Role of A-type lamins in signaling, transcription, and chromatin organization

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A-type lamins (lamins A and C), encoded by the *LMNA* gene, are major protein constituents of the mammalian nuclear lamina, a complex structure that acts as a scaffold for protein complexes that regulate nuclear structure and functions. Interest in these proteins has increased in recent years with the discovery that *LMNA* mutations cause a variety of human diseases termed laminopathies, including progeroid syndromes and disorders that primarily affect striated muscle, adipose, bone, and neuronal tissues. In this review, we discuss recent research supporting the concept that lamin A/C and associated nuclear envelope proteins regulate gene expression in health and disease through interplay with signal transduction pathways, transcription factors, and chromatin-associated proteins.

Introduction

The mammalian nuclear envelope (NE) consists of the nuclear pore complexes, the outer and inner nuclear membranes separated by a luminal space, and the nuclear lamina, which is a thin proteinaceous meshwork tightly associated with several inner nuclear membrane–associated proteins (e.g., SUN, MAN1, lamina-associated polypeptides, lamin B receptor, and emerin; Broers et al., 2006). The main components of the nuclear lamina are the type V intermediate filaments A- and B-type lamins, which exist as coiled-coil dimers and associate in head to tail polymers. Alternative splicing of a common pre-mRNA transcribed from the *LMNA* gene gives rise to precursor

forms of lamin A and C (the predominant A-type lamins), lamin AΔ10, and the germline-specific lamin C2 (Broers et al., 2006). Pre–lamin A undergoes a series of posttranslational modifications that culminate with the cleavage of its farnesylated 15 C-terminal residues to generate mature lamin A (Broers et al., 2006).

Besides their well-established role in maintaining the mechanical stability of the nucleus, it is becoming increasingly evident that A-type lamins and associated NE proteins are scaffolds for proteins that regulate DNA synthesis, responses to DNA damage, chromatin organization, gene transcription, cell cycle progression, cell differentiation, and cell migration (Broers et al., 2006; Verstraeten et al., 2007). A-type lamins have been in the limelight since the discovery that *LMNA* mutations or defective posttranslational processing of pre–lamin A causes the majority of human diseases termed laminopathies, which include systemic disorders and tissue-restricted diseases (Table I; Capell and Collins, 2006; Verstraeten et al., 2007). The tissue-specific phenotypes frequently associated with *LMNA* mutations are surprising given that A-type lamins are expressed in nearly all differentiated cell types. Skeletal and cardiac abnormalities might be explained by the structural hypothesis, according to which laminopathy mutations result in a weakened NE, cell damage, and eventually death in tissues exposed to high mechanical stress (Hutchison, 2002). The gene expression hypothesis proposes that defects in NE proteins lead to pathogenic and tissue-specific alterations in gene expression, and is based on recent studies proposing that A-type lamins and other NE proteins form a docking platform for regulatory proteins and that some of these interactions are altered by laminopathy-causing mutations (Hutchison, 2002). In this paper, we review studies in mammalian cells and genetically modified mice that support these emerging concepts, focusing on the interplay of A-type lamins and associated proteins with signal transduction pathways, transcription factors, and chromatin-associated proteins and on mechanisms by which NE defects might alter these interactions to cause disease.

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Table I. **Classification and clinical phenotype of laminopathies**

Laminopathies	Clinical manifestations
Systemic	
HGPS	Premature aging, hair loss, loss of subcutaneous fat, premature atherosclerosis, myocardial infarction, stroke
Atypical Werner's syndrome	Premature aging, cataracts, scleroderma-like skin changes, premature atherosclerosis, hair graying
Restrictive dermopathy	Intrauterine growth retardation, skin alterations, multiple joint contractures, skull defects
MAD	Skull/face abnormalities, clavicular hypoplasia, joint contractures/lipodystrophy, alopecia, insulin resistance
Tissue restricted	
EDMD	Early contractures of the neck/elbows/Achilles tendons, muscle contractures, wasting of skeletal muscle, cardiomyopathy with conduction disturbance
DCM	Ventricular dilatation, systolic dysfunction, arrhythmias, conduction defects
Limb-girdle muscular dystrophy 1B	Slowly progressive shoulder and pelvic muscle weakness/wasting, contractures, cardiac defects
Charcot-Marie-Tooth neuropathy type 2B1	Axonal degeneration, lower-limb motor deficits, walking difficulty, secondary foot deformities, reduced/absent tendon reflexes starting in the second decade of life
Dunningan-type FPLD	Dramatic absence of adipose tissue in the limbs/trunk and accumulation in the neck/face, hypertriglyceridemia, increased susceptibility to atherosclerosis/diabetes

Lamin-associated signaling pathways

A-type lamins and associated proteins engage in a wide variety of intermolecular interactions that affect signal transduction pathways (see following paragraphs). Specifically, several studies implicate NE proteins as regulators of the activity and/or availability of components of the MAPK, Wnt–β-catenin, TGF-β, and Notch signaling cascades. This section reviews evidence that signaling via these pathways is defective in several laminopathies and might contribute to the etiopathogenesis of these diseases.

Extracellular signal-regulated kinase (ERK).
Two tissue-restricted laminopathies associated with mutations in *LMNA* are Emery–Dreifuss muscular dystrophy (EDMD) and dilated cardiomyopathy (DCM; Table I). The pathogenesis of these diseases is associated with perturbed MAPK signaling, as abnormal activation of ERK and JNK is observed before clinical signs or detectable expression of molecular markers of disease in the hearts of $LMNA^{H222P/H222P}$ knock-in mice, a model of autosomal EDMD that features DCM (Muchir et al., 2007b). ERK and JNK signaling are also induced in cardiomyocytes, HeLa, and COS-7 cells expressing the lamin A–H222P mutant (Muchir et al., 2007b), and ERK activation is reduced in C2C12 skeletal myoblasts and HeLa cells treated with siRNA to knock down A-type lamins or emerin (Muchir et al., 2009b), which is a type II protein anchored to the inner nuclear membrane by interactions with lamin A/C (Vaughan et al., 2001). Hyperactivation of ERK1/2 also occurs in the hearts of emerin-deficient mice ($EMD^{-/y}$), a model of x-linked EDMD with DCM (Muchir et al., 2007a). These findings are consistent with experiments using skin fibroblasts from three patients with EDMD and one with DCM bearing missense lamin A/C mutations (Emerson et al., 2009). These cells exhibit an impaired emerin–lamin A/C interaction and altered ERK1/2 function, inducing a lag in ERK1/2 activation followed by hyperactivation 2 h after cell attachment. Moreover, these effects coincided with enhanced proliferation and defects in parameters related to cell spreading such as elevated cell migration and polarization. An important role for ERK1/2 hyperactivation in the pathogenesis of DCM

is further supported by the finding that the development of cardiomyopathy in $LMNA^{H222P/H222P}$ mice is blocked by chronic systemic treatment with the ERK1/2 inhibitor PD98059 before the appearance of clinical symptoms (Muchir et al., 2009a). However, it remains unknown whether ERK1/2 inhibition can ameliorate cardiac abnormalities once DCM is established or impede the muscle weakening and degeneration associated with EDMD. More work is also needed to unravel the mechanisms by which expression of mutant lamin A/C and emerin deficiency lead to ERK1/2 hyperactivation. Our recent findings that ERK1 and ERK2 interact with A-type lamins at the nuclear periphery and participate in the rapid regulation of activator protein 1 (AP-1) activity are consistent with the possibility that the NE directly modulates ERK1/2 activity and downstream signaling and that alterations in lamin A/C expression might perturb NE structure sufficiently to directly affect these processes (see Lamin-dependent regulation of…; González et al., 2008).

