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Laminopathies and Lamin-Associated Signaling Pathways

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ABSTRACT

Laminopathies are genetic diseases due to mutations or altered post-translational processing of nuclear envelope/lamina proteins. The majority of laminopathies are caused by mutations in the *LMNA* gene, encoding lamin A/C, but manifest as diverse pathologies including muscular dystrophy, lipodystrophy, neuropathy, and progeroid syndromes. Lamin-binding proteins implicated in laminopathies include lamin B2, nuclear envelope proteins such as emerin, MAN1, LBR, and nesprins, the nuclear matrix protein matrin 3, the lamina-associated polypeptide, LAP2alpha and the transcriptional regulator FHL1. Thus, the altered functionality of a nuclear proteins network appears to be involved in the onset of laminopathic diseases. The functional interplay among different proteins involved in this network implies signaling partners. The signaling effectors may either modify nuclear envelope proteins and their binding properties, or use nuclear envelope/lamina proteins as platforms to regulate signal transduction. In this review, both aspects of lamin-linked signaling are presented and the major pathways so far implicated in laminopathies are summarized. J. Cell. Biochem. 112: 979–992, 2011. © 2010 Wiley-Liss, Inc.

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In the last 15 years, increasing interest in the functions of the nuclear envelope has been kindled by the finding that some 15 human diseases are linked to mutations in nuclear envelope proteins. Among these diseases, referred to as "laminopathies," more than half are caused by mutations of the *LMNA* gene, which encodes lamin A/C [Worman et al., 2010]. However, other nuclear envelope constituents have been implicated: mutations in the genes encoding for emerin, the nuclear envelope partner of lamin A/C, the lamin B receptor (LBR), MAN1, nesprin 1 and nesprin 2, give rise to tissue-specific laminopathies, while mutations in the prelamin A endoprotease cause systemic laminopathies [Worman et al., 2010]. Moreover, LAP2 alpha, lamin B1 and lamin B2, the nuclear lamina partners of lamin A/C, have been implicated in genetic disorders affecting heart, brain and nervous system [Dauer and Worman, 2009]. Matrin3, a nucleoskeleton constituent, has been further associated with autosomal dominant distal myopathy [Senderek et al., 2009]. Thus, it appears that proteins once considered mere structural constituents of the nucleus, play key roles in tissue and organ functionality in a cell-type specific way. Systemic laminopathies, on the other hand, implicate nuclear envelope/lamina proteins in more general mechanisms regulating cellular and organismal growth and senescence.

Based on this complex and intriguing picture of genetic disorders linked to nuclear envelope/lamina genes two major hypotheses come into play. First, since many overlapping clinical phenotypes are observed in laminopathies linked to different genes, there must be a functional interplay among some, if not all, the different proteins causing diseases. Secondly, the interplay among laminopathy-associated proteins must involve versatile cellular tools, mostly the signaling pathways. These two hypotheses will be presented in this review, based on available experimental data, bioinformatics prediction and proved or suggested mechanisms. We will present different proteins linked to laminopathies, signaling pathways involving these proteins, either as targets or effectors of cellular signals, and pathogenetic mechanisms involving these signaling pathways.

THE PROTEIN NETWORK

The nuclear lamina is a stress-resistant elastic meshwork of type V intermediate filaments, the type-A and type-B lamins [Prokocimer et al., 2009]. Although it has been assumed that the nuclear lamina is a structural support to the nuclear envelope membranes, many

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experimental data indicate that it is directly or indirectly, through interactions with integral proteins of the inner nuclear membrane (INM proteins), involved in a variety of cell functions [Prokocimer et al., 2009]. The nuclear membrane is a double membrane interrupted by the nuclear pore complexes, which constitutes a structural continuum with the endoplasmic reticulum membranes. The peripheral lamins interact with chromatin associated proteins on the nucleoplasmic side and with nuclear envelope proteins on the membrane side [Shimi et al., 2008]. Multiple interactions between lamins and nuclear envelope KASH and SUN proteins establish a link between the nucleus and the cytoskeleton [Schneider et al., 2010], thereby contributing to the maintenance of nuclear architecture, high-order chromatin arrangement, nuclear anchorage and positioning, as well as modulation of transcriptional regulator availability. The role of lamins is likely to coordinate all the functions mentioned above.

The major isoforms of A-type lamins (lamin A and lamin C) are generated by use of an alternative 5′ splice site in exon 10. Unlike lamin C, lamin A is translated as prelamin A and undergoes post-translational processing steps at the C-terminal CaaX motif [Rusinol and Sinensky, 2006; Lattanzi et al., 2007a]. B-type lamins are encoded by two genes, *LMNB1* and *LMNB2*, and at least one B-type lamin is expressed in all cell types throughout development. B-type lamins undergo post-translational modifications similar to those of lamin A; however they remain farnesylated [Malhas et al., 2007]. As a consequence, B-type lamins remain attached to the nuclear membrane even in mitosis, whilst mature lamin A and lamin C are solubilized in mitosis and can also localize throughout the nucleoplasm in interphase cells [Naetar et al., 2008; Naetar and Foisner, 2009]. Because no association has been found between human diseases and loss-of-function mutations in lamin B genes, it is possible that loss of these genes causes embryonic lethality [Vergnes et al., 2004].

In the nucleoplasm, LAP2alpha is the most intriguing binding partner of lamin A/C, since it serves as anchoring protein for nucleoplasmic lamins [Naetar et al., 2008] and mediates lamin interaction with cell cycle regulators in the pRb-E2F pathway [Markiewicz et al., 2002]. The DNA binding protein BAF is a mediator of lamin A/C interplay with chromosomes and interphase chromatin [Montes de Oca et al., 2009]. However, BAF mutations have not been so far identified in any laminopathic disease. On the nuclear envelope side, lamin A binds emerin, nesprins 1 and 2, and the nuclear envelope bridging proteins SUN1 and SUN2 [Prokocimer et al., 2009] (not implicated, so far, in laminopathies). Interestingly, SUN1 and SUN2 connect the inner nuclear membrane to the perinuclear space and to cytoplasmic nesprins, thus providing a structural and functional link between the nucleus and the cytoplasm [Ostlund et al., 2009; Haque et al., 2010]. MAN1 also binds to lamins at the nuclear envelope, and is part of a protein platform regulating cellular signaling pathways, mostly those dependent on TGF-β [Konde et al., 2010]. Lamin B, as well as lamin A, bind LBR, a key constituent of the nuclear envelope which harbors eight transmembrane domains [Worman et al., 1990]. Although the functional significance of lamin-LBR interplay has been elusive, LBR has been demonstrated to regulate changes in nuclear morphology and chromatin compaction during the cell cycle and cellular differentiation, a function also involving lamins [Zwerger et al., 2010]. Finally, matrin 3, a nuclear matrix protein, has been involved in chromosome anchorage and gene expression regulation [Zeitz et al., 2009], a function overlapping with those of lamins. In the same context, FHL1, a transcriptional regulator recently associated with Emery–Dreifuss muscular dystrophy, has been shown to play a key role in nuclear anchorage and myotube hypertrophy [Cowling et al., 2008].

