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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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.

**Extracelluar 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* 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 intermolecular interactions with lamin A/C (Vaughan et al., 2001). Hyperactivation of ERK1/2 also occurs in the hearts of emerin-deficient mice (*GFP-emerin*), a model of x-linked EDMD with DCM (Muchir et al., 2009a), 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 (*GFP-emerin*), a model of x-linked EDMD with DCM (Muchir et al., 2009a), 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 (*GFP-emerin*), a model of x-linked EDMD with DCM (Muchir et al., 2009a), 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 (*GFP-emerin*), a model of x-linked EDMD with DCM (Muchir et al., 2009a), 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).
For example, although treatment with the nuclear export inhibitor leptomycin B abrogates the effect of emerin overexpression on the subcellular distribution of \( \beta \)-catenin (Markiewicz et al., 2006), the precise mechanisms of emerin-dependent \( \beta \)-catenin shuttling into and out of the nucleus remain obscure. It will also be of interest to investigate whether disease-causing LMNA mutations alter \( \beta \)-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-\( \gamma \) and whether the regulation of adipogenesis (and perhaps other differentiation programs) requires direct interaction between emerin and \( \beta \)-catenin, which could be tested by overexpressing the GFP-emerin \( \Delta \) 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–\( \beta \)-catenin interaction in vivo. It will also be important to ascertain whether the emerin–\( \beta \)-catenin–PPAR-\( \gamma \) interaction 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–\( \beta \)-catenin signaling may

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–\( \beta \)-catenin, emerin, and the adipogenic transcription factor peroxisome proliferator-activated receptor \( \gamma \) (PPAR-\( \gamma \)). Adipogenesis is repressed via Wnt–\( \beta \)-catenin–dependent inhibition of PPAR-\( \gamma \) (Ross et al., 2000), which promotes progestational degradation of \( \beta \)-catenin (Moldes et al., 2003). Remarkably, emerin and \( \beta \)-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 \( \beta \)-catenin, emerin-null dermal fibroblasts exhibit abnormal PPAR-\( \gamma \)-dependent signaling and enhanced adipogenic conversion, both of which are reversed upon transfection with \( \beta \)-catenin–specific siRNA (Tilgner et al., 2009).

Figure 1. Control of Wnt–\( \beta \)-catenin and TGF-\( \beta \) signaling by A-type lamins and associated proteins. (A, left) In the absence of Wnt, cytoplasmic \( \beta \)-catenin (\( \beta \)-cat) undergoes proteasomal degradation, and TCF-dependent transcription is repressed. (right) Upon Wnt binding to its receptors (e.g., frizzled), \( \beta \)-catenin accumulates in the cytoplasm, translocates to the nucleus, and induces TCF-dependent transcription. Emerin exports nuclear \( \beta \)-catenin to the cytoplasm, thereby inhibiting TCF-dependent transcription. GSK3\( \beta \), glycogen synthase kinase 3\( \beta \). (B, left) In the absence of TGF-\( \beta \), hypophosphorylated R-Smads accumulate in the cytoplasm. (right) Binding of TGF-\( \beta \) 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 R-Smads and ppRb.
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 dimers 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; Helleman 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 coactivator 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 (Abedín 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. ppRb 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
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), 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), and RNAi-mediated down-regulation of LAP2-α enhances proliferation and interferes with cell cycle withdrawal upon serum starvation (Dorner et al., 2006). More 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 pRb dephosphorylation. Moreover, A-type lamins modulate TGF-β1–induced Smad phosphorylation. Further work is needed 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.

**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.
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 pRb 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 pRb 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<sup>H222P/R222P</sup> 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 (pRb 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<sup>H222P/R222P</sup> 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-1/2 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 nuclopleasmic LAP2-α (see pRb, E2F-1/2, 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 (Olgun 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...
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).