Wnt–β-catenin. Wnts are secreted lipid-modified signaling proteins involved in many aspects of embryonic development and homeostatic self-renewal in adult tissues (Clevers, 2006). A key downstream effector of Wnt is β-catenin, a transcriptional cofactor of T cell factor (TCF)/lymphoid enhancer factor and structural adaptor that links cadherins to the actin cytoskeleton during cell–cell adhesion. In the absence of Wnts, cytoplasmic β-catenin undergoes proteasomal degradation (Fig. 1 A). Once bound by Wnt, the coreceptor complex comprising frizzled/lipoprotein receptor–related proteins 5 and 6 causes cytoplasmic accumulation of β-catenin, which is then translocated to the nucleus where it binds TCF/lymphoid enhancer factor and induces target gene expression.

There is evidence that the Wnt–β-catenin pathway is regulated by emerin. First, β-catenin binds to the adenomatous polyposis coli (APC)–like domain of emerin, and GFP-emerin overexpression in HEK293 cells causes cytoplasmic accumulation of β-catenin and inhibits its activity; conversely, GFP-emerinΔ (a mutant lacking the APC-like domain) dominantly increases β-catenin nuclear accumulation and activity
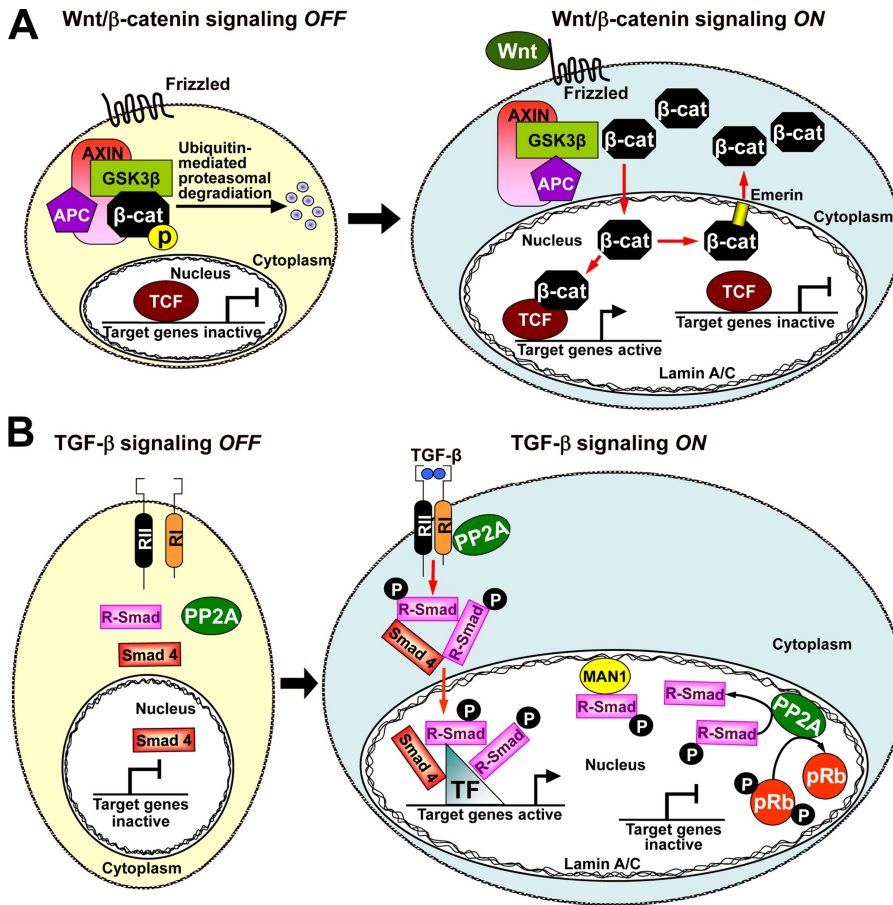
A Wnt/β-catenin signaling *OFF*   Wnt/β-catenin signaling *ON*

B TGF-β signaling *OFF*   TGF-β signaling *ON*

Figure 1. **Control of Wnt–β-catenin and TGF-β signaling by A-type lamins and associated proteins.** (A, left) In the absence of Wnt, cytoplasmic β-catenin (β-cat) undergoes proteasomal degradation, and TCF-dependent transcription is repressed. (right) Upon Wnt binding to its receptors (e.g., frizzled), β-catenin accumulates in the cytoplasm, translocates to the nucleus, and induces TCF-dependent transcription. Emerin exports nuclear β-catenin to the cytoplasm, thereby inhibiting TCF-dependent transcription. GSK3β, glycogen synthase kinase 3β. (B, left) In the absence of TGF-β, hypophosphorylated R-Smads accumulate in the cytoplasm. (right) Binding of TGF-β to its receptors leads to R-Smad phosphorylation and the formation and nuclear import of R-Smad–Smad4 complexes, which induce target gene expression in conjunction with other transcription factors (TF). MAN1 might sequester active R-Smads at the NE, preventing them from oligomerizing with co-Smads. A-type lamins interact with activated PP2A, which can dephosphorylate R-Smads and ppRb.

(Markiewicz et al., 2006). Second, x-linked EDMD fibroblasts lacking emerin show enhanced growth and nuclear accumulation and activity of β-catenin (Markiewicz et al., 2006). Thus, interaction of β-catenin with emerin might inhibit Wnt–β-catenin–TCF-dependent transcription by restricting access of β-catenin to the nucleus (Fig. 1 A).

Some laminopathies are characterized by alterations in adipose tissue. For example, localization of this tissue is altered in Dunningan-type familial partial lipodystrophy (FPLD), skeletal myocytes and cardiomyocytes are progressively replaced with fatty fibrotic tissue in x-linked EDMD, and subcutaneous fat is lost in Hutchinson–Gilford progeria syndrome (HGPS; Table I). The appearance of these alterations might involve interplay between Wnt–β-catenin, emerin, and the adipogenic transcription factor peroxisome proliferator-activated receptor γ (PPAR-γ). Adipogenesis is repressed via Wnt–β-catenin–dependent inhibition of PPAR-γ (Ross et al., 2000), which promotes proteasomal degradation of β-catenin (Moldes et al., 2003). Remarkably, emerin and β-catenin influence each other's levels of expression and the onset of adipogenesis in cellular models of differentiating preadipocytes. Moreover, in the presence of activated β-catenin, emerin-null dermal fibroblasts exhibit abnormal PPAR-γ–dependent signaling and enhanced adipogenic conversion, both of which are reversed upon transfection with β-catenin–specific siRNA (Tilgner et al., 2009).

