | in vitro |
| Tyrosine kinases |                 |       |
| Src             | Y199, Y194, Y195| in vitro, MS/in vivo |
| Abi             | Y167            | in vitro, MS |
| Her2            | Y167            | in vitro |
| Phosphatases    |                 |       |
| PTP, B          | n.d.            | in vitro |
| Glyco-transferases |             |       |
| OGT             | 533, 54, 575, 578, 587, 571, 573 | in vitro, MS |

*MS, mass spectrometry; nd, not determined.

Figure 6 (See opposite page). Published human emerin phosphorylation sites. X indicates emerin phosphorylation sites identified in asynchronous or mitotic cells. Grey columns indicate emerin-specific studies; other columns are high-throughput studies. (S), Ser; (T), Thr; (Y), Tyr. These results are compiled from references 157-156.
**Figure 6.** For figure legend, see page 308.

|               | Asynchronous | Mitotic |
|---------------|--------------|---------|
|               | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| Y4            | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S8            | X  | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| T10           | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S29           |    | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Y49           | X  | X  | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S52           |    |    |    |    | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S53           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S54           |    | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S57           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S58           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Y59           |    | X  | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S60           |    | X  | X  | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S62           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S66           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| T67           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Y74           |    | X  | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Y85           |    | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S87           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Y90           | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Y94           |    | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Y95           |    | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Y99           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Y105          |    | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S110          |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S120          |    | X  | X  | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| T122          |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S123          |    | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S141          |    | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S142          |    | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S143          |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S159          |    | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Y161          | X  | X  | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S163          |    | X  | X  | X  | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |
| T165          |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Y167          | X  | X  | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S171          |    | X  | X  | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S173          |    | X  | X  | X  | X  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S175          |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| S180          |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
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Nucleus
Lamin A/C and emerin regulate MKL1-SRF activity

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Abstract

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