Understanding the Roles of Nuclear A- and B-type Lamins in Brain Development*

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The nuclear lamina is composed mainly of lamins A and C (A-type lamins) and lamins B1 and B2 (B-type lamins). Dogma has held that lamins B1 and B2 play unique and essential roles in the nucleus of every eukaryotic cell. Recent studies have raised doubts about that view but have uncovered crucial roles for lamins B1 and B2 in neuronal migration during the development of the brain. The relevance of lamins A and C in the brain remains unclear, but it is intriguing that prelamin A expression in the brain is low and is regulated by miR-9, a brain-specific microRNA.

The nuclear lamina, an intermediate filament meshwork lying beneath the inner nuclear membrane, consists mainly of four proteins, lamins A, C, B1, and B2. Prelamin A (the precursor to mature lamin A) and lamin C are alternatively spliced products of LMNA (1), whereas lamins B1 and B2 are products of independent genes, Lmnb1 and Lmnb2 (2, 3).

The nuclear lamina provides a structural support for the cell nucleus and interacts with both the chromatin and inner nuclear membrane proteins. Those functions (and the association of the nuclear lamina with disease) have been covered in other reviews (4–11). This minireview will focus on a pair of new discoveries on the biology of nuclear lamins. The first is that the B-type lamins are critical for neuronal migration in the developing brain (12–14); the second is that the expression of lamin A is negligible in mouse brain and that lamin A expression is regulated by miR-9, a brain-specific microRNA (15).

B-type Lamins

The B-type lamins, lamins B1 and B2, are expressed in nearly every cell type, starting at the earliest stages of development, and for that reason alone, they have been considered fundamental constituents of the nuclear lamina (6). This view has been supported by two arguments. First, RNAi inhibition of Lmnb1 and Lmnb2 expression in HeLa cells has been reported to arrest cell growth and lead to apoptosis, whereas knocking down LMNA expression had no such effects (16). Second, many studies have linked B-type lamins to crucial functions in the cell nucleus. For example, electron microscopy studies of B-type lamin localization in cultured cells suggested that these lamins were important for heterochromatin organization (17). Another group used a dominant-negative lamin B1 mutant to show that B-type lamins are crucial in the organization of the mitotic spindle (18). Others have suggested vital roles for B-type lamins in DNA replication (19), gene transcription (20, 21), formation of nucleoli (22), responses to oxidative stress (23), positioning of chromosomes during interphase (24), and regulating the cell cycle (25).

The welter of reports suggesting unique and crucial functions for B-type lamins in the cell nucleus almost certainly waylaid enthusiasm for generating knock-out mouse models. However, in 2004, Vergnes et al. (26) created a Lmnb1-deficient mouse (Lmnb1Δ/Δ) with a gene-trap embryonic stem cell clone (27) that yielded a lamin B1-βgeo fusion protein. This fusion lacked crucial domains of the lamin B1 protein (26) and was clearly nonfunctional. Lmnb1Δ/Δ embryos survived development but were small and died shortly after birth, with evidence of immature lungs, abnormalities in several bones, and a misshapen cranium. There were also multiple abnormalities in Lmnb1Δ/Δ fibroblasts, including misshapen cell nuclei. However, the most impressive finding in the report by Vergnes et al. (26) was that mouse embryos actually survived development without lamin B1 and that many tissues (e.g. skin, liver, heart, and skeletal muscle) were free of significant pathology.

A subsequent study of Lmnb1Δ/Δ fibroblasts by Lammerding and co-workers (28) showed that lamin B1 is crucial for anchoring the cell nucleus to the cytoskeleton. Using video microscopy, they found that the nuclei of Lmnb1Δ/Δ fibroblasts, unlike those of wild-type fibroblasts, actually spin within cells. They went on to show that the spinning could be reduced by expressing certain nesprin isoforms.

Lamins B1 and B2 have a carboxyl-terminal CAAAX motif and undergo farnesylation and methylation. Cell culture studies have indicated that these modifications are important (29), but the physiologic relevance of these modifications remains uncertain and needs testing with knock-in mouse models.