Much work is needed to define the molecular mechanisms underlying the functional interactions between Wnt–β-catenin and emerin and to ascertain their pathophysiological implications. For example, although treatment with the nuclear export inhibitor leptomycin B abrogates the effect of emerin overexpression on the subcellular distribution of β-catenin (Markiewicz et al., 2006), the precise mechanisms of emerin-dependent β-catenin shuttling into and out of the nucleus remain obscure. It will also be of interest to investigate whether disease-causing *LMNA* mutations alter β-catenin subcellular localization because nuclear protein import is reduced in cells expressing lamin A mutants that cause prenatal skin disease restrictive dermopathy and HGPS (Busch et al., 2009). Other questions of interest are whether emerin interacts with PPAR-γ and whether the regulation of adipogenesis (and perhaps other differentiation programs) requires direct interaction between emerin and β-catenin, which could be tested by overexpressing the GFP-emerinΔ mutant lacking the APC-like domain responsible for this interaction. Furthermore, because the major sites of emerin phosphorylation are all within or immediately upstream of its APC-like domain, it is possible that phosphorylation regulates the emerin–β-catenin interaction in vivo. It will also be important to ascertain whether the emerin–β-catenin–PPAR-γ interplay observed in cultured cells occurs in vivo. If so, it may be that the growth phenotype (Markiewicz et al., 2006) and enhanced adipogenic potential (Tilgner et al., 2009) of x-linked EDMD fibroblasts contribute to the progressive replacement of skeletal muscle fibers and cardiomyocytes with fatty fibrotic tissue in x-linked EDMD. Reduced Wnt–β-catenin signaling may

also underlie NE defects and stem cell dysfunction in progeroid syndromes because abnormal accumulation of pre–lamin A and NE defects observed in a mouse model of progeria in which lamin A processing is defective coincides with Wnt–β-catenin down-regulation and abnormalities in the number and proliferative capacity of epidermal stem cells (Espada et al., 2008).

TGF-β. The TGF-β cytokine superfamily regulates differentiation, proliferation, and apoptosis in many cell types (Massagué, 2000). Binding of TGF-β to type I and II receptors triggers phosphorylation of receptor-regulated Smads (R-Smads). These form oligomers with co-Smads (Smad4), which are imported into the nucleus where they regulate transcription of a large number of target genes (Fig. 1 B). MAN1 (also named lamina-associated peptide 2 [LAP2]–emerin–MAN [LEM] domain–containing protein 3), a protein that interacts with lamin A and emerin (Gruenbaum et al., 2005), can inhibit TGF-β–mediated signaling by binding R-Smads (Osada et al., 2003; Raju et al., 2003; Hellemans et al., 2004; Lin et al., 2005; Pan et al., 2005; Pinto et al., 2008). MAN1 can sequester active R-Smads at the NE, preventing them from forming active R-Smad/co-Smad oligomers (Fig. 1 B), and can also affect the phosphorylation, oligomerization, and nuclear translocation of Smads (Pan et al., 2005; Bengtsson, 2007). Moreover, A-type lamins can modulate TGF-β–dependent signaling through interaction with protein phosphatase 2A (PP2A; Fig. 1 B; Van Berlo et al., 2005). Further work is needed to elucidate the molecular mechanisms and pathophysiological implications underlying the functional link between MAN1, A-type lamins, and Smads at the NE.

Notch. Notch-dependent signaling regulates cell fate and stem cell differentiation (Bray, 2006). Notch proteins are cell surface receptors that harbor transmembrane domains, a large extracellular domain consisting primarily of epidermal growth factor–like repeats, and a Notch intracellular domain (NICD; Fig. 2). Activation of Notch by ligands produced by neighboring cells leads to cleavage of the NICD, which translocates to the nucleus and regulates downstream gene expression by acting as a coactivator of the transcription factor suppressor of hairless (also named CSL, CBF1, and LAG-1; Fiúza and Arias, 2007).

Defective Notch signaling has been implicated in HGPS, an exceedingly rare childhood state of premature senescence characterized by alopecia, wrinkled skin, disproportionately large head, loss of subcutaneous fat, joint abnormalities, premature development of atherosclerosis, and death at a mean age of 13, most frequently from heart attack or stroke (Pereira et al., 2008). HGPS is caused by constitutive expression of a truncated form of pre–lamin A termed progerin, whose accumulation dominantly produces DNA damage and aberrant nuclear shape and chromatin structure, mainly in mesenchymal tissues. Human mesenchymal stem cells (MSCs) expressing progerin change their molecular identity and differentiation potential, exhibiting enhanced osteogenesis and reduced adipogenesis, whereas chondrogenesis is unaffected (Scaffidi and Misteli, 2008). Interestingly, the same effects in human MSCs are seen upon overexpression of the NICD. Moreover, both HGPS fibroblasts and progerin-transduced immortalized human MSCs upregulate major downstream effectors of Notch, including HES1,

HES5, HEY1, and TLE1. These alterations are not caused by changes in NICD expression or the levels of the Notch ligands DLL and Jag but, instead, correlate with reduced levels of the transcriptional corepressor NcoR and increased levels of SKIP, a transcriptional coactivator of Notch target genes that is associated with the nuclear matrix in normal cells but is found in the nuclear interior of HGPS cells (Fig. 2). Despite these interesting correlations, many questions need to be answered to clarify the connection between Notch signaling and HGPS. One issue is whether SKIP, and possibly other Notch effectors, is anchored to the NE in normal cells through physical interactions with A-type lamins and whether progerin interferes with this interaction because of a reduced affinity for SKIP. It will also be of interest to determine whether the altered epigenetic modifications frequently found in HGPS cells contribute to misregulation of Notch effector genes. Another issue is the possible involvement of Notch misregulation in physiological aging because low levels of progerin are detected in cells of healthy individuals (Scaffidi and Misteli, 2006). Finally, given that MSCs within the artery wall might contribute to vascular regeneration (Abedin et al., 2004) and that Notch3 modulates the response to vascular injury (Wang et al., 2008), it is possible that progerin-induced defects in Notch signaling in arterial MSCs contribute to the alterations in the large arteries of HGPS patients. Addressing these questions would not only shed light on how interplay between progerin and Notch causes HGPS but would also extend our knowledge of normal aging.

Lamin-dependent regulation of transcription factors

Direct interaction of A-type lamins and associated proteins with transcription factors constitutes an additional mechanism by which the NE regulates gene expression. These interactions appear to regulate transcription in several ways, for example, by sequestering transcription factors in inactive complexes at the NE, altering posttranslational modifications important for their function, and regulating transcriptional complexes. Importantly, laminopathy-causing mutations appear to disrupt these processes.