C-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 SREBP1, 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; Capannì 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 (Capannì et al., 2005; Maralldi 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
Nuclear lamins play an important role in the control of gene expression through effects on the organization and regulation of chromatin complexes. Interactions of A-type lamins and pertonicity responses (Favale et al., 2007). 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 (Dreuil 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/G–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 toxicity-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
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; Gajewska 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., 2004) 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 barrier 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 reduce nuclear envelopathy-causing lamin A and lamin B. Brehm, A., E.A. Miska, D.J. McCance, J.L. Reid, A.J. Bannister, and T. Kouzarides. 1998. K profilin, a nuclear lamina protein, recruits histone deacetylase to repress transcription. *Nature*. 391:597–601. doi:10.1038/35404

**References**

Abedin, M., Y. Tintut, and L.L. Demer. 2004. Mesenchymal stem cells and the artery wall. *Circ. Res.* 95:671–676. doi:10.1161/01.RES.0000013421.27684.12

Andrés, V., and K. Walsh. 1996. Myogenic expression, cell cycle withdrawal, and phenotypic differentiation are temporally separable events that precede cell fusion upon myogenesis. *J. Cell Biol.* 132:657–666. doi:10.1083/jcb.132.4.657

Arranz, V., F. Harper, Y. Florentin, E. Puvion, M. Kress, and M. Ermoltz-Lange. 1997. Human and mouse MOK2 proteins are associated with nuclear ribonucleoprotein components and bind specifically to RNA and DNA through their zinc finger domains. *Mol. Cell. Biol.* 17:2116–2126.

Bakay, M., Z. Wang, G. Melcon, L. Schiltz, J. Xuan, P. Zhao, V. Sartorelli, J. Seo, E. Pegoraro, C. Angelini, et al. 2006. Nuclear envelope dystrophies show a transcriptional fingerprint suggesting disruption of RB-RbMD pathways in muscle regeneration. *Brain*. 129:996–1013. doi:10.1093/brain/aw023

Bengtsson, L. 2007. What MAN1 does to the Smads. *TGFbeta/BMP signalling and the nuclear envelope. FERS J.* 274:1374–1382. doi:10.1111/j.1742-4658.2007.05696.x

Bengtsson, L., and K.L. Wilson. 2004. Multiple and surprising new functions for emerin, a nuclear membrane protein. *Curr. Opin. Cell Biol.* 16:73–79. doi:10.1016/j.ccell.2003.11.012

Bengtsson, L., and K.L. Wilson. 2006. Barrier-to-autointegration factor phosphorylation on Ser-7 regulates emerin binding to lamin A in vitro and emerin localization in vivo. *Mol. Cell. Biol.* 17:1154–1163. doi:10.1091/mcb.E05-04-0354

Bray, S.J. 2006. Notch signalling: a simple pathway becomes complex. *Nat. Rev. Mol. Cell Biol.* 7:678–689. doi:10.1038/nrm2009

Brehm, A., E.A. Miska, D.J. McCance, J.L. Reid, A.J. Bannister, and T. Kouzarides. 1998. K profilin, a nuclear lamina protein, recruits histone deacetylase to repress transcription. *Nature*. 391:597–601. doi:10.1038/35404

Breiling, A., B.M. Turner, M.E. Bianchi, and V. Orlando. 2001. General transcription factors bind promoters repressed by Polycomb group proteins. *Nature*. 412:651–655. doi:10.1038/350808090

Broers, J.L., F.C. Ramaekers, G. Bonne, R.B. Yaou, and C.J. Hutchison. 2006. Nuclear lamins: laminopathies and their role in premature ageing. *Physiol. Rev.* 86:967–1008. doi:10.1152/physrev.00047.2005

Busch, A., T. Kiel, W.M. Heupel, M. Wehnert, and S. Hubner. 2009. Nuclear protein import is reduced in cells expressing nuclear envelopathy-causing lamin A mutants. *Exp. Cell Res.* 315:2573–2585.