A common feature of several proteins causing laminopathies is the regulation of the import/export of transcription factors and transcriptional regulators at the nuclear envelope [Kind and van Steensel, 2010]. Mature lamin A, MAN1, and emerin have been demonstrated to negatively regulate the amount of translocated transcriptional regulators, by either limiting their import or favoring their export rate [Capanni et al., 2005; Markiewicz et al., 2006; Gonzalez et al., 2008; Konde et al., 2010].

Thus, at least two functions, chromatin functional organization and exchange of transcriptional regulators, are clearly shared by diverse proteins implicated in laminopathies. Moreover, two additional roles are being associated to several proteins causing laminopathic disorders: regulation of nuclear positioning and mechanosignaling transduction. In the latter functions nesprins, emerin, lamin A, and FHL1 appear to be involved.

NUCLEAR ENVELOPE PROTEINS AND SIGNALING

A TYPE LAMINS

The major splicing products of the *LMNA* gene, lamin A and lamin C, harbor several serine and threonine residues, which constitute potential or proved targets of phosphorylating enzymes (Fig. 1) [Prokocimer et al., 2009]. The known phosphorylation sites (Fig. 2) in the lamin A/C sequence are serine 404, targeted by AKT1, serine 392 targeted by cdc2 kinase, serine 5, serine 525 and serine 625, targeted by PKC isozymes [Martelli et al., 2002; Marmiroli et al., 2009; Kuga et al., 2010]. The best known effect of lamin A/C phosphorylation is protein de-polymerization, which allows break-down of the nuclear lamina at the onset of mitosis. Cdk1 has also been implicated in this process and it is necessary for lamina disassembly [Heald and McKeon, 1990]. However, lamins are stably phosphorylated in interphase cells and even in post-mitotic nuclei, such as those of muscle fibers, where phosphorylation is dependent on the insulin pathway [Cenni et al., 2005]. Moreover, we found that reduced lamin A N-terminal phosphorylation is associated with LMNA-linked muscle diseases [Cenni et al., 2005], while it has been recently reported that specific phosphorylation at serine 458 of A-type lamins occurs in muscle laminopathies [Mitsuhashi et al., 2010]. Phosphoserine 458 is not found in normal cells or in non-muscular laminopathies [Mitsuhashi et al., 2010]. Thus, lamin A/C phosphorylation at specific sites plays a major role in muscle function, possibly interfering with lamin intermolecular interactions. Phosphorylation of lamins at S404 is specifically triggered by Akt in the PI3-kinase insulin pathway and it has been implicated in proper nuclear lamina organization [Cenni et al., 2008]. Interestingly, the EDMD2 *LMNA* R401C mutation, within the Akt consensus site of lamin A, reduces protein phosphorylation [Cenni et al., 2008]. Phosphorylation of S404 occurs throughout the cell cycle and likely

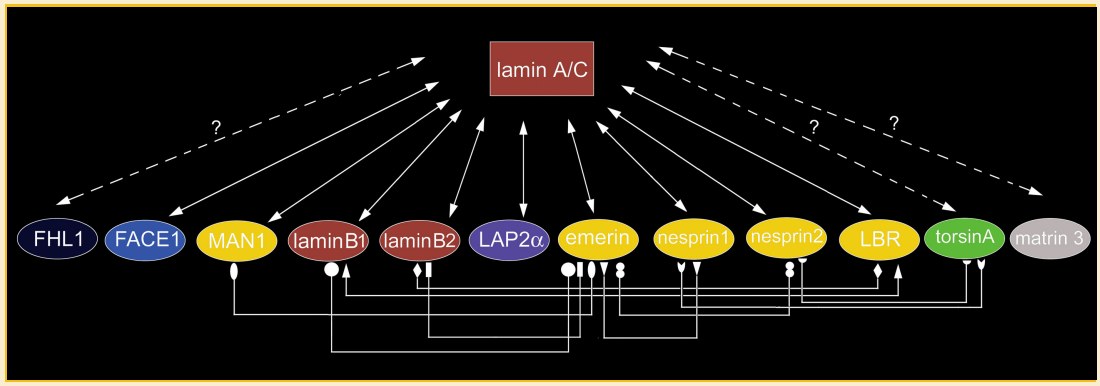

Fig. 1. The network of proteins mutated in laminopathies. FHL1, four and a half LIM domain 1; FACE1, farnesylated proteins-converting enzyme 1; LAP2α, lamina-associated polypeptide 2 alpha; LBR, lamin B receptor. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

regulates the levels of the lamin A precursor protein [Marmiroli et al., 2009]. It is conceivable that prelamin A phosphorylation at this residue is necessary, for protein degradation. Dephosphorylation of lamin A/C is mostly carried out by protein phosphatase 1 (PP1) at the end of mitosis and it allows assembly of the nuclear lamina [Steen and Collas, 2001]. PP1 activity is also important to maintain nuclear envelope integrity in G1 phase and to prevent apoptotic breakdown of the lamina [Steen et al., 2003]. Lamin A/C is also sumoylated on lysine 201 [Zhang and Sarge, 2008]. Sumoylation appears to mediate proper assembly of the nuclear lamina, yet the downstream events deserve further investigation. Farnesylation of prelamin A occurs at a key aminoacid, cysteine 661, within the C-terminal CaaX box. Cysteine 661 is farnesylated by the dimeric protein farnesyl transferase [Barrowman et al., 2008]. The modification is necessary for further processing of the lamin A precursor, consisting of methylation of the same residue by the enzyme Icmt, and double cleavage leading to production of mature lamin A. While the biological significance of prelamin A farnesylation is clearly the creation of a recognition site for the prelamin A endoprotease ZMPSTE24, methylation does not always appear a limiting step [Coffinier et al., 2007] for protein maturation and its biological role is still matter of debate. Post-translational processing of prelamin A ends with cleavage of all the modified protein domains. Thus, farnesylation and methylation do not seem to influence the biological properties of mature lamin A. Prelamin A processing could be a fine tool to modulate lamin A levels. Alternatively, or additionally, it could facilitate nuclear envelope localization of lamin A [Sinensky et al., 1994; Corrigan et al., 2005]. Importantly, prelamin A has been shown to play itself a biological role in the regulation of chromatin dynamics [Lattanzi et al., 2007b], transcription factor translocation [Capanni et al., 2005] and cellular differentiation [Capanni et al., 2008].