Retinoblastoma gene protein (pRb), E2F-DP, and cell cycle control. The alterations associated with laminopathies might be caused in part by defects in the cell cycle and differentiation, two processes regulated by the pocket proteins pRb, p107, and p130 (Korenjak and Brehm, 2005). The nuclei of healthy quiescent cells accumulate hypophosphorylated pRb, which binds to and inactivates the dimeric transcription factor E2F-DP. In contrast, in proliferating cells, cyclin/Cdk activity triggers the accumulation of hyperphosphorylated pRb (ppRb) during late G1 phase. In turn, this causes the release of E2F-DP and the transactivation of target genes necessary for S phase progression. pRb also suppresses cell proliferation by recruiting histone deacetylases (HDACs; Brehm et al., 1998), components of the human switch/sucrose nonfermentable complex (Trouche et al., 1997), polycomb group proteins (Breiling et al., 2001), histone methyltransferases (Nielsen et al., 2001), and DNA methyltransferases (Robertson et al., 2000).

The nucleoli of primary fibroblasts in early G1 are surrounded by a limited number of foci that contain replication proteins, lamin A/C, and pRb. Both lamin A/C and pRb are later
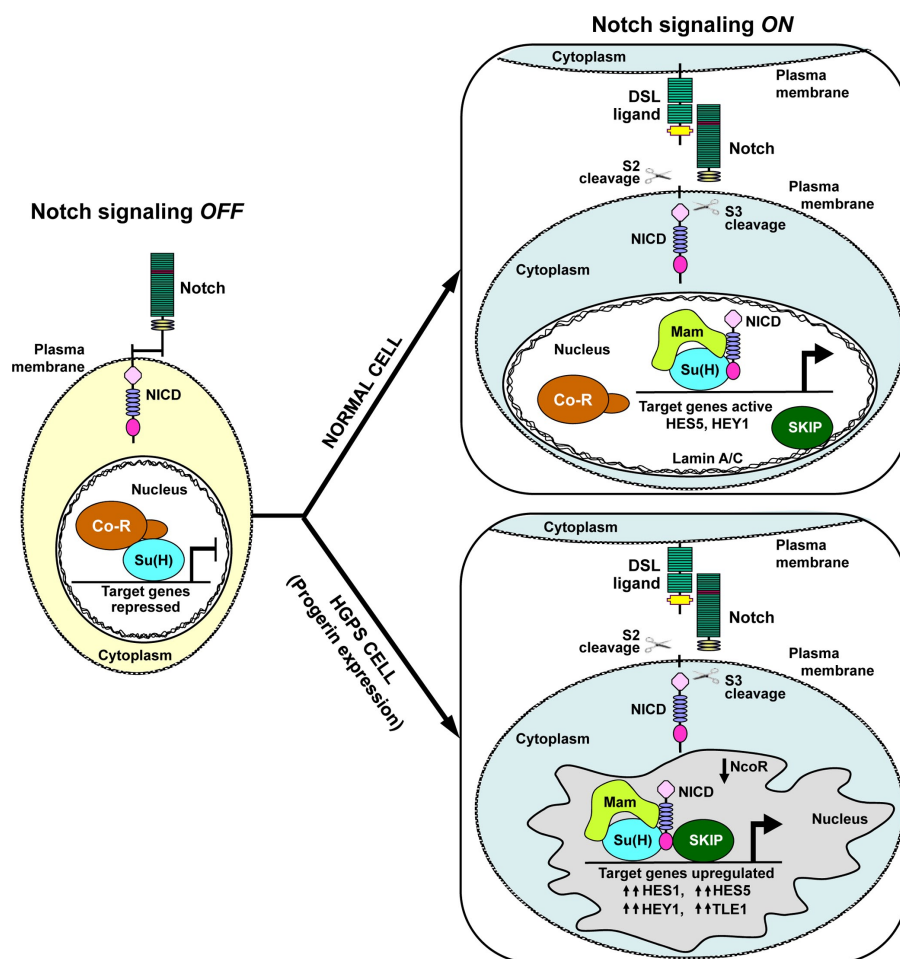
Figure 2. **Control of Notch signaling by lamin A/C and progerin.** (left) In the absence of Notch ligands, transcription of target genes is repressed. (right) Notch activation by neighboring cells leads to proteolytic release of the NICD, which translocates to the nucleus, where it activates target genes upon binding to coactivators and the release of corepressors (Co-R) from the promoter. Stem cells from HGPS patients express progerin. Notch signaling is elevated in these cells, and there is an up-regulation in the expression of Notch target genes, coincident with reduced amounts of the repressor NcoR and increased availability of the coactivator SKIP in the nuclear interior. Mam, Mastermind; DSL, Delta/Serrate/LAG-2 family of proteins.

lost from these foci in S phase, when DNA replication sites distribute to regions located throughout the nucleus (Kennedy et al., 2000). Although A-type lamins and pRb have been shown to heterodimerize in vitro (Mancini et al., 1994; Ozaki et al., 1994; Van Berlo et al., 2005), it remains to be determined whether they interact or simply colocalize in the perinucleolar foci. There is also evidence that LAP2-α, an interaction partner of nucleoplasmic A-type lamins, binds pRb, causing its hypophosphorylation and thereby reducing E2F-dependent gene expression and delaying cell cycle entry from G0 arrest (Markiewicz et al., 2002; Dorner et al., 2006). A third possibility is that A-type lamins might also control cell proliferation and gene activity downstream of TGF-β1 via nuclear PP2A-dependent control of pRb (Fig. 1 B; Van Berlo et al., 2005). A-type lamins are essential for TGF-β1–dependent dephosphorylation of ppRb and inhibition of fibroblast proliferation, and PP2A binds to lamin A/C and is responsible for TGF-β1–induced ppRb dephosphorylation. Moreover, A-type lamins modulate TGF-β1–induced Smad phosphorylation. Further work is needed to assess the model proposed by Van Berlo et al. (2005), which suggests that PP2A–lamin A/C docking restores pRb functionality via rapid TGF-β1–dependent ppRb dephosphorylation. It is also important to determine whether lack or mutation of A-type lamins renders PP2A–pRb complexes unable to inactivate target genes owing to defective subnuclear localization of one or both factors.

Loss of function experiments in cultured cells appear to confirm a role for A-type lamins and LAP2-α as regulators of pRb function. Lamin A/C ablation causes mislocalization and increased proteasomal degradation of pRb and alters its post-translational modifications (Johnson et al., 2004; Van Berlo et al., 2005), and RNAi-mediated down-regulation of LAP2-α enhances proliferation and interferes with cell cycle withdrawal upon serum starvation (Dorner et al., 2006). Moreover, lack of LAP2-α prevents the nucleoplasmic localization of A-type lamins in early G1, affects pRb function, and alters the balance between proliferation and differentiation with consequences in early progenitor cell proliferation in regenerative tissues (Naetar and Foisner, 2009). Notably, both lamin A/C– and pRb-null cells display increased proliferation (Johnson et al., 2004; Van Berlo et al., 2005; Ivorra et al., 2006; Nitta et al., 2006). These studies identify A-type lamins and LAP2-α as key regulators of the cell cycle, at least in part through modulation of the protein levels, subcellular localization, and phosphorylation of pRb. More work is warranted to identify the precise molecular mechanisms underlying the functional cross talk among these proteins and to ascertain whether laminopathy-causing mutations affect cell cycle activity through alterations in their interaction.

pRb, myogenic regulatory factors (MRFs), and skeletal myogenesis. The MRFs MyoD, myogenin, Myf5, and Myf6/Mrf4 are essential for mammalian skeletal myogenesis (Parker et al., 2003), a differentiation program that

begins with cell commitment and permanent growth arrest and continues with phenotypic differentiation and cell fusion to form multinucleated myotubes (Andrés and Walsh, 1996). MRFs share a homologous basic helix-loop-helix motif required for DNA binding and heterodimerization with transcription factors of the helix-loop-helix–containing E-protein family. MRF monomers and MRF-E heterodimers regulate transcription of muscle-specific genes containing a consensus E-box sequence in their promoter. MyoD-dependent transcription is also regulated by histone acetyltransferases (Favreau et al., 2008), and myogenesis is inhibited by the interaction of MyoD with class I HDACs (Legerlotz and Smith, 2008).