Cai, M., Y. Huang, R. Ghirlando, K.L. Wilson, R. Craigie, and G.M. Clore. 2001. Solution structure of the constant region of nuclear envelope protein LAP2 reveals two LEM-domain structures: one binds BAF and the other binds DNA. *EMBO J.* 20:4399–4407. doi:10.1093/emboj/20.16.4399

Campisi, J. 2005. Aging, tumor suppression and cancer: high wire-act! *Mech. Ageing Dev.* 126:51–58. doi:10.1016/j.mad.2004.09.024

Capanni, C., E. Mattioli, M. Columbaro, E. Lucarelli, V.K. Parnaik, G. Novelli, M. Wehnert, V. Cenni, N.M. Malardi, S. Squarzoni, and G. Lattanzi. 2005. Altered pre-lamin A processing is a common mechanism leading to lipodystrophy. *Hum. Mol. Genet.* 14:1489–1502. doi:10.1093/hmg/ddi158

Capell, B.C., and F.S. Collins. 2006. Human laminopathies: nuclear gene genetically awry. *Nat. Rev. Genet.* 7:940–952. doi:10.1038/nrg1906

Chen, P.L., D.J. Riley, Y. Chen, and W.H. Lee. 1996. Retinoblastoma protein position and posttranslational modifications, modulation of transcription, and regulation of the activity or availability of signaling pathway components and regulators of chromatin or-
Gajewski, A., E. Csaszar, and R. Foisner. 2004. A phosphorylation cluster in the
A-type lamins: when structure meets function. Adv. Exp. Med. Biol. 549:157–166.
doi:10.1016/j.dcsb.2004.12.003

González, J.M., A. Navarro-Puche, B. Casar, P. Crespo, and V. Andrés. 2008. The
interaction between human transcription factor MOK2 and lamin A/C. Genes
Dev. 22:2803–2818. doi:10.1101/gad.1714608

Hansen, J.B., C. Jørgensen, R.K. Petersen, P. Hallenberg, R. De Matteis, H.A.
Boye, N. Petrovic, S. Enerbäck, J. Nedergaard, S. Cinti, et al. 2004. Retinoblastoma
protein functions as a molecular switch determining white versus brown adipocyte
differentiation. Proc. Natl. Acad. Sci. USA. 101:1412–1417. doi:10.1073/pnas.0309641101

Haraguchi, T., J.M. Holaska, M. Yamane, T. Kojun, N. Hashiguchi, C. Mori,
K.L. Wilson, and Y. Hiraoka. 2004. Eemer binding to Btf, a death-
proliferating transcriptional repressor, is disrupted by a missense
mutation that causes Emyr-Dreifuss muscular dystrophy. Eur. J. Biochem.
271:3345–3353. doi:10.1016/j.jbc.2003.10.040

Harper, M., J. Tillit, M. Kress, and E. Harlow. 2003. AP-1 repression in vivo.
J. Biol. Chem. 278:9699–9705. doi:10.1074/jbc.M208812200

Holaska, J.M., K.K. Lee, A.K. Kowalski, and K.L. Wilson. 2003. Transcriptional
repressor germ cell-less (GCL) and barrier to autointegration factor (BAF)
compete for binding to emerin in vitro. J. Biol. Chem. 278:29617–29622.
doi:10.1074/jbc.M204620200

Hutchison, C.J. 2002. Laminin: building blocking or regulators of gene expression?
Nat. Rev. Cell Biol. 3:859–868. doi:10.1038/nrc9920

Kennedy, B.K. 2008. Nuclear envelope defects cause stem cell dysfunction in
premature-pathies. Biol. Cell. 100:967–968. doi:10.1042/bc20080103

Kerr, D.C., L. Wilson, and K.L. Wilson. 2003. Distinct functional domains in
emerin bind lamin A and DNA-binding protein BAF. J. Cell Sci. 116:4567–4573.