Discovery of Role for Lamin B2 in Brain Development

In 2010, Coffinier et al. (12) reported a key discovery in the biology of nuclear lamins: that lamin B2 is essential for neuronal migration in the developing brain. They used gene targeting to inactivate Lmnb2 (and simultaneously introduce a β-gal reporter). Lmnb2-deficient embryos (Lmnb2−/−) were normal in size during development, and the only significant pathology was in the brain. The cerebral cortex was small, and the layering of neurons was abnormal; the cerebellum was also small, devoid of sulci and with abnormal layering of neurons. Like the Lmnb1Δ/Δ mice, the Lmnb2−/− mice died immediately after birth. However, Lmnb2−/− embryonic fibroblasts grew normally in culture, were euploid, and had normally shaped cell nuclei (12).
The abnormal layering of neurons in the cerebral cortex of Lmnb2−/− embryos was prominent at embryonic day 16.5 (E16.5) and at all subsequent time points (Fig. 1A). Because these findings were similar to those occurring in mice with known defects in cortical neuron migration (30–32), the same authors examined neuronal migration in Lmnb2−/− embryos with BrdU birth-dating experiments (injecting BrdU at E13.5 and then assessing location of BrdU-positive cells in the brain 5 days later) (12). When embryos are injected with BrdU, neural progenitors in the ventricular zone incorporate BrdU into their DNA, and because these cells no longer divide, BrdU levels remain constant as the cells migrate to the cortical plate. The neurons that are born later, which have low levels of BrdU incorporation, migrate to higher levels in the cortical plate. In wild-type embryos, the neurons that stained intensely for BrdU were found in lower portions of the cortical plate, as expected. In contrast, the most intense BrdU staining in Lmnb2−/− embryos was observed in the superficial layers of the cortical plate, suggesting that newer (BrdU-negative) neurons lacked the ability to migrate to the superficial layers of the cortical plate (12). When BrdU was injected at E15.5, BrdU staining was intense in wild-type embryos was intense in the superficial layers of the cortical plate. In Lmnb2−/− embryos, the BrdU-positive neurons stayed in the lower layers of the cortex, again implying that they were defective in their ability to migrate to the superficial layers of the cortex (12).

Defective neuronal migration in Lmnb2−/− embryos was further supported by immunohistochemical studies with cortical layer-specific markers. In E19.5 wild-type embryos, newer NeuN-positive neurons migrated past Ctip2-positive neurons (cortical layers V and VI) into the superficial layers of the cortex. However, in Lmnb2−/− embryos, many NeuN-positive neurons accumulated in the lower levels of the cortex (below cortical layers V and VI). Also, in Lmnb2−/− embryos, FoxP1-positive neurons accumulated in the lower levels of the cortical plate and never reached their appropriate position in layers III–V of the cortex. Recently, another group generated Lmnb2−/− mice, performed similar types of BrdU labeling and immunohistochemical studies outlined earlier (12), and confirmed the involvement of lamin B2 in neuronal migration (33).

The discovery by Coffinier et al. (12) of defective glial-directed neuronal migration in Lmnb2−/− embryos might seem surprising. However, the authors argued that the role of lamin B2 in neuronal migration makes perfect sense, given that this developmental process is utterly dependent on the cell’s ability to move the cell nucleus (34). The initial step in the migration of neurons to the cortical plate is movement of a centrosome into the leading process of the cell. The next step is for cytoplasmic motors (acting along microtubules) to pull the nucleus forward toward the centrosome. Finally, once the nucleus has been translocated, the trailing process of the cell is remodeled, and the net effect is to move the cell forward (Fig. 2, left) (34). Repeated cycles of this process make it possible for neurons to traverse long distances and reach the proper layer in the cortical plate (34). The cytoplasmic proteins involved in nuclear translation and neuronal migration, e.g. LIS1, had been studied for years (31, 35, 36), but the nuclear proteins involved in this process had remained mysterious. The studies by Coffinier et al. (12) showed, for the first time, that B-type lamins play a crucial role in this process. As discussed further below, the most parsimonious model is that cytoplasmic motors tug on proteins that interact with the nuclear lamina.

The discovery of lamin B2 involvement in mammalian neuronal migration (12) had been foreshadowed by a study in Drosophila. Patterson et al. (37) showed that the Drosophila B-type lamin was involved in the migration of photoreceptor nuclei in the formation of the eye. In their study, they speculated that the Drosophila findings might be relevant to the pathogenesis of LMNA diseases in humans (e.g. muscular dystrophy and cardiomyopathy).