Accumulation of hypophosphorylated pRb and interaction of pRb with MyoD are required for cell cycle arrest and differentiation of skeletal myoblasts (Walsh, 1997). Studies on muscle from EDMD patients with either *LMNA* or *EMD* mutations suggest that key interactions between the NE and pRb and MyoD fail at the point of myoblast cell cycle withdrawal, leading to poorly coordinated phosphorylation and acetylation steps (Bakay et al., 2006). Accordingly, defective muscle regeneration in emerin-null mice is coincident with abnormalities in cell cycle parameters and a delayed myogenic differentiation associated with prolonged ppRb accumulation and perturbations in pRb- and MyoD-dependent transcription (Melcon et al., 2006).

In vitro myogenesis is also impaired in *LMNA*-null skeletal myocytes and in wild-type cells with RNAi-mediated knockdown of lamin A/C or emerin, which display decreased pRb and MyoD protein levels (Frock et al., 2006; Melcon et al., 2006). Moreover, cell cycle exit and differentiation of C2C12 myoblasts is impaired by ectopic expression of the EDMD-causing lamin A mutants W520S, G232E, Q294P, R386K, and R453W but not the FPLD-causing R482W mutant; this effect is possibly caused by the persistence of a large pool of ppRb and reduced expression of myogenin and MyoD (Favreau et al., 2004; Markiewicz et al., 2005; Parnaik, 2008). Notably, Favreau et al. (2008) detected two distinct populations of lamin A–R453W-expressing cells that both appeared to be incapable of fusing to form mature myotubes: one fraction that still expressed proliferation markers and another that seemed committed to differentiation according to its expression of early myogenesis markers. Defective differentiation of this second population of lamin A–R453W myoblasts did not correlate with ERK1/2 hyperactivation, a feature of heart tissue of the EDMD model *LMNA*[H222P/H222P] and emerin-null mice (see Lamin-associated signaling pathways; Muchir et al., 2007a,b). However, myogenesis in these cells was enhanced by treatment with a mixture of PD98059 (an ERK1/2 inhibitor that stimulates differentiation of normal C2C12 myoblasts) and insulin-like growth factor II (an activator of phosphoinositide 3-kinase that contributes to myoblast survival at the onset of myogenesis). Favreau et al. (2008) propose that PD98059 stimulates myogenesis of lamin A–R453W myoblasts by acting on downstream effectors of ERK1/2 that promote a switch from cellular proliferation to differentiation. The effect of PD98059 and insulin-like growth factor II coincided with down-regulation of proliferation markers (ppRb and cyclinD3), up-regulation of myogenin, and sustained activation of p21 and cyclinD3.

However, drug treatment did not completely restore the defective nuclear matrix anchorage of p21 and cyclinD3 in a complex with hypophosphorylated pRb in these cells. This association is critical for cell cycle arrest and myogenin induction, and the inability of PD98059 and insulin-like growth factor II to reverse this defect might be caused by alterations to the cyclinD3–lamin A–R453W interaction (Favreau et al., 2008). It is also noteworthy that skeletal muscle from *LMNA*[H222P/H222P] and *LMNA*-null mice and denervated muscle from wild-type controls up-regulates MyoD and myogenin and down-regulates HDAC9, which controls chromatin acetylation in presynaptic neurons and electrical activity–dependent expression of *MYOD1* and *MYOGENIN* (Méjat et al., 2005, 2009).

These studies suggest that NE defects resulting from *LMNA* and *EMD* mutations lead to muscle alterations at least in part through deregulation of the expression and function of pRb/E2F-DP and MRFs. More work is needed to define the molecular and cellular interactions that govern the interplay between pRb, MRFs, and the NE in normal and dystrophic myocytes. For example, it will be interesting to learn whether A-type lamins, emerin, and nucleoplasmic LAP2-α (see pRb, E2F-DP, and cell cycle control; also a partner of pRb) affect cell cycle activity by affecting the cooperation between pRb and HDACs to repress E2F-dependent transcription or by inactivating oligomers containing Cdk4, cyclinD3, p21, and PCNA. Moreover, lamin A/C, emerin, and LAP2-α might indirectly regulate the expression or activity of myogenic genes through pRb/MyoD-dependent and -independent mechanisms operating both in precursor cells and mature myocytes. In this regard, a cross-inhibitory interaction between the transcription factor Pax7 and MyoD and myogenin appears to modulate fate decisions of satellite cells (Olguin et al., 2007), a small population of resident myogenic cells required for postnatal growth and regeneration of skeletal muscle that express A-type lamins and emerin in the NE (Gnocchi et al., 2009). Remarkably, chromatin alterations, increased numbers of Pax7-positive nuclei, and a reduced number of MyoD-positive nuclei are all features of satellite cells in skeletal muscle from four patients with autosomal-dominant EDMD or limb-girdle muscular dystrophy 1B, a disease characterized by slowly progressive shoulder and pelvic muscle weakness and wasting, contractures, and cardiac defects (Park et al., 2008). Moreover, neuromuscular junctions are defective in patients with autosomal-dominant EDMD and in mouse models of this disease (Méjat et al., 2009). Defects in satellite cells and neuromuscular junctions might therefore contribute to muscular dystrophies in these laminopathies.