Langer, J., G. Bunce, and M. Haurani. 2005. The retinoblastoma protein Rb
promotes transcriptional repression. J. Biol. Chem. 280:19873–19882.
doi:10.1074/jbc.M310293200

Mancini, M.A., B. Shan, J.A. Nickerson, S. Pennman, and W.H. Lee. 1994. The
retinoblastoma gene product is a cell cycle-dependent, nuclear
matrix-associated protein. Proc. Natl. Acad. Sci. USA. 91:4148–4152.
doi:10.1073/pnas.91.41.4148

Mansharamani, M., and K.L. Wilson. 2005. Direct binding of nuclear membrane
protein MAN1 to emerin in vitro and two modes of binding
to barrier-to-autointegration factor. J. Biol. Chem. 280:13863–13870. doi:10.1074/jbc.M413020200

Maraldi, N.M., C. Capanni, E. Mattioli, M. Columbaro, S. Squarzon, W.K. Parnai, M. Wehnert, and G. Lattanzi. 2007. A pathogenic mechanism leading to partial lipodystrophy and prospects for pharmacological treatment of resistance syndromes. Annu. Biomed. 78:207–215. doi:10.1016/j.abc.2007.04.004

Margalit, A., E. Neufeld, N. Feinstein, K.L. Wilson, B. Podbielny, and W. Gruenbaum. 2007. Barrier to autointegration factor blocks premature cell fusion and maintains adult muscle integrity in C. elegans. J. Cell Biol. 178:661–673. doi:10.1038/jcb.200704049

Markiewicz, E., T. Dechat, R. Foisier, R.A. Quinlan, and C.J. Hutchison. 2002. Lamin A/C-binding protein LAP2alpha is required for nuclear anchorage of retinoblastoma protein. Mol. Biol. Cell. 13:4401–4413. doi:10.1091/mbc.E02-07-0450

Markiewicz, E., M. Ledran, and C.J. Hutchison. 2005. Remodelling of the nuclear lamina and nucleoskeleton is required for skeletal muscle differentiation in vitro. EMBO J. 25:3275–3285. doi:10.1038/sj.emboj.7601230

Muchir, A., J. Shan, G. Bonne, S.E. Lehnart, and H.J. Worman. 2009a. Inhibition of lamin A/C by NIPBL renders cells refractory to p53-induced apoptosis. J. Cell Sci. 122:3781–3792. doi:10.1242/jcs.031630

Muchir, A., P. Pavlidis, G. Bonne, Y.K. Hayashi, and H.J. Worman. 2007a. Activation of MAPK pathways links LMNA mutations to cardiomyopathy in Emery-Dreifuss muscular dystrophy. J. Biol. Chem. 282:15992–16001. doi:10.1074/jbc.M411234200

Park, Y.E., Y.K. Hayashi, K. Goto, H. Komaki, Y. Hayashi, T. Inuzuka, S. Noguchi, I. Nonaka, and I. Nishino. 2008. Nuclear changes in skeletal muscle extend to satellite cells in autosomal dominant Emery-Dreifuss muscular dystrophy/limb-girdle muscular dystrophy type II. Neuromuscul. Disord. 19:29–36.

Parker, M.H., P. Peale, and M.A. Rudniki. 2003. Looking back into the embryo: defining transcriptional networks in adult myogenesis. Nat. Rev. Genet. 4:497–507. doi:10.1038/nrg1109

Parnai, V.K. 2008. Role of nuclear laminas in nuclear organization, cellular signaling, and inherited diseases. Int. Rev. Cell Mol. Biol. 266:157–206. doi:10.1016/S0074-7649(08)60004-X

Perea, S., P. Bourgeois, C. Navarro, V. Esteves-Vieira, P. Cau, A. De Sandre-Giovannoli, and N. Lévy. 2008. HGPS and related premature aging disorders: from genomic identification to the first therapeutic approaches. Mech. Ageing Dev. 129:449–459. doi:10.1016/j.mad.2008.04.003