The nuclear lamina is located within the nucleus, separated from the cytoplasm by the nuclear membrane. In mammals, the interaction of the B-type lamins and the cytoplasmic machinery for nucleokinesis almost certainly involves nuclear envelope-spanning complexes of SUN and KASH domain proteins (14). Interestingly, Zhang et al. (38) showed that the loss of both
SUN1 and SUN2 or the deletion of the KASH domain proteins Syne-1/Nesprin-1 and Syne-2/Nesprin-2 resulted in defective neuronal migration in the developing brain.

**Discovery of Role for Lamin B1 in Brain Development**

In the initial publication on Lmnb2 knock-out mice (12) and in a subsequent commentary (14), we suggested that lamin B1 might also be important for brain development. This prediction was borne out. In 2011, we reported that in a subsequent commentary (14), we suggested that lamin B1 has roles in neuronal migration and other processes. As stated in a more recent publication (33).

Lmnb1 appears to play a role in the brain. In wild-type mice, lamins B1 and B2 are expressed at much higher levels throughout the cerebral cortex (13). In the initial publication on Lmnb2 knock-out mice (12), it was observed that lamins B1 and B2 play unique and essential functions in the cell nucleus. Rapid and complex developmental processes that would surely be affected if B-type lamins played truly unique and essential functions in the cell nucleus. For these reasons, few would have predicted that mammalian cells would be able to survive in the absence of both B-type lamins. To test this idea, Yang et al. (39) created conditional knock-out alleles for both genes (Lmnb1fl/fl and Lmnb2fl/fl) and used a keratin 14-Cre transgene (40, 41) to create mice lacking both Lmnb1 and Lmnb2 in skin keratinocytes. They chose to create keratinoocyte-specific knock-out mice because those cells proliferate rapidly and are involved in very complex developmental programs, processes that would surely be affected if B-type lamins played truly unique and essential functions in the cell nucleus. The conditional knock-out alleles and the keratin 14-Cre transgene worked as planned, completely abolishing Lmnb1 and Lmnb2 expression in skin keratinocytes (39). Remarkably, the loss of both lamins B1 and B2 in skin keratinocytes caused no pathology in skin, hair, or nails, as judged by histology, immunofluorescence microscopy, and electron microscopy. Of note, the proliferation of skin keratinocytes was unaffected (39). The loss of both B-type lamins did not lead to aneuploidy, nor did it elicit misshapen cell nuclei in keratinocytes within skin biopsies. However, when the double knock-out skin keratinocytes...
were grown on plastic plates, the frequency of nuclear blebs was increased (39).

The dispensability of B-type lamins was not a peculiarity of skin keratinocytes. Yang et al. (42) generated mice lacking both lamins B1 and B2 in liver hepatocytes. The absence of both B-type lamins had no apparent effect on liver development or liver histology, and the liver function tests were invariably normal. No misshapen nuclei were detected in the livers of Lmnb1/Lmnb2-deficient hepatocytes, although once again, the frequency of nuclear blebs was increased in hepatocytes plated on plastic dishes. The dispensability of B-type lamins in keratinocytes and hepatocytes challenges the notion that B-type lamins have *unique and essential* functions in the nucleus of all eukaryotic cells.

**Consequences of Combined Lamin B1/Lamin B2 Deficiency in Adult Brain**

To define the impact of deficiencies in lamin B1, lamin B2, or both in the adult brain, we also used conditional knock-out alleles in combination with the Ener1-Cre transgene to create forebrain-specific Lmnb1, Lmnb2, and combined Lmnb1/Lmnb2 knock-out mice (13). Each of the three forebrain-specific knock-out models exhibited neuronal migration and cortical layering defects similar to those in Lmnb2-/- and Lmnb1Δ/Δ embryos. However, unlike Lmnb2-/- and Lmnb1Δ/Δ mice, the forebrain-specific Lmnb1, Lmnb2, and Lmnb1/Lmnb2 knock-out mice were viable and appeared grossly normal, except that the cranial vault was slightly smaller than normal. The forebrain in the cranial-specific Lmnb2 knock-out mice was quite small, and it was even smaller in the forebrain-specific Lmnb1 knock-out mice (Fig. 3B). In both mice, the cellularity of the forebrain was markedly reduced (to a greater degree than in newborn Lmnb2-/- and Lmnb1Δ/Δ mice), suggesting that the loss of even one of the B-type lamins compromises the survival of neurons.