B TYPE LAMINS

B type lamins are ubiquitously expressed at the nuclear envelope and at least one B type lamin is found in any developmental stage. Lamin B1 is encoded by the *LMNB1* gene on chromosome 5, while lamin B3 and B2 are alternative splicing products of the *LMNB2* gene on chromosome 19 [Biamonti et al., 1992]. Multiple serine/threonine residues in lamins undergo phosphorylation (Fig. 2). The major phosphorylation sites in lamin B2 are threonine 14, serine 17, serine 385, serine 387, and serine 401 [Kuga et al., 2010]. Threonine phosphorylation has been associated with mitotic breakdown of the lamina [Peter et al., 1990], while interphase, mostly S-phase, phosphorylation of lamin B2 has been demonstrated [Kill and Hutchison, 1995]. Some of the residues undergoing phosphorylation in lamin B1 or B2 may be also phosphorylated in other lamin forms, including lamin A or C, which suggests a concerted mechanism of regulation of some fundamental functions. Interphase phosphorylation of serine 387 is mediated by PKC [Kuga et al., 2010], while mitotic phosphorylation is mediated by cdc2 kinase, which also modifies other aminoacids. Dephosphorylation of lamin B is elicited by PP1 and it is linked to assembly of the nuclear lamina at the end of mitosis [Steen and Collas, 2001]. Importantly, lamin B, as well as lamin A/C and emerin, can be also phosphorylated during viral infections, a mechanism allowing breakdown of the lamina and representing a potential target of anti-viral therapy [Jacque and Stevenson, 2006; Camozzi et al., 2008; Leach and Roller, 2010].

The CaaX box of B type lamins is farnesylated. However, B type lamins undergo partial proteolysis by the enzyme Rce1 and remain permanently farnesylated. Farnesylation of B type lamins has been implicated in their anchorage to the nuclear membrane, but might also mediate protein–protein interactions [Maske et al., 2003; Delbarre et al., 2006].

EMERIN

Emerin is the first nuclear envelope protein associated with laminopathies [Bione et al., 1994]. It is encoded by the *EMD* gene on chromosome X and spans one transmembrane domain and a LEM domain, which binds BAF [Tifft et al., 2009]. Phosphorylation of emerin may potentially occur at 21 serine, 18 tyrosine, and 3 threonine residues (Fig. 2). Proven phosphorylation sites are serine 49, which is phosphorylated by PKA along with another as yet unidentified residue [Roberts et al., 2006] and several tyrosine residues, phosphorylated by specific kinases. Emerin is phosphorylated by non-receptor tyrosine kinases Src and Abl at residues Y59, Y74 and Y95, Y19 and Y161 [Tifft et al., 2009]. Phosphorylation is