Pinto, B.S., S.R. Wilkinson, E.H. Hornick, L.L. Waltraeth, and P.K. Geyer. 2008. Time-course-specific defects in the transforming growth factor-beta superfamily of cytokines. J. Cell Biol. 180:133–145. doi:10.1016/j.jcb.2008.04.002

Qi, J., L. Chi, S. Labeit, and A.J. Banes. 2008. Nuclear localization of the titin Z1ZZz domain and role in regulating cell proliferation. Am. J. Physiol. Cell Physiol. 295:C975–C985. doi:10.1152/ajpcell.90619.2007

Raghow, R., C. Yelluturu, X. Deng, E.A. Park, and M.B. Elam. 2008. SREBPs: the crossroads of physiological and pathological lipid homeostasis. Trends Endocrinol. Metab. 19:65–73. doi:10.1016/j.tem.2007.10.009

Raju, K.L., J.M. Zullo, E. Bertolino, and H. Singh. 2008. Transcriptional repression mediated by repositioning of genes to the nuclear lamina. Nature 452:243–247. doi:10.1038/nature06727

Robertson, K.D., S. Att-Si-Ali, T. Yokochi, P.A. Wade, P.L. Jones, and A.P. Wolfe. 2000. DNM1 forms a complex with Rb, E2F1 and HDAC1 and represses transcription from E2F-responsive promoters. Nat. Genet. 25:338–342. doi:10.1038/ng.7712

Ross, S.E., N. Hemiad, K.A. Longo, C.N. Bennett, P.C. Lucas, R.L. Erickson, and O.A. MacDougall. 2000. Inhibition of adipogenesis by Wnt signaling. Science. 289:950–953. doi:10.1126/science.289.5481.950

Ruiz, S., M. Santos, C. Segregles, H. Leis, J.L. Jorcano, A. Berns, J.M. Paramio, and M. Voojs. 2004. Unique and overlapping functions of pRb and p107 in the control of proliferation and differentiation in epidermis. Development. 131:2737–2748. doi:10.1242/dev.01148

Scaffidi, P., and T. Misteli. 2005. Reversal of the cellular phenotype in the premature aging disease Hutchinson-Gilford progeria syndrome. Nat. Med. 11:440–445. doi:10.1038/nm1204

Scaffidi, P., and T. Misteli. 2006. Lamin A-dependent nuclear defects in human aging. Science. 312:1059–1063. doi:10.1126/science.1127168

Scaffidi, P., and T. Misteli. 2008. Lamin A-dependent misregulation of adult stem cells associated with accelerated ageing. Nat. Cell Biol. 10:452–459. doi:10.1038/ncb1708

Segura-Totten, M., and K.L. Wilson. 2004. BAF: roles in chromatin, nuclear structure and retrovirus integration. Trends Cell Biol. 14:261–266. doi:10.1016/j.tcb.2004.04.004

Sterlé, V., J. Couprie, C. Oxlund, I. Krimm, S. Zinn-Justin, P. Hossenlopp, H.J. Worman, J.C. Courvalin, and I. Dubaud-Goulet. 2003. The carboxy-terminal region common to laminas A and C contains a DNA binding domain. Biochemistry. 42:4819–4828. doi:10.1021/bi020704g

Thomas, D.M., S.A. Carty, D.M. Piscopo, J.S. Lee, W.F. Wang, W.C. Forrester, and P.W. Hinds. 2001. The retinoblastoma protein acts as a transcriptional corepressor required for osteogenic differentiation. Mol. Cell. 8:303–316. doi:10.1016/S1097-2765(01)00327-6