A more severe phenotype, complete atrophy of the forebrain, was observed in adult forebrain-specific Lmnb1/Lmnb2 double knock-out mice (Fig. 3B). Of note, no viable Lmnb1/Lmnb2-deficient neurons could be found in the forebrains of these mice. Thus, in contrast to the situation with Lmnb1/Lmnb2-deficient keratinocytes and hepatocytes, the loss of both B-type lamins in the forebrain is incompatible with neuronal survival. Later, another group bred mice homozygous for conventional knock-out mutations in both Lmnb1 and Lmnb2 (33). As expected, the double knock-out mice, like single knock-out mice, died at birth with severe neurodevelopmental defects.

Why are the B-type lamins seemingly dispensable in keratinocytes and hepatocytes but so crucial for survival of neurons? The answer to this question is not known with certainty, but Coffinier et al. (13) and Yang et al. (39, 42) have suggested that the explanation could relate to the fact that Lmna expression is robust in peripheral tissues such as skin and liver but negligible in the developing brain (13, 43). Thus, lamins A and C may be all that is needed for the vitality of peripheral cell types, whereas the absence of lamins A and C in the developing brain renders Lmnb1 and Lmnb2 expression essential. Circumstantial evidence leads credence to this notion. In the cortical neurons of forebrain-specific Lmnb1 knock-out embryos, there is a very high frequency of misshapen nuclei, but misshapen nuclei are largely absent in the cortical neurons of adult forebrain-specific Lmnb1 knock-out mice, when Lmna is expressed at high levels. Interestingly, misshapen cell nuclei were still observed in the dentate gyrus of those mice, a site where Lmna expression is low.

**Relevance of B-type Lamins to Human Disease**

To date, the only link of B-type lamins to human disease has been the discovery that an adult-onset autosomal-dominant leukodystrophy can be caused by LMNB1 duplications (44–47). The discovery of neurodevelopmental abnormalities in LMNB2-/- and Lmnb1Δ/Δ mice (12, 13) raises the possibility that LMNB1 and LMNB2 mutations in humans could lead to similar abnormalities. No loss-of-function mutations in LMNB1 and LMNB2 have been uncovered thus far, but we predict that, sooner or later, defects in lamins B1 and B2 will be identified in human fetuses with neurodevelopmental abnormalities. Also, because defective neuronal migration has been implicated in milder neurological diseases, e.g., epilepsy, it seems possible that LMNB1 and/or LMNB2 mutations might be uncovered in outpatients of neurology clinics, particularly with whole-exome and whole-genome sequencing becoming more common.

**A-type Lamins**

Lamins A and C, the A-type lamins, have attracted considerable scrutiny because these proteins have been linked to multiple diseases, mainly cardiomyopathy and muscular dystrophy, but also adult-onset partial lipodystrophy, peripheral neuropathy, mandibuloacral dysplasia, and Hutchinson-Gilford progeria syndrome (HGPS) (5). Gene expression and cell biological abnormalities underlying several “LMNA diseases” have been uncovered (48–54); however, the mechanisms by which specific structural alterations in A-type lamins cause one particular disease and not another are poorly understood.

Prelamin A and lamin C are identical through their first 566 amino acids, but then their sequences diverge (1). Lamin C (562 amino acids) terminates with exon 10 sequences and has six unique amino acids at its carboxyl terminus; prelamin A (664 amino acids) terminates with exon 12 sequences and has 98 unique amino acids at its carboxyl terminus (1). Lamins A and C are expressed at very low levels early in embryonic development but are expressed at high levels in most differentiated cells (13, 43). This expression pattern, combined with the fact that Lmna knock-out mice have little or no pathology at birth but later die from cardiomyopathy and muscular dystrophy (55), has fostered the view that lamins A and C have specialized functions in differentiated cells but are not important for development (6).