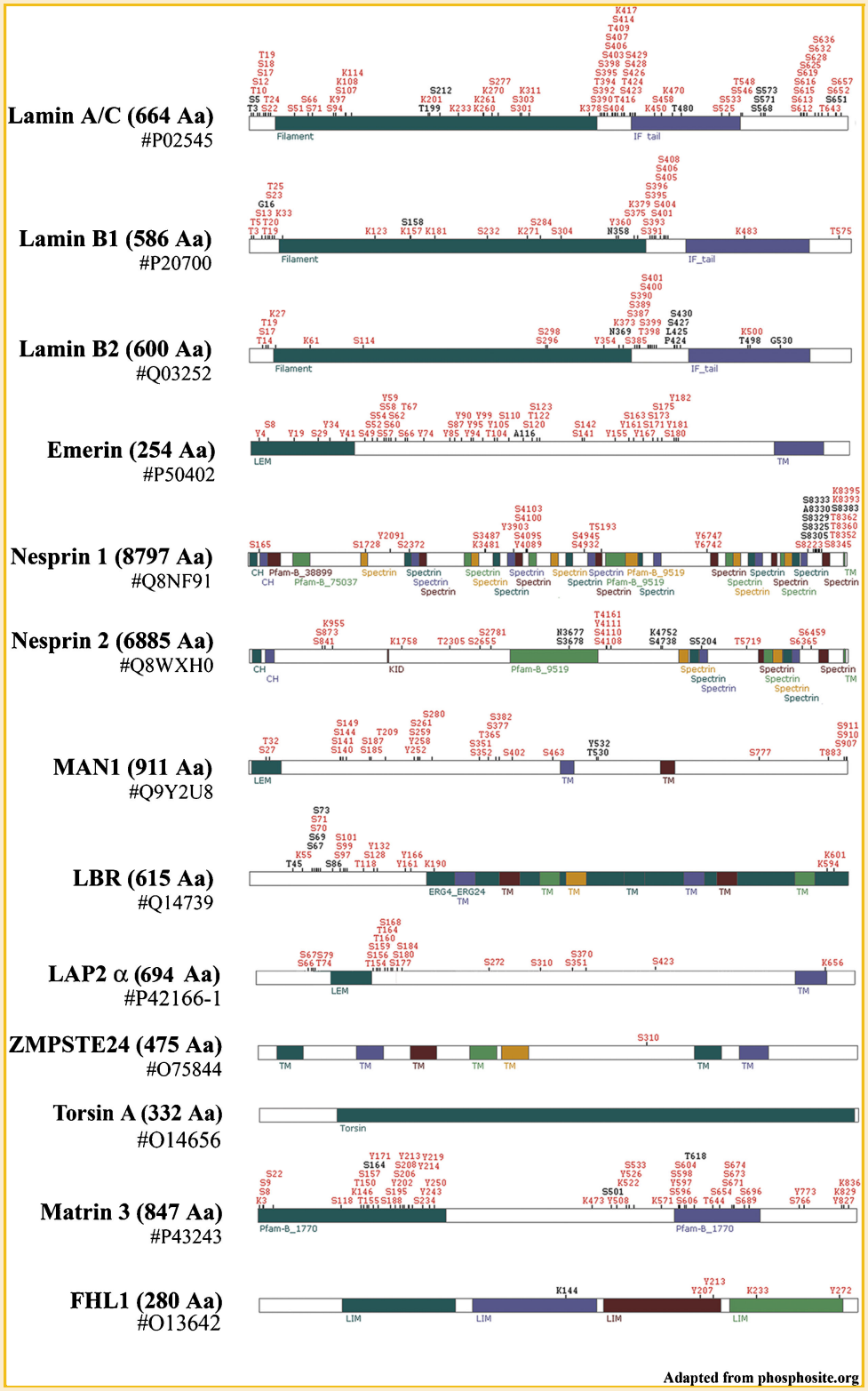

Fig. 2. Phosphosite results for the indicated human proteins (available at www.phosphosite.org). UniProtKB/SwissProt accession number and the number of amino acids are also indicated. Post-translational modification (PTM) reported are: phosphorylation at Serine (S), Threonine (T), Tyrosine (Y), and acetylation at Lysine (K). Sites are represented in red (validated) or in black (predicted). Domains abbreviations are: intermediate filament tail (IF tail); LAP2, Emerin, and MAN1 domain (LEM); trans membrane domain (TM); ergosterol biosynthesis domain (ERG4/ERG 24); calponin Homology domain (CH); KID repeat domain (KID); LIN-11, Isl1, and MEC-3 domain (LIM). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Laminopathies	Proteins and phenotypes	Signalling pathways affected
Emery-Dreifuss muscular dystrophy, X-linked (EDMD1) Emery-Dreifuss muscular dystrophy, autosomal dominant (EDMD2) Emery-Dreifuss muscular dystrophy, autosomal recessive (EDMD3) Limb-girdle muscular dystrophy type 1B (LGMD1B) Cardiomyopathy dilated	Emerin Lamin A/C Skeletal and cardiac muscular dystrophies	pRB Smads ERK/JNK MAPK Wnt
Cardiomyopathy dilated	LAP2α cardiomyopathy	pRB
Dunningham-type familial partial lipodystrophy (FPLD)	Lamin A/C lipodystrophy	SREBP1/PPARγ insulin-signaling Wnt Notch
Mandibuloacral Dysplasia type A (MADA)	Lamin A/C dysplasia and lipodystrophy	SREBP1/PPARγ TGF-β-Smads Wnt
Mandibuloacral Dysplasia type B (MADB)	FACE1 dysplasia and lipodystrophy	
Osteopoikilosis, Buschke-Ollendorff syndrome, Melorheostosis	LEMD3 skeletal dysplasia	TGF-β-Smads
Atypical Werner syndrome Hutchinson-Gilford progeria syndrome (HGPS)	Lamin A/C progeroid syndromes	IGF1 Wnt p53 Notch ING1
Restrictive dermopathy (RD)	FACE1	

Fig. 3. Signaling pathway involved in laminopathies.

required to bind BAF and to regulate BAF interaction, even if some of the phosphorylated aminoacids are outside the LEM domain [Tifft et al., 2009]. Thus, emerin can be targeted by several kinases including PKA [Roberts et al., 2006], Src, Abl, Her2 [Tifft et al., 2009], and potentially casein kinase II [Ellis et al., 1998]. Dephosphorylation of emerin occurs in vivo and it is inhibited by okadaic acid [Cartegni et al., 1997; Lattanzi et al., 2003]. Dephosphorylation by PP1 may influence emerin binding properties: in particular, the interaction of emerin with nuclear and cytoplasmic actin in mouse myoblasts is weakened by PP1 activity [Lattanzi et al., 2003]. However, since less specific dephosphorylation increases actin binding [Lattanzi et al., 2003], we suggest that there must be specific phosphorylated residues which mediate protein interaction. The significance of emerin phosphorylation/dephosphorylation events may be summarized as follows. Emerin binding to its partner proteins, including BAF and actin, is regulated by its phosphorylation status. This events may in turn affect emerin association with chromatin. Moreover, since Her2 and Src kinases regulate striated muscle function, emerin has been suggested to integrate signals at the myocyte nuclear envelope [Tifft et al., 2009].

NESPRINS

Nesprins are giant proteins of the nuclear envelope and the cytoskeleton. Nesprin 1 and 2, mutated in Emery–Dreifuss muscular dystrophy [Zhang et al., 2007] and cerebellar ataxia [Dupre et al., 2007], are encoded by the *SYNE1* and *SYNE2* genes. Fifteen serine residues in nesprin 1 and ten serine residues in nesprin 2 are potential phosphorylation sites (Fig. 2). Moreover, tyrosine and threonine residues are potential targets of phosphorylating enzymes. A proteomic study has identified acetylated lysines [Zhao et al., 2010] in the nesprin 1 sequence. Another proteomic study has shown that phosphorylation sites in the isoform 1 of nesprin 2 may be detected both in mitotic and interphase HeLa cell extracts [Dephoure et al., 2008].

MAN1

MAN1 is an integral membrane protein of the nuclear envelope which is also called LEMD3. It is encoded by the *LEMD3* gene on chromosome 12q14 [Lin et al., 2000]. Mutations in the gene give rise to Osteopoikilosis, Buschke–Ollendorff syndrome and Melorheostosis, diseases affecting bone mineralization. Twenty serine, five threonine and three thyrosine residues are potential or proven phosphorylation sites in the MAN1 sequence (Fig. 2). MAN1 is phosphorylated in mitotic Xenopus egg extracts at Thr-209, Ser-351 and Ser-402 and phosphorylation abolishes binding of the LEM domain to BAF, which in turn mediates DNA interaction [Hirano et al., 2009]. Moreover, Ser-463 is phosphorylated in interphase extracts, but the downstream events are as yet unknown [Hirano et al., 2009].