Tilgner, K., K. Wojciechowicz, C. Jahoda, C. Hutchison, and E. Markiewicz. 2009. Dynamic complexes of A-type lamins and emerin influence adi- pogenic capacity of the cell via nucleocytoplasmic distribution of beta-catenin. J. Cell Sci. 122:401–413.
Trouche, D., C. Le Chalony, C. Muchardt, M. Yaniv, and T. Kouzarides. 1997. RB and brm cooperate to repress the activation functions of E2F1. Proc. Natl. Acad. Sci. U.S.A. 94:11268–11273. doi:10.1073/pnas.94.21.11268

Tsukahara, T., S. Tsujino, and K. Arahata. 2002. CDNA microarray analysis of gene expression in fibroblasts of patients with x-linked Emery-Dreifuss muscular dystrophy. Muscle Nerve. 25:898–901. doi:10.1002/mus.10085

Van Berlo, J.H., J.W. Voncken, N. Kubben, J.L. Broers, R. Duisters, R.E. van Leeuwen, H.J. Crijns, F.C. Ramaekers, C.J. Hutchison, and Y.M. Pinto. 2005. A-type lamins are essential for TGF-beta1 induced PP2A to de-phosphorylate transcription factors. Hum. Mol. Genet. 14:2839–2849. doi:10.1093/hmg/ddi316

Varela, I., J. Cadiñanos, A. Gutiérrez-Fernández, A.R. Folgueras, L.M. Sánchez, Z. Zhou, F.J. Rodríguez, C.L. Stewart, J.A. Vega, et al. 2005. Accelerated ageing in mice deficient in Zmpste24 protease is linked to p53 signalling activation. Nature. 437:564–568. doi:10.1038/nature04019

Verstraeten, V.L., J.L. Broers, F.C. Ramaekers, and M.A. van Steensel. 2007. The nuclear envelope, a key structure in cellular integrity and gene expression. Curr. Med. Chem. 14:1231–1248. doi:10.2174/092986707780598032

Vlcek, S., and R. Foisner. 2007. A-type lamin networks in light of lamino-pathic diseases. Biochim. Biophys. Acta. 1773:661–674. doi:10.1016/j.bbamcr.2006.07.002

Vlcek, S., H. Just, T. Dechat, and R. Foisner. 1999. Functional diversity of LAP2alpha and LAP2beta in postmitotic chromosome association is caused by an alpha-specific nuclear targeting domain. EMBO J. 18:6370–6384. doi:10.1093/emboj/18.22.6370

Vlcek, S., B. Korbei, and R. Foisner. 2002. Distinct functions of the unique C terminus of LAP2alpha in cell proliferation and nuclear assembly. J. Biol. Chem. 277:18989–18907. doi:10.1074/jbc.M200048200

Wagner, N., and G. Krohne. 2007. LEM-domain proteins: new insights into lamin-interacting proteins. Int. Rev. Cytol. 261:1–46. doi:10.1016/S0074-7696(07)61001-8

Walsh, K. 1997. Coordinate regulation of cell cycle and apoptosis during myogenesis. Prog. Cell Cycle Res. 3:53–58.

Wang, Z.Q., C. Ovitt, A.E. Grigoriadis, U. Möhle-Steinlein, U. Rüther, and E.F. Wagner. 1992. Bone and haematopoietic defects in mice lacking c-fos. Nature. 360:741–745. doi:10.1038/360741a0

Wang, X., S. Xu, C. Rivolta, Y.L. Li, G.H. Peng, P.K. Swain, C.H. Sung, A. Swaroop, E.L. Berson, T.P. Dryja, and S. Chen. 2002. Barrier to autointegration factor interacts with the cone-rod homeobox and represses its transactivation function. J. Biol. Chem. 277:43288–43300. doi:10.1074/jbc.M207952200

Zhong, N., G. Radu, W. Ju, and W.T. Brown. 2005. Novel progerin-interactive partner proteins hnRNP E1, EGF, Mel 18, and UBC9 interact with lamin A/C. Biochem. Biophys. Res. Commun. 338:855–861. doi:10.1016/j.bbrc.2005.10.020