Other cellular processes regulated by pRb–lamin A/C–LAP2-α complexes

The interactions of pRb with A-type lamins, emerin, and LAP2-α may also play roles in laminopathies affecting other tissues whose differentiation is regulated by pRb, including adipose tissue (Chen et al., 1996; Hansen et al., 2004), bone (Thomas et al., 2001), and epidermis (Ruiz et al., 2004). This is supported by the observation that LAP2-α overexpression in proliferating preadipocytes causes accumulation of hypophosphorylated
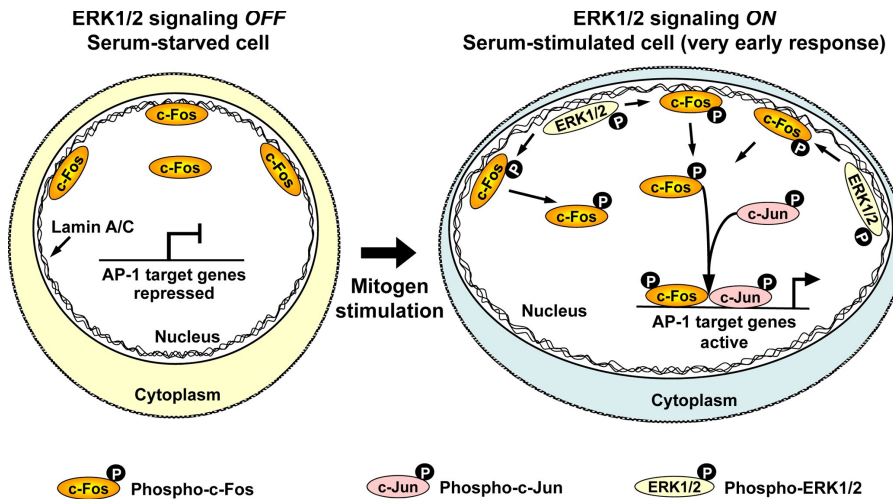
Figure 3. Fast regulation of AP-1 activity through interaction of lamin A/C, ERK1/2, and c-Fos at the NE. (left) Quiescent cells contain low levels of c-Fos, which is predominantly hypophosphorylated and sequestered at the NE through its interaction with A-type lamins. (right) Upon mitogen stimulation, phosphorylated (active) ERKs 1 and 2 interact with A-type lamins and phosphorylate c-Fos, releasing it from the NE. The released c-Fos can heterodimerize in the nucleoplasm with other AP-1 family members (e.g., c-Jun), allowing the activation of AP-1 target genes before de novo c-Fos synthesis.

pRb and initiates partial differentiation into adipocytes (Dorner et al., 2006). Moreover, LAP2-α affects the targeting of lamin A/C to the nuclear interior, pRb function, and progenitor cell proliferation (Naetar and Foisner, 2009). pRb also regulates cellular responses to DNA damage and senescence, two processes that contribute to normal and premature aging (Campisi, 2005). Indeed, pRb is down-regulated in a mouse model of progeria in which progerin, a truncated form of pre–lamin A, accumulates abnormally (Varela et al., 2005). Moreover, altered pRb distribution and increased apoptosis are detected in fibroblasts from patients with Charcot–Marie–Tooth neuropathy type 2B, limb-girdle muscular dystrophy, mandibuloacral dysplasia (MAD), and EDMD (Meaburn et al., 2007).

Fos. c-Fos is a member of the AP-1 family of transcription factors, which regulate multiple cellular processes, including proliferation and differentiation, neoplastic transformation, and apoptosis (Eferl and Wagner, 2003). c-Fos has a DNA-binding domain that recognizes target sequences and a leucine zipper domain that mediates heterodimerization with transcriptional regulators, including other AP-1 proteins. Our work suggests that A-type lamins regulate AP-1 activity by sequestering c-Fos at the NE in an ERK1/2-dependent manner (Ivorra et al., 2006; González et al., 2008). We showed that c-Fos and lamin A/C interact in vitro and in vivo through leucine residues and that these proteins colocalize at the NE in starvation-synchronized quiescent cells, which lack detectable AP-1 DNA-binding activity. Serum-induced up-regulation of AP-1 DNA-binding activity coincides with c-Fos nucleoplasmic accumulation, and serum stimulation rapidly releases preexisting c-Fos from the NE via ERK1/2-dependent phosphorylation, thus leading to fast AP-1 activation in advance of de novo c-Fos synthesis. Moreover, ERK1/2 interacts with lamin A/C and colocalizes with c-Fos and A-type lamins at the NE, and lamin A/C overexpression impairs c-Fos/c-Jun heterodimer formation, inhibits AP-1–dependent DNA-binding activity and transcription, and causes a growth arrest that can be partially rescued by c-Fos overexpression. Conversely, *LMNA*-null cells exhibit scant perinuclear c-Fos localization, increased AP-1 DNA-binding and transcriptional activity, and enhanced proliferation. NE-bound ERK1/2 may therefore function as a molecular switch for rapid

mitogen-dependent AP-1 activation through phosphorylation-induced release of preexisting c-Fos from its inhibitory interaction with lamin A/C (Fig. 3). Future studies should address whether other signal transducers and AP-1 family members are regulated by interactions with A-type lamins and other NE proteins and whether disease-causing lamin A/C mutations affect the c-Fos–ERK1/2 interplay at the NE with consequent changes in AP-1 activity and cell cycle progression. In this regard, both *c-FOS*–and *LMNA*-deficient mice exhibit defects in bone (Johnson et al., 1992; Wang et al., 1992), a tissue affected in several laminopathies.

Sterol regulatory element–binding protein 1 (SREBP1). In some laminopathies such as FPLD and MAD, the predominantly affected tissue is adipose tissue (Capell and Collins, 2006; Verstraeten et al., 2007). Expression of lamin A mutants can perturb adipogenesis by altering the localization and function of SRBP1, a transcription factor that regulates the expression of genes involved in cholesterol biosynthesis and adipogenic differentiation (Raghow et al., 2008). SREBP1c interacts with pre–lamin A and is abnormally retained in the NE of NIH-3T3 fibroblasts treated with a farnesyl transferase inhibitor, thus hampering the proper translocation of SREBP1c from the endoplasmic reticulum to the nucleus. Moreover, SREBP1c is similarly retained in the NE of fibroblasts from patients with lipodystrophy-linked MAD, FPLD, and atypical Werner's syndrome (Lloyd et al., 2002; Capanni et al., 2005). Interestingly, NE retention in FPLD fibroblasts correlates with weaker in vitro binding of SREBP1 to FPLD-causing lamin A mutants compared with binding to wild-type lamin A (Lloyd et al., 2002). Finally, pre–lamin A overexpression impairs preadipocyte differentiation and reduces expression of the adipogenic transcription factor PPAR-γ, which is regulated by SREBP1 (Capanni et al., 2005; Maraldi et al., 2007). Given that the expression of progerin in HGPS patients causes loss of subcutaneous fat and reduces the adipogenic potential of human MSCs (see Lamin-associated signaling pathways; Scaffidi and Misteli, 2008), it will be of interest to assess whether progerin also affects SREBP1 localization and function.

MOK2. *MOK2* encodes Krüppel/TFIIIA-related proteins that bind both DNA and RNA through their zinc finger

motifs (Arranz et al., 1997). MOK2 is partially associated with the nuclear matrix and binds A-type lamins in vitro and in vivo, resulting in transcriptional repression of MOK2 target genes (Dreuillet et al., 2002). One possible scenario is that lamin A/C–MOK2 complexes stabilize a repressive complex on DNA and that release of MOK2 from A-type lamins is required for gene activation. This might take place through aurora A/PKA–dependent phosphorylation of MOK2 at serine 46, which is located in the lamin A/C–binding N-terminal acidic domain of MOK2; phosphomimetic substitution of this residue markedly decreases the binding of ectopically expressed MOK2 to GST–lamin C in vitro and prevents its colocalization with lamin A/C in vivo (Harper et al., 2009). Moreover, because aurora A kinase is specifically activated before mitosis, aurora A–dependent MOK2 dissociation from A-type lamins at MOK2-regulated loci might contribute to the cytoplasmic dispersion of lamin A/C in early mitosis. Little is known about the potential pathological implications of these findings except that none of six tested disease-causing *LMNA* mutations located in the MOK2-binding domain affect the lamin A/C–MOK2 interaction in vitro or in vivo but do cause aberrant MOK2 nuclear aggregation (Dreuillet et al., 2007).