Prelamin A terminates with a CAAX motif, triggering farnesylation of the carboxyl-terminal cysteine, release of the final three amino acids of the protein, and methylation of the newly exposed farnesylcysteine (10, 11, 56, 57). In a final post-translational processing step, the terminal 15 amino acids, including the farnesylcysteine methyl ester, are clipped off by ZMP-STE24, releasing mature lamin A (58–60). Thus, mature lamin A lacks a farnesyl lipid anchor. Lamin C does not have a CAAX motif and is never farnesylated in the first place (1).
Why mammals synthesize both prelamin A and lamin C, rather than just one of the isoforms, is unclear. To gain insights into that issue, Lmna knock-in mice that produce exclusively lamin C or exclusively prelamin A were generated by Fong et al. (61) and Davies et al. (62). Both “lamin C-only” and “prelamin A-only” mice were fertile, healthy, and free of pathology. Thus, the unique functions for the two protein isoforms are still unclear. However, given that lamins A and C are conserved in mammalian evolution, we suspect that, with persistence and the ideal assays, unique functions for the two different proteins will eventually be uncovered.

The physiologic importance of prelamin A processing also remains unclear. To gain insights into this topic, our group created Lmna knock-in mice that produce exclusively mature lamin A (by introducing a stop codon after the last amino acid of lamin A) (63). These mice (“lamin A-only” mice) produce the mature form of lamin A directly, bypassing prelamin A synthesis and processing. The lamin A-only mice were healthy, fertile, and free of pathology. The farnesylation of prelamin A was assumed to be important for the targeting of mature lamin A to the inner nuclear membrane; however, the mature lamin A in lamin A-only mice was positioned normally at the nuclear rim, indistinguishable from mature lamin A in wild-type mice (63). In related studies, Davies et al. (62) generated Lmna knock-in mice expressing full-length non-farnesylated prelamin A and found that it also reached the nuclear rim in a normal fashion, indistinguishable from lamin A in wild-type mice.

**Prelamin A Farnesylation and Disease**

Recently, the post-translational processing of the carboxyl terminus of prelamin A has attracted considerable attention (10, 29, 57, 64, 65). When ZMPSTE24 is absent, the final endoproteolytic cleavage step does not occur, leading to an accumulation of farnesyl-prenylated prelamin A (59, 60). The farnesyl-prenylated prelamin A is targeted to the nuclear lamina and accounts for a number of disease phenotypes resembling those in progeria (e.g. slow growth, osteolytic lesions, alopecia, and loss of adipose tissue). Complete loss of ZMPSTE24 in humans causes restrictive dermopathy, a perinatal-lethal progeroid syndrome. HGPS, a progeria-like progeroid syndrome, is caused by an accumulation of a mutant farnesyl-prelamin A (called progerin) that cannot undergo the final ZMPSTE24 processing step that would normally release mature lamin A (66). The production of progerin elicits multisystem disease phenotypes resembling premature aging (e.g. atherosclerosis and osteoporosis). In mouse models of HGPS, the disease phenotypes can be ameliorated by inhibiting protein farnesylation (67–72).

**Regulation of Prelamin A in Brain by Brain-specific MicroRNA**

Progerin, the mutant prelamin A in HGPS, causes devastating disease involving multiple tissues, but affected patients are spared from senile dementia and neurodegenerative disease. Why HGPS leads to disease in some tissues but not others has been a mystery. However, in a recent study, Jung et al. (15) proposed a simple explanation: that the brain might synthesize mainly lamin C and little of the other splice isoform, prelamin A. Indeed, this is the case, at least in the laboratory mouse. In most peripheral tissues, lamins A and C are found in roughly similar amounts, but the situation is quite different in the brain (Fig. 4A). Lamin C is abundant in neurons and glial cells of the brain, whereas lamin A is restricted to vascular endothelial and meningeal cells (15).