LBR

The lamin B receptor is a transmembrane protein interacting with lamin B and chromatin. Mutations in LBR are associated with mild clinical phenotypes [Shultz et al., 2003] or severe diseases such as Greenberg dysplasia, depending on the mutated site [Waterham et al., 2003]. Four potential acetyl-lysine residues have been mapped in LBR (Fig. 2). Moreover, phosphorylable sites are detected by bioinformatics analysis. A key phosphorylated site, serine 71 in LBR, is required for the assembly of the nuclear envelope at the end of mitosis [Lu et al., 2010]. Phosphorylation of serine 71 is elicited by p34(cdc2), a kinase also involved in mitotic phosphorylation of other residues in the nuclear envelope protein [Lu et al., 2010; Nikolakaki et al., 1997]. On the other hand, PP1 dephosphorylates aminoacidic residues required for binding of LBR to chromatin [Ito et al., 2007]. Thus, phosphorylation/dephosphorylation of LBR by cell cycle-dependent enzymes is used to regulate chromatin association and membrane vescicles targeting at the end of mitosis, the latter process also implicating physical interaction of LBR with importins [Lu et al., 2010; Zwerger et al., 2010].

LAP2alpha

LAP2alpha is one of the splicing products of the *TMPO* gene and it is a nuclear lamina-associated polypeptide [Dechat et al., 2000], which is prevalently localized in the nucleoplasm [Naetar et al., 2008]. LAP2alpha is phosphorylated in interphase cells and undergoes hyperphosporylation at the onset of mitosis (Fig. 2). The protein kinase CKII phosphorylates the N-terminus of LAP2alpha, while up to seven mitotic phosphorylated serines are located in the C-terminal chromatin binding domain of LAP2alpha [Dechat et al., 1998]. Phosphorylation of the latter residues by Cdk1 allows detachment of LAP2alpha from chromatin, while does not affect nuclear envelope breakdown [Gajewski et al., 2004]. The major Cdk1 phosphorylation site in LAP2alpha is serine 423, which is not sufficient, however, to allow chromatin detachment [Gajewski et al., 2004]. Nevertheless, impairment of phosphorylation at all the target sites in the protein C-terminus, makes LAP2alpha constitutively associated with chromosomes, throughout cell division [Gajewski et al., 2004].

ZMPSTE24

A relevant advance in lamin and laminopathies research will be the identification of enzymes and pathways involved in the regulation of prelamin A processing enzymes. ZMPSTE24 is a transmembrane protein of the endoplasmic reticulum and the nuclear envelope, which catalyses cleavage of prelamin A to yield mature lamin A. It has been demonstrated that its activity on prelamin A is restricted to the nuclear envelope [Barrowman et al., 2008], while prelamin A is the only substrate so far identified for this enzyme in mammalian cells [Barrowman et al., 2008]. Mutations in the FACE1 gene encoding ZMPSTE24 cause Restrictive Dermopathy (RD), when occurring in the homozygous state, or several forms of premature aging syndromes including progeria or Mandibuloacral Dysplasia (MADB), when mutations are in the heterozygous state [Agarwal et al., 2003]. Although ZMPSTE24 activation has been demonstrated to be zinc-dependent, at least in one out of the two prelamin A cleavage steps [Corrigan et al., 2005], the factors regulating its expression levels and activity are largely unknown. The best human model to study ZMPSTE24 activity should be Restrictive Dermopathy cells, which represent a knockout model for FACE1. An intriguing yet unsolved question is whether expression of ZMPSTE24 is modulated in cells during either cellular proliferation/differentiation or during cellular or organismal ageing

[Ukekawa et al., 2007]. Some evidence has been published that ZMPSTE24 expression is reduced in senescent tissues [Ukekawa et al., 2007]. However, the signaling pathways affecting ZMPSTE24 levels have not been elucidated. Interestingly, a bioinformatics analysis has identified MEF2 and p53 dependent sequences in the FACE1 promoter, suggesting that both muscle differentiation and ageing (implying MEF2 and p53 regulation, respectively) could require modulation of ZMPSTE24 expression. Consistent with these possibilities, prelamin A accumulation was determined in endothelial vascular cells during ageing [Ragnauth et al., 2010].

TORSINA

TorsinA is a nuclear membrane AAA ATPase, which is mutated in Torsion dystonia [Kim et al., 2010]. Nuclear envelope binding partners of torsinA are LAP1 and LULL1 [Kim et al., 2010]. The most likely function of torsinA is to mediate nuclear movement, while maintaining nuclear envelope integrity. Consistent with this proposed function, torsinA mutations alter the morphology of the perinuclear space [Goodchild et al., 2005], an effect also observed in Mandibuloacral Dysplasia and nesprin-linked EDMD. Nesprin 1 and 2 are, in fact, binding partners of torsinA [Nery et al., 2008]. An unbalanced cholinergic transmission plays a pivotal role in dystonia [Martella et al., 2009], but the signaling mechanisms leading to this pathogenetic effects are still elusive (Fig. 2).

MATRIN 3

Matrin 3 is a nuclear matrix protein associated with another inherited muscle disease, the autosomal dominant distal myopathy [Senderek et al., 2009]. Matrin 3 harbors 23 potentially phosphorylated serines and 12 potential phosphotyrosine residues (Fig. 2). Moreover, six lysine residues are potentially acetylated. The best known kinase targeting matrin 3 is PKA, which has been shown to phosphorylate the nuclear matrix protein in neuronal nuclei downstream of the NMDA receptors [Giordano et al., 2005]. Phosphorylation by PKA triggers matrin 3 degradation, while inhibition of PKA activity causes neuronal death [Giordano et al., 2005]. Thus, altered protein phosphorylation could be implicated in pathogenetic processes. This is particularly relevant, since matrin 3 has been shown to associate with specific chromosome territories and to be excluded from heterochromatin [Zeitz et al., 2009]. Hypothetically, it could be affected not only in autosomal dominant distal myopathy, but also in other laminopathies known to feature chromatin defects [Maraldi et al., 2006].

FHL1

FHL1, also known as SLIM1, is a LIM protein, that is, a protein harboring domains capable of binding both the transcriptional machinery and the actin cytoskeleton [Shathasivam et al., 2010]. FHL1, has been localized in the I-discs of mature muscle fibers and in the plasmalemma [Schessl et al., 2008] and it has been reported to shuttle between the nucleus and the cytoplasm in myoblasts, while it is excluded from the nucleus in myotubes [Cottle et al., 2009]. Subcellular localization of FHL1 involves its interaction with the protein phosphatase 2 (PP2) [Wong et al., 2010]. However, pathogenetic mutations in FHL1 cause massive protein mislocalization and accumulation into perinuclear aggregates called aggresomes [Schessl et al., 2008]. Importantly, FHL1 has been implicated in the regulation of myotube hypertrophy and myonuclear positioning [Cowling et al., 2008], a function shared by nesprins and SUN proteins, which is emerging as a key aspect in muscle differentiation and disease.