Other transcription factors that interact with A-type lamins and associated NE proteins

Lamin A/C can interact with polycomb group ring finger protein 2 (also named MEL18 and ZNF144; Zhong et al., 2005), a transcriptional repressor involved in the development, differentiation, and self-renewal of stem cells (Gil et al., 2005). Moreover, emerin coimmunoprecipitates with the transcriptional repressor germ cell less (GCL) and forms stable complexes with either lamin A–GCL or lamin A barrier to autointegration factor (BAF; Holaska et al., 2003). GCL also binds DP3, thereby repressing E2F-DP–dependent gene transcription in a pRb-independent manner (de la Luna et al., 1999; Nili et al., 2001). Therefore, the GCL–lamin A interaction might provide a pRb-independent mechanism for controlling cell proliferation or differentiation. There is also evidence of an association between lamin A and tonicity-responsive enhancer-binding protein (TonEBP; also called NFAT5), a transcriptional activator of hypertonicity-induced gene transcription (Favale et al., 2007). Physical interaction of lamin A/C and TonEBP is demonstrated by immunoprecipitation, and hypertonicity increases lamin A/C expression and its distribution in TonEBP-containing nucleoplasmic speckles. Functional evidence comes from TonEBP silencing, which causes redistribution of lamin A/C from nucleoplasmic speckles to the perinuclear rim followed by a decline in A-type lamin levels. Thus, lamin A/C–containing speckles might provide a scaffold for TonEBP, promoting its role in hypertonicity responses (Favale et al., 2007).

Interactions of A-type lamins and associated proteins with chromatin complexes

Nuclear lamins play an important role in the control of gene expression through effects on the organization and regulation of chromatin. This is strongly supported by loss of function experiments in *Caenorhabditis elegans* and *Drosophila melanogaster* that revealed aberrant chromatin organization and developmental alterations (Parnaik, 2008) and by in vitro studies showing that A-type lamins bind DNA both directly through their rod and globular domains and indirectly through interaction with core histones and BAF and LEM domain proteins (Vlcek and Foisner, 2007; Dechat et al., 2009). Studies in mammalian cells include microscopy analyses showing a close association of nuclear lamins with peripheral heterochromatin and the demonstration that A-type lamins and LAP2-α can anchor heterochromatin to the NE, possibly causing transcriptional repression (Verstraeten et al., 2007; Reddy et al., 2008; Dechat et al., 2009; Lee et al., 2009). Moreover, expression of mutant lamins and lamin deficiency both cause alterations of chromatin organization and function. For instance, loss of heterochromatin from the nuclear periphery or a general loss of heterochromatin is seen in cells from HGPS, x-linked EDMD, autosomal-dominant EDMD, FPLD, and MAD patients and in *LMNA*-null mouse cells (Parnaik, 2008; Dechat et al., 2009), and the FPLD-causing *LMNA*-R482W/Q mutation reduces lamin A/DNA binding (Stierlé et al., 2003). Finally, defects in the epigenetic regulation of chromatin and alterations in chromosome positioning are a common feature of various types of laminopathies (Parnaik, 2008; Dechat et al., 2009). In this section, we summarize known interactions of A-type lamins and associated proteins with proteins potentially involved in higher order chromatin organization (Fig. 4) and discuss their possible involvement in the etiopathogenesis of laminopathies.

BAF. BAF is a chromatin-associated protein involved in nuclear assembly, chromatin organization, and gene expression by virtue of its capacity to bind DNA, lamin A, histone H3, linker histones, and the LEM domain proteins LAP2, emerin, and MAN1 (Segura-Totten and Wilson, 2004; Wagner and Krohne, 2007). BAF may also repress transcription through interaction with the transcription factor cone-rod homeobox (Wang et al., 2002) and by competing with the transcriptional regulator GCL for binding to emerin (Holaska et al., 2003). It has been suggested that phosphorylation of BAF at serine 4 inhibits its binding to emerin and lamin A and weakens emerin–lamin A interactions during both mitosis and interphase, causing emerin mislocalization (Bengtsson and Wilson, 2006). However, the mechanisms that regulate the binding of BAF to other NE proteins and the consequences of these interactions for chromatin organization and structure remain undefined. Likewise, it is unknown whether laminopathy-causing mutations affect binding to BAF. Also, given that loss of BAF-1 in *C. elegans* causes rapid deterioration of body and tail muscles (Margalit et al., 2007), it will be of interest to ascertain whether BAF plays a role in human muscular dystrophies caused by mutations in lamin A/C and emerin.

LEM domain proteins. The LEM domain is a 40-aa structural motif shared by many inner nuclear membrane and intranuclear proteins, including emerin, MAN1, several LAP2 isoforms, LEM-2/NET25, and LEMs 3, 4, and 5, which mediate their interaction with lamin A/C and BAF (Wagner and Krohne, 2007). There is evidence that LEM domain proteins regulate
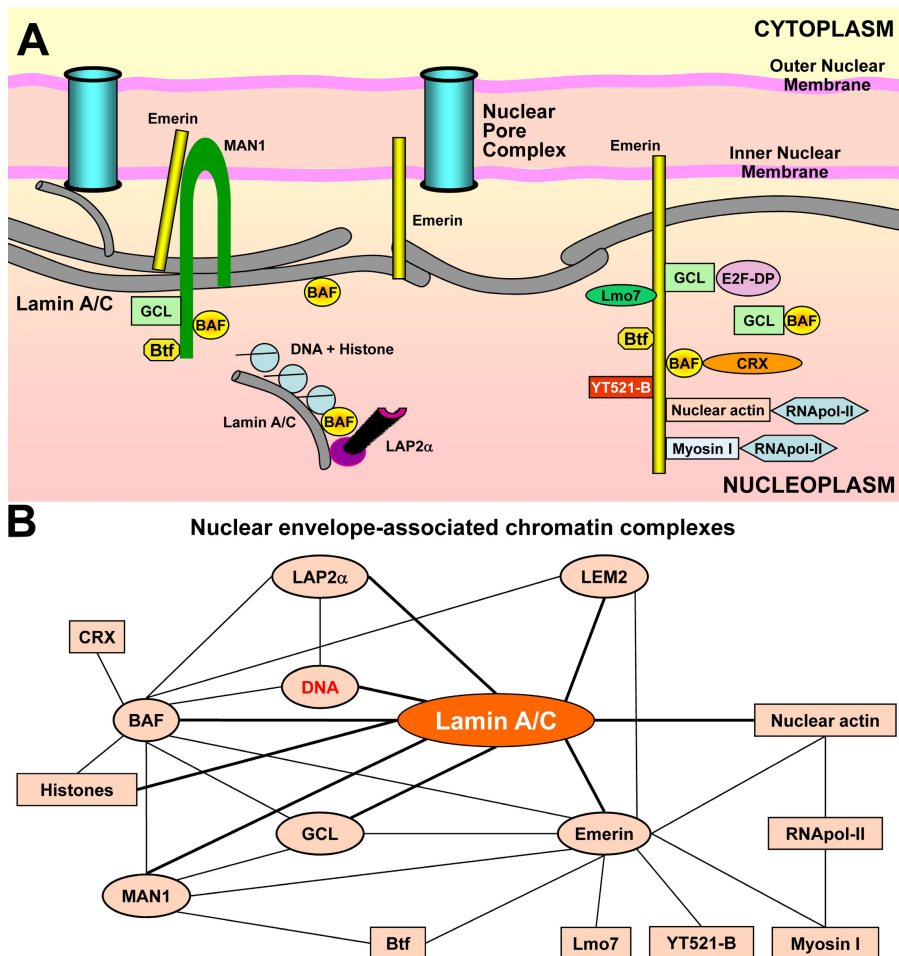
Figure 4. **Interactions of A-type lamins and NE-associated proteins with DNA, chromatin complexes, and related transcription factors.** (A) Schematic illustration of the mammalian NE showing proteins involved in the organization and regulation of chromatin and gene expression. (B) Network of NE-associated chromatin complexes. The thick lines indicate direct interactions with lamin A/C. CRX, cone-rod homeobox.