The distinct expression pattern of lamins A and C in the brain is not due to alternative splicing. In lamin A-only knock-in mice (in which alternative splicing is absent, and all of the output of the Lmna gene is channeled into prelamin A tran-
scripts), lamin A expression in the brain was still extremely low (63). Also, in “progerin-only” knock-in mice (71), the expression of progerin in the brain was very low (Fig. 4A) (15). Jung et al. (15) went on to show that low levels of prelamin A and lamin A expression in the brain are due to a brain-specific microRNA, miR-9, which binds to the 3′-UTR of prelamin A (Fig. 4). When miR-9 is expressed in HeLa cells and cultured fibroblasts, the expression of prelamin A transcripts and lamin A protein is reduced (Fig. 4B), whereas lamin A expression in neurons is increased when miR-9 expression is inhibited with an antisense oligonucleotide (15). Mutating the miR-9 seed-binding sequences in the 3′-UTR of prelamin A abolishes the ability of miR-9 to reduce prelamin A expression levels. The expression of lamin C (which has a distinct 3′-UTR) is unaffected by miR-9 expression (15).

Prelamin A regulation in peripheral tissues and brain is depicted in Fig. 4C. The miR-9 regulation of prelamin A expression in the brain could explain why the brain is spared in children with HGPS and in mouse models of HGPS (69, 71). Whether additional factors, aside from miR-9, contribute to prelamin A regulation in the brain has not been excluded, but this issue could easily be further investigated by creating Lmna knock-in mice with a mutation in the miR-9-binding site in the 3′-UTR of prelamin A.

At this point, the “physiologic rationale” for low levels of prelamin A expression in the brain is unknown; no one knows if the expression of lamin A, rather than lamin C, would adversely affect neurons or glia in the brain. Once again, appropriate knock-in models could help to address this issue.

In addition to providing a new window into nuclear lamin biology, the studies by Jung et al. (15) suggest a potential avenue for treating prelamin A-related progeroid disorders. The brain synthesizes little prelamin A/lamin A and is unaffected by prelamin A progeroid disorders. What the brain achieves with miR-9 (i.e. down-regulating prelamin A expression) would be desirable for the tissues affected by disease. Thus, down-regulating prelamin A expression in peripheral tissues with an antisense oligonucleotide, as was suggested by Fong et al. (61), could prove useful for treating patients with prelamin A-related progeroid disorders.