SIGNALING PATHWAYS AFFECTED IN LAMINOPATHIES

To understand how genetic or epigenetic variations in nuclear envelope/lamina proteins result in significant changes in cellular signaling pathways is a major goal of clinical research. This is because components of potentially affected signaling pathways turn into targets of therapeutic protocols and give hope of rescuing the disease phenotype. We will summarize in the following paragraphs the main signaling pathways which appear to be implicated in laminopathies (Fig. 3).

MUSCULAR DYSTROPHIES

pRb. pRb is implicated in the regulation of cell cycle exit through modulation of the E2F transcription factor. Deregulation of the interplay of the nuclear envelope-associated proteins with pRb and muscle regulatory factors (MRFs) results from altered expression of A-type lamins and emerin [Favreau et al., 2008]. Regenerating muscle from *Emd*-deficient mice shows altered pRb activity and a consequent delay in the induction of the muscle transcription factor MyoD [Melcon et al., 2006]. In *Lmna*-null mice, the pRb/MyoD pathway is affected and targets of pRb signaling such as MyoD, desmin and M-cadherin are downregulated [Frock et al., 2006]. Consistently, in LAP2alpha knockout muscle satellite stem cells, myogenic differentiation is delayed possibly due to lack of LAP2alpha-mediated regulation of pRb activity [Gotic et al., 2010b]. Thus, since both A-type lamins and LAP2-α are involved in the regulation of cell cycle exit through modulation of the pRb expression, localization and phosphorylation [Naetar and Foisner, 2009], altered expression of lamin A/C and emerin in EDMD muscle cells should cause altered pRb-mediated activation of cellular differentiation [Markiewicz et al., 2005; Bakay et al., 2006].

Smads. MAN1 is a negative regulator of regulatory Smad-mediated signal transduction [Lin et al., 2005]. MAN1 co-purifies with A-type lamins and binds to them directly as well to emerin. The absence of A-type lamins also affects the localization at the inner nuclear membrane of MAN1. Hence, altered expression of MAN1 or A-type lamins may impact on the ability of MAN1 to bind and regulate Smads [Bengtsson, 2007].

In fact, defects in regulatory Smads have been reported in laminopathic cells. In embryonic fibroblasts from *Lmna* null mice, it has been shown that phosphorylation kinetics of Smad2 and Smad3 induced by TGF-β are altered, with a more rapid phosphorylation occurring that dissipates faster [Van Berlo et al., 2005]. Moreover, cardiac and skeletal muscle from homozygous mice carrying the lamin A/C H222P substitution, which causes EDMD in humans, show an excess accumulation of phosphorylated Smad2 and Smad3 in nuclei [Arimura et al., 2005]. These effects could also be due to

altered interaction of A-type lamins with PPA2 phosphatase, which could result into a A-type lamin-mediated dephosphorylation of Smads [Van Berlo et al., 2005].

ERK. In satellite cells, p38 MAP kinase activation is necessary to exit the cell cycle for differentiation. ERK activation is reduced in C2C12 skeletal myoblasts treated with siRNA to knock down A-type lamins or emerin [Muchir et al., 2009]. Defective differentiation of myoblasts expressing the pathogenetic R453W *LMNA* mutation was observed, but it did not correlate with ERK 1/2 activation [Favreau et al., 2008]. Nevertheless, myogenesis was enhanced by a treatment with the ERK1/2 inhibitor PD98059 and insulin-like growth factor II, which increased the pool of dephosphorylated pRb [Favreau et al., 2008]. Thus, it is expected that, although Erk 1/2 activation may not be affected in EDMD skeletal myoblasts, stimulation of pRB dephosphorylation by inhibition of its kinase cdk4, might prove useful to rescue myogenic differentiation.

CARDIOMYOPATHY

ERK/JNK. Activated ERK 1/2 binds to lamin A/C, releasing the transcription factor cFos, which is bound to lamin A/C: this event makes cFos available for pERK-mediated activation [Gonzalez et al., 2008]. Abnormal activation of ERK and JNK activity has been reported to occur in the cardiac muscle of animal models of EDMD that feature dilated cardiomyopathy [Muchir et al., 2009], or in muscle cells lacking emerin [Muchir et al., 2007a]. In hearts of mice carrying the H222P *Lmna* mutation, the levels of phosho-JNK and phospho-ERK1/2, mediators of hypertrophic response, are increased [Muchir et al., 2007b]. A further demonstration of the key role of ERK activation in the pathogenesis of dilated cardiomyopathy is represented by the finding that the ERK inhibitor PD98059 is able to block the development of cardiomyopathy in $Lmna^{H222P/H222P}$ mice [Muchir et al., 2009]. These findings suggest that both emerin and lamin A/C are negative regulators of MAPK signaling, although the mechanism of activation of this signaling cascade following mutation of these proteins is still unclear.

Stretching forces are mediators of ERK1/2 signaling; in this contest, both lamin A/C deficient and emerin-deficient fibroblasts, in response to mechanical strain, display a reduced expression of the mechanosensitive genes *egr-1* and *iex-1* and increased percentage of apoptotic cells [Lammerding et al., 2005]. Also NF-kB has been reported to be involved in pathological cardiac hypertrophy; interestingly, NF-kB-regulated transcription in response to mechanical stress is attenuated in $Lmna^{-/-}$ cells [Lammerding et al., 2005].

pRb. A large amount of data indicate that expression of components of the pRb-MyoD signaling cascade is disrupted in both animal models of EDMD, and in EDMD1 and EDMD2 skeletal muscle [Melcon et al., 2006]. Some evidence suggests that this could also occur in cardiac tissue. A major lamin binding partner, which regulates pRb activation is LAP2alpha. A mutation in LAP2α, that interferes with lamin A binding, has been reported to cause dilated cardiomyopathy in humans [Taylor et al., 2005]. Moreover, it has been shown that knockout mice for LAP2alpha are affected by systolic dysfunction and late onset fibrosis [Gotic et al., 2010a]. The direct involvement of pRb defects in the pathogenesis of lamin-linked cardiomyopathy remains to be established.

Wnt-β-catenin. An involvement of β-catenin in the development of EDMD1 was suggested, by the observation that emerin is localized both in the nucleus and in the intercalated discs of myocardium [Cartegni et al., 1997]. Recent data have highlighted a major role of emerin in β-catenin signaling in the heart [Wheeler et al., 2010]. Emerin-β-catenin interactions, when analyzed in HEK-293 cells, indicate that over-expression of emerin inhibits β-catenin nuclear accumulation and downstream signaling, while emerin absence, as in EDMD cells, causes nuclear accumulation of β-catenin due to impaired export [Markiewicz et al., 2006; Wheeler et al., 2010]. It has been then hypothesized that the observed rapid growth of $Emd^{-/-}$ fibroblasts could depend on the activation of β-catenin [Markiewicz et al., 2006], which could account for cardiac fibrosis. More importantly, emerin has been shown to mislocalize β-catenin from the intercalated discs, a key location of β-catenin in heart, which could have deleterious effects on cardiac conduction and stress resistance [Wheeler et al., 2010].

Fibrosis has been implicated in the pathogenesis of cardiomyopathy [Kaye et al., 2010]. Increased collagen production might depend on the deregulation of TGF-β/Smad signaling in *Lmna*-null mice, which results into tissue fibrosis in both skeletal muscle and heart [Van Berlo et al., 2005]. However, increased fibrosis can also be induced by the MAPK stress signaling [Muchir et al., 2007a], as well as by the Wnt signaling, which appears to implicated into abnormal fibrogenic conversion of aged muscle satellite cells during muscle regeneration.

LIPODYSTROPHY

SREBP1/PPARgamma. Some laminopathies, including FPLD and MADA show partial lipodystrophy, whilst generalized lipodystrophy is present in MADB and HGPS. These laminopathies share the molecular defect, consisting of impaired or reduced processing of the lamin A precursor [Capanni et al., 2005; Araujo-Vilar et al., 2009; Columbaro et al., 2005] reviewed in Maraldi and Lattanzi [2007]. Adipocyte differentiation involves the induction of the transcription factor PPAR-γ, triggered by active SREBP1. A direct link between accumulation of prelamin A and alterations in the adipogenic differentiation occurring in FPLD has been then established [Capanni et al., 2005]. In cells accumulating prelamin A, an in vivo binding occurs between prelamin A and SREBP1; prelamin A sequesters SREBP1 at the nuclear rim, reducing the pool of DNA-bound active transcription factor; retention of SREBP1 causes down-regulation of PPAR-γ expression and reduces the rate of pre-adipocyte differentiation [Barroso et al., 1999; Caron et al., 2001; Capanni et al., 2005].

Importantly, PPAR-γ mutations cause FPLD3, a largely overlapping disease of adipose tissue [Barroso et al., 1999] supporting the view that a major pathogenetic pathway is triggered by altered PPAR-γ expression in FPLD. Interestingly, treatment of pre-adipocytes accumulating prelamin A with the PPAR-γ ligand TDZ elicited rescue of adipogenic program [Capanni et al., 2005], giving insight into current therapeutic approaches to lipodystrophy [Gambineri et al., 2008].

Wnt-β-catenin. Regulation of PPAR-γ levels during adipogenic conversion of human precursors has been shown to require also emerin presence in cells [Tilgner et al., 2009]. Emerin has been

shown to play a role of molecular sensor, which senses the increase in lamin A/C levels at the onset of adipogenesis. Moreover, emerin-null fibroblasts have been reported to show increased β-catenin activity and PPAR-γ accumulation in the nucleus [Tilgner et al., 2009]. The complex mechanism involving β-catenin, PPAR-γ, lamin A/C, and emerin in the regulation of adipogenic differentiation [Boguslavsky et al., 2006; Tilgner et al., 2009] needs to be further investigated and reconciled with the clinical data showing far different pathogenetic effects of emerin and lamin mutations on adipose tissue homeostasis. However, the whole evaluation of these data and of data showing prelamin A role in PPAR-γ regulation [Capanni et al., 2005; Araujo-Vilar et al., 2008] establish a central role of nuclear envelope proteins in PPAR-γ-dependent signaling.

Notch. Evidence of Notch-dependent signaling in lipodystrophy has been obtained in HGPS cells. Hyperactivation of Notch-dependent signaling has been reported. Intriguingly, hyperactivation of Notch appears to be dependent on failure of the Notch transcriptional coactivator to be retained at the nuclear lamina, as it occurs in control cells [Scaffidi and Misteli, 2008]. This finding adds to those previously reported showing that transcription factors, including SREBP1, cFos, Smads, pRb, are anchored by nuclear lamina proteins in order to regulate their localization and activity. Altered Notch signaling results into decreased adipogenic conversion of human mesenchimal stem cells, without reduction of PPAR-γ levels, but with altered PPAR-γ transactivation activity [Scaffidi and Misteli, 2008].

Insulin/IGF. Although not directly linked to lamins, insulin signaling has been demonstrated to be altered in lipodystrophy and metabolic syndromes caused by LMNA mutations [Young et al., 2005]. Impaired response to insulin signaling is a major impairment in FPLD2 and metabolic syndrome, yet it can be rescued by treatment with metformin, in combination with pioglitazone [Gambineri et al., 2008].

As a general comment on data obtained on adipocyte differentiation in laminopathies, a caveat should be considered. Diverse cellular models from different species and origin, including pre-adipocytes, mesenchimal stem cells, fibroblasts have been tested in different studies. This may account for such a complex picture emerging from the whole evaluation of published data and further suggests that the cell type truly involved in laminopathies pathogenesis in different tissues (or a common progenitor) remains to be identified.

BONE ABNORMALITIES

TGF-β-Smads. MAN1 binds to regulatory Smads, antagonizing cellular responses to TGF-β and bone morphogenic protein [Konde et al., 2010]. Human subjects with heterozygous loss of function mutations in the gene encoding MAN1 exhibit increased bone density [Hellemans et al., 2004], and overexpression of TGF-β. This causes enhanced expression of genes activated by TGF-β and BMPs, possibly due to failure of mutated MAN1 to anchor Smads [Bengtsson, 2007].

In Mandibuloacral Dysplasia, as well as in Restrictive Dermopathy and HGPS, bone resorption due to osteolysis of phalanges, clavicle, and mandible are observed [Columbaro et al., 2005; Moulson et al., 2005; Lombardi et al., 2007]. We have tested the effects of accumulation of prelamin A in peripheral blood monocytes induced to differentiate into osteoclasts by the receptor activator of NF-kB ligand (RANKL) [Zini et al., 2008]. Increased rate of cell differentiation, but reduced resorption activity of osteoclasts has been determined in the presence of high prelamin A levels [Zini et al., 2008]. Osteoclasts lacking resorptive activity, however, play a role in the regulation of osteoblast number [Karsdal et al., 2008], suggesting a function independent on bone resorption. Thus it appears likely that osteoblast proliferation/differentiation and osteoclast-osteoblast interplay are affected in laminopathic patients due to altered inter-cellular signaling. Regarding intracellular signaling, cFos, the transcription factor anchored by lamin A at the nuclear envelope, has been implicated in the osteoclast differentiation pathway [Ivorra et al., 2006; Gonzalez et al., 2008]. The actual levels and localization of cFos in laminopathic osteoblasts and osteoclasts deserves investigation.

SYSTEMIC DISORDERS IN LAMINOPATHIES

Many tissues in laminopathies are affected by degenerative processes resembling ageing, including sarcopenia, osteopenia, cardiomyopathy, lipo-atrophy, atherosclerosis, and dermo-athrophy. These disorders might reflect an altered balance between cell loss and cell replacement in stem cells. In this context, altered pRb, Wnt, and p53 signaling have been proposed as pathogenetic pathways [Hernandez et al., 2010; Liu et al., 2010; Marji et al., 2010]. Moreover, altered IGF-growth hormone dependent metabolism has been implicated in the pathogenesis of progeroid laminopathies [Marino et al., 2010].

p53. Hyperactivation of the p53 pathway occurs in *Zmpste24*-null mice and it is directly linked to premature ageing, since double knockout of p53 and Zmpste24 partially rescues the ageing phenotype [Varela et al., 2005]. Consistently, hyperactivation of p53 in p53 knockin mice triggers the ageing process, through depletion of adult stem cells [Liu et al., 2010].

Notch. Notch-dependent signaling regulates cell fate and stem cell differentiation. Defective Notch signaling has been implicated in HGPS, because stem cells from HGPS patients present an up-regulation in the expression of Notch target genes, possibly due to the increased levels of progerin [Scaffidi and Misteli, 2008]. Expression of progerin in human MSCs impairs their differentiation potential by interfering with the Notch signaling pathway, which is essential in stem cell regulation [Scaffidi and Misteli, 2008]. Because Notch3 modulates the response to vascular injury, it has been suggested that progerin-induced defects in Notch signaling contribute to alterations in the large arteries of HGPS patients [Andres and Gonzalez, 2009].

Wnt. Impaired Wnt signaling leads to dysfunction of epidermal cell renewal in Zmpste24-null mice undergoing accelerated aging [Espada et al., 2008]. This is consistent with recent data showing altered Wnt signaling in a mouse model of HGPS featuring farnesylated prelamin A accumulation [Hernandez et al., 2010]. Again, altered nuclear localization and transcriptional activity of a transcription factor, Lef1, occurs upstream of the signaling defect, a finding also confirmed in human cells [Hernandez et al., 2010]. On the other hand, altered Wnt signaling in progeroid cells affects several target genes, including those encoding extra-cellular matrix

proteins such as fibronectin and collagen I chains, leading to production of an altered matrix that affects cellular proliferation [Hernandez et al., 2010].

IGF1/GH. IGF1 signaling is an important regulator of longevity in many organisms [Fadini et al., 2010]. Progeroid Zmpste24−/− mice present transcriptional alterations in genes that regulate the somatotroph axis, as well as high circulating levels of growth hormone and reduction of IGF-1 [Marino et al., 2010]. The basis for this defective signaling appears to be an impaired response to GH, which in turn elicits altered expression of IGF1. Importantly, administration of IGF1 extends life span in progeroid mice, thus showing a major role of low IGF1 levels in the onset of premature ageing [Marino et al., 2010].

The latter observation, along with data reported on Wnt/β catenin and insulin signaling defects, suggests that signaling effectors represent promising targets of therapeutic interventions in laminopathies, provided that molecules capable of modifying these effectors are often already available.

CONCLUSIONS

The increasing interest of research on nuclear lamins and laminopathies appears mainly to depend on the unexpected finding that studies on disease pathogenesis of these very rare diseases might yield crucial insights into processes involved in metabolic disorders, cardiomyopathy and normal aging. Studies in both cellular and animal models of laminopathies have provided valuable information into the role of lamins in signaling pathways. It is evident that lamins or lamin-associated nuclear envelope proteins are required to sequester tissue-specific regulatory factors, along specific signaling pathways. This and other as yet unknown mechanisms allow lamins and their partner proteins to regulate signaling pathways involved in cell cycle exit and cellular differentiation, ultimately modulating stem cell activity and tissue homeostasis. Lamin A/C mutations may alter or upregulate the activity of multiple signaling effectors such as ERK 1/2, c-Fos, IGF, Wnt/β-catenin, SREBP1-PPAR-γ, insulin-AKT, Smads-TGF-β. Since all these molecules are involved in diverse signaling pathways, while several laminopathic disorders are tissue-specific, it remains to be established the factor(s) that confers such a specificity to the pathogenetic mechanism. Among these factors, not only lamin-binding proteins, but also epigenetic regulators such as microRNAs and modifying genes appear to play a relevant role.

So far, promising therapeutic approaches for lipodystrophy, progeria, or cardiac laminopathies have been based on medicines counteracting PPAR-γ downregulation, such as TZDs [Gambineri et al., 2008], prelamin A farnesylation, such as statins [Columbaro et al., 2005; Varela et al., 2008], or Erk 1/2 hyperactivation, such as PD98059 [Muchir et al., 2009]. Stimulation of the GH-IGF pathway is now emerging as new therapeutic approach for progeroid laminopathies [Marino et al., 2010]. Thus, it appears that improvement of our knowledge of the signaling network implicated in laminopathies will provide further targets for therapeutic strategies.

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