gene expression through interaction with BAF, DNA, or transcription factors. For example, in addition to its participation in TGF-β–mediated signaling (see Lamin-associated signaling pathways), MAN1 can regulate gene expression through interaction with BAF, Btf, and GCL (Furukawa, 1999; Segura-Totten and Wilson, 2004; Gruenbaum et al., 2005; Mansharamani and Wilson, 2005). Likewise, aside from its involvement in MyoD/pRb-dependent signaling (see Lamin-dependent regulation of…), emerin interacts with proteins that directly or indirectly control gene transcription, such as BAF, Btf, GCL, Lmo7, and the splicing factor YT521-B (Lee et al., 2001; Nili et al., 2001; Holaska et al., 2003, 2006; Wilkinson et al., 2003; Bengtsson and Wilson, 2004; Haraguchi et al., 2004; Markiewicz et al., 2006). Emerin can also indirectly regulate gene expression through interaction with myosin I and nuclear actin (Bengtsson and Wilson, 2004; Holaska et al., 2004; Holaska and Wilson, 2007), which in turn regulate RNA polymerase II–dependent transcription (Vlcek and Foisner, 2007). In addition, a role for LAP2-α in chromatin organization is suggested by its relocation from throughout the nucleus during interphase (Dechat et al., 1998; Vlcek et al., 1999) to telomeric regions during mitosis (Dechat et al., 2004; Gajewski et al., 2004). The interaction of LAP2-α with chromatin (Cai et al., 2001) and BAF (Vlcek et al., 1999, 2002; Dechat et al., 2004) suggests a function of LAP2-α–lamin A/C–BAF complexes in the control of higher order chromatin organization and epigenetic gene regulation that should be explored.

X-linked EDMD cells carrying mutated *EMD* exhibit altered expression of 60 genes, 28 of which are rescued by emerin overexpression (Tsukahara et al., 2002). Moreover, the following *EMD* mutations affect binding of emerin to proteins that regulate gene expression: Δ95–99 disrupts binding to lamin A (Lee et al., 2001), GCL (Holaska et al., 2003), and Btf (Haraguchi et al., 2004); S54F impairs binding to Btf (Haraguchi et al., 2004); P183H decreases binding to Lmo7 (Holaska et al., 2006) and increases binding to YT521-B (Wilkinson et al., 2003); P183H and Q133H alter affinity for nesprin-1α and nesprin-2β (Wheeler et al., 2007); and Δ95–99 and Q133H alter affinity for MAN1 (Mansharamani and Wilson, 2005). Further work is needed to determine the pathophysiological consequences of these alterations at the cellular and organismal level.

Titin. The giant sarcomeric protein titin is generally known as a provider of elasticity to striated muscles (Granzier and Labeit, 2004). However, studies with human, *D. melanogaster*, and *C. elegans* nonmuscle cells have identified titin as a nuclear protein involved in the control of chromosome dynamics, gene expression, signal transduction, and cell proliferation (Machado and Andrew, 2000; Zastrow et al., 2006; Qi et al., 2008). Using the yeast two-hybrid system and several biochemical assays with recombinant proteins, Zastrow et al. (2006) found that human titin interacts

with both A- and B-type lamins. They also detected NE localization of endogenous titin at different stages of mitosis in *C. elegans* embryos, which could be abrogated by silencing of lamin B. In contrast, the human titin epitope they investigated (M-is6) localized throughout the nucleus and appeared to be excluded from the NE in HeLa cells. However, transient overexpression of the titin-specific domain that binds lamins (M-is7) increased the frequency of aberrantly shaped nuclei and the formation of NE herniations in HeLa cells. As pointed out by Zastrow et al. (2006), it will be important to define the splicing pattern and subnuclear localization of titin during different phases of the cell cycle. Future studies should also assess whether endogenous titin and lamins interact and, if they do, unravel the molecular mechanisms that regulate this interaction and determine the extent and nature of titin's nuclear roles.

Conclusions and perspectives

It has become clear that the NE can no longer be viewed as a merely structural element but should be regarded as a highly dynamic structure involved in the regulation of gene expression, at least in part through the interaction of A-type lamins and associated proteins with components of signaling pathways, transcriptional regulators, and chromatin-associated proteins both in adult stem cells and differentiated cells in health and disease. The NE appears to function as a docking platform for the binding of regulatory proteins, thus providing a powerful and simple mechanism for the control of gene expression at several levels. These mechanisms include sequestration of transcription factors into inactive complexes, regulation of their concentration and posttranslational modifications, modulation of transcriptional complexes, and regulation of the activity or availability of signaling pathway components and regulators of chromatin organization. A major challenge for cellular and molecular biologists is to determine how the interactions of lamins with these regulatory proteins are regulated and how they affect cell functions in health and disease.

The discovery that NE-dependent interactions affect the function of myogenic and adipogenic transcription factors sheds light on the muscular and adipose tissue alterations associated with some laminopathies. More work is now needed to further delineate how laminopathy-causing mutations trigger cell- and tissue-specific phenotypes through perturbations in cell signaling and gene transcription. Research efforts should also focus on identifying novel proteins anchored to and regulated by lamins and associated proteins. A better understanding of the NE-associated interactome will not only improve our basic knowledge of the regulatory functions of the NE but should also stimulate the development of new approaches to the treatment of laminopathies. Indeed, the discovery that the accumulation of farnesylated progerin in HGPS is caused by the generation of an aberrant splicing site in *LMNA* has already led to strategies to reverse nuclear abnormalities in HGPS cells. These approaches include antisense oligonucleotides to prevent abnormal splicing, farnesyl transferase inhibitors, and other inhibitors of protein prenylation such as statins and aminobisphosphonates, and some are currently under test in clinical trials (Scaffidi and Misteli, 2005; Pereira et al., 2008; Varela et al., 2008). Finally,

given that with age, cell nuclei accumulate progerin and acquire HGPS-like defects (Scaffidi and Misteli, 2006), research into laminopathies promises to yield a better understanding of normal physiological aging.

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