REFERENCES

1. Lin, F., and Worman, H. J. (1993) Structural organization of the human gene encoding nuclear lamin A and nuclear lamin C. J. Biol. Chem. 268, 16321–16326
2. Lin, F., and Worman, H. J. (1995) Structural organization of the human gene (LMNB1) encoding nuclear lamin B1. Genomics 27, 230–236
3. Biamonti, G., Giacca, M., Perini, G., Contreas, G., Zentilin, L., Weighardt, F., Guerra, M., De la Valle, G., Saccone, S., and Riva, S. (1992) The gene for a novel human lamin maps at a highly transcribed locus of chromosome 19 which replicates at the onset of S-phase. Mol. Cell. Biol. 12, 3499–3506
4. Worman, H. J., and Bonne, G. (2007) “Laminopathies”: a wide spectrum of human diseases. Exp. Cell Res. 313, 2121–2133
5. Worman, H. J., Fong, L. G., Muchir, A., and Young, S. G. (2009) Laminopathies and the long strange trip from basic cell biology to therapy. J. Clin. Invest. 119, 1825–1836
6. Broers, J. L., Ramaekers, F. C., Bonne, G., Yaou, R. B., and Hutchinson, C. J. (2006) Nuclear laminas: laminopathies and their role in premature aging. Physiol. Rev. 86, 967–1008
7. Wilson, K. L., Zastrov, M. S., and Lee, K. K. (2001) Lamins and disease: insights into nuclear infrastructure. Cell 104, 647–650
8. Burke, B., and Stewart, C. L. (2002) Life at the edge: the nuclear envelope and human disease. Nat. Rev. Mol. Cell Biol. 3, 575–585
9. Dechat, T., Pfeffhaer, K., Sengupta, K., Shimizu, T., Shumaker, D. K., Solimando, L., and Goldman, R. D. (2008) Nuclear laminas: major factors in the structural organization and function of the nucleus and chromatin. Genes Dev. 22, 832–853
10. Young, S. G., Meta, M., Yang, S. H., and Fong, L. G. (2006) Prelamin A farnesylation and progeroid syndromes. J. Biol. Chem. 281, 39741–39745
11. Davies, B. S., Fong, L. G., Yang, S. H., Coffinier, C., and Young, S. G. (2009) The post-translational processing of prelamin A and disease. Annu. Rev. Genomics Hum. Genet. 10, 153–174
12. Coffinier, C., Chang, S. Y., Nobumori, C., Tu, Y., Farber, E. A., Toth, J. I., Fong, L. G., and Young, S. G. (2010) Abnormal development of the cerebral cortex and cerebellum in the setting of lamin B2 deficiency. Proc. Natl. Acad. Sci. U.S.A. 107, 5067–5081
13. Coffinier, C., Jung, H. J., Nobumori, C., Chang, S. Tu, Y., Barnes, R. H., 2nd, Yoshinaga, Y., de Jong, P. J., Vergnes, L., Reue, K., Fong, L. G., and Young, S. G. (2011) Deficiencies in lamin B1 and lamin B2 cause neurodevelopmental defects and distinct nuclear shape abnormalities in neurons. Mol. Biol. Cell 22, 4683–4693
14. Coffinier, C., Fong, L. G., and Young, S. G. (2010) LINCing lamin B2 to neuronal migration: growing evidence for cell-specific roles of B-type laminas. Nuclear 1, 407–411
15. Jung, H. J., Coffinier, C., Choe, Y., Beigneux, A. P., Davies, B. S., Yang, S. H., Barnes, R. H., 2nd, Hong, J., Sun, T., Pleasure, S. J., Young, S. G., and Fong, L. G. (2012) Regulation of prelamin A but not lamin C by miR-9, a brain-specific microRNA. Proc. Natl. Acad. Sci. U.S.A. 10.1073/pnas.111780109
16. Harborth, J., Elbashir, S. M., Bechert, K., Tuschi, T., and Weber, K. (2001) Identification of essential genes in cultured mammalian cells using small interfering RNAs. J. Cell Sci. 114, 4557–4565
17. Belmont, A. S., Zhai, Y., and Thilenius, A. (1993) Lamin B2 and association with peripheral chromatin revealed by optical sectioning and electron microscopy tomography. J. Cell Biol. 123, 1671–1685
18. Tsai, M. Y., Wang, S., Heidinger, J. M., Shumaker, D. K., Adam, S. A., Goldman, R. D., and Zheng, Y. (2006) A mitotic lamin B matrix induced by RanGTP required for spindle assembly. Science 311, 1887–1893
19. Moir, R. D., Montag-Lowry, M., and Goldman, R. D. (1994) Dynamic properties of nuclear laminas: lamin B is associated with sites of DNA replication. J. Cell Biol. 125, 1201–1212
20. Shimi, T., Pfeffhaer, K., Kojima, S., Pack, C. G., Solovei, I., Goldman, A. E., Adam, S. A., Shumaker, D. K., Kinjo, M., Cremer, T., and Goldman, R. D. (2008) The A- and B-type nuclear lamin networks: microdomains involved in chromatin organization and transcription. Genes Dev. 22, 3409–3421
21. Tang, C. W., Maya-Mendoza, A., Martin, C., Zeng, K., Chen, S., Feret, D., Wilson, S. A., and Jackson, D. A. (2008) The integrity of a lamin B1-dependent nucleoskeleton is a fundamental determinant of RNA synthesis in human cells. J. Cell Sci. 121, 1014–1024
22. Martin, C., Chen, S., Maya-Mendoza, A., Lovric, J., Sims, P. F., and Jackson, D. A. (2009) Lamin B1 maintains the functional plasticity of nucleoli. J. Cell Sci. 122, 1551–1562
23. Malhas, A. N., Lee, C. F., and Vaux, D. J. (2009) Lamin B1 controls oxidative stress responses via Oct-1. J. Cell Biol. 184, 45–55
24. Malhas, A., Lee, C. F., Sanders, R., Saunders, N. J., and Vaux, D. J. (2007) Defects in lamin B1 expression or processing affect interphase chromosome position and gene expression. J. Cell Biol. 176, 593–603
25. Malhas, A., Saunders, N. J., and Vaux, D. J. (2010) The nuclear envelope can control gene expression and cell cycle progression via microRNA regulation. Cell Cycle 9, 531–539
26. Vergnes, L., Péterfy, M., Bergo, M. O., Young, S. G., and Reue, K. (2004) Lamin B1 is required for mouse development and nuclear integrity. Proc. Natl. Acad. Sci. U.S.A. 101, 10428–10433
27. Stryke, D., Kawamoto, M., Huang, C. C., Johns, S. J., King, L. A., Harper, C. A., Meng, E. C., Lee, R. E., Yee, A., L’Italien, L., Chuang, P. T., Young, S. G., Skarnes, W. C., Babbitt, P. C., and Ferrin, T. E. (2003) BayGenomics: A resource of insertional mutations in mouse embryonic stem cells. Nucleic Acids Res. 31, 278–281
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28. Ji, J. Y., Lee, R. T., Vergnes, L., Fong, L. G., Stewart, C. L., Reue, K., Young, S. G., Zhang, Q., Shanahan, C. M., and Lammerding, J. (2007) Cell nuclei spin in the absence of lamin B1. J. Biol. Chem. 282, 20015–20026

29. Hennenes, H., and Nigg, E. A. (1994) The role of isoprenylation in membrane attachment of nuclear lamins. A single point mutation prevents proteolytic cleavage of the lamin A precursor and confers membrane binding properties. J. Cell Sci. 107, 1019–1029

30. Gupta, A., Tsai, L. H., and Wynshaw-Boris, A. (2002) Life is a journey: a genetic look at neocortical development. Nat. Rev. Genet. 3, 342–355

31. Wynshaw-Boris, A. (2007) Lissencephaly and LIS1: insights into the molecular mechanisms of neuronal migration and development. Clin. Genet. 72, 296–304

32. Gambello, M. J., Hirotsune, S., and Wynshaw-Boris, A. (1999) Murine modeling of classical lissencephaly. Neurogenetics 2, 77–86

33. Kim, Y., Sharov, A. A., McDole, K., Cheng, M., Hao, H., Fan, C. M., Gaiano, N., Ko, M. S., and Zheng, Y. (2011) Mouse B-type lamins are required for proper organogenesis but not by embryonic stem cells. Science 334, 1706–1710

34. Soleczi, D. J., Govek, E. E., Tomoda, T., and Hatten, M. E. (2006) Neuronal polarity in CNS development. Genes Dev. 20, 2639–2647

35. Wynshaw-Boris, A., and Gambello, M. J. (2001) LIS1 and dynein motor function in neuronal migration and development. Genes Dev. 15, 639–651

36. Vallee, R. B., and Tsai, J. W. (2006) The cellular roles of the lissencephaly gene LIS1, and what they tell us about brain development. Genes Dev. 20, 1384–1393

37. Patterson, K., Molofsky, A. B., Robinson, C., Acosta, S., Cater, C., and Fischer, J. A. (2004) The functions of Klarischt and nuclear lamin in developmentally regulated nuclear migrations of photoreceptor cells in the Drosophila eye. Mol. Biol. Cell 15, 600–610

38. Zhang, X., Lei, K., Yuan, X., Wu, X., Zhuang, Y., Xu, T., Xu, R., and Han, M. (2009) SUN1/2 and Syne/Nesprin-1/2 complexes connect centrosome to the nucleus during neurogenesis and neuronal migration in mice. Neuron 64, 173–187

39. Yang, S. H., Chang, S. Y., Yin, L., Tu, Y., Hu, Y., Yoshiyaga, Y., de Jong, P. J., Fong, L. G., and Young, S. G. (2011) An absence of both lamin B1 and lamin B2 in keratinocytes has no effect on cell proliferation or the development of skin and hair. Hum. Mol. Genet. 20, 3537–3544

40. Dassule, H. R., Lewis, P., Bei, M., Maas, R., and McMahon, A. P. (2000) Proper organogenesis but not by embryonic stem cells. J. Biol. Chem. 275, 16217–16225

41. Lee, R., Chang, S. Y., Trinh, H., Tu, Y., White, A. C., Davies, B. S., Bergo, M. O., Bennett, C. F., Bergo, M. O., and Young, S. G. (2006) Prelamin A processing of the lamin A precursor. J. Cell Biol. 174, 913–920

42. Corrigan, D. P., Kuszczak, D., Rusinol, A. E., Thewke, D. P., Hrycyna, C. A., Michaelis, S., and Sinensky, M. S. (2005) Prelamin A endoproteolytic processing in vitro by recombinant Zmpste24. Biochem. J. 387, 129–138

43. Bergo, M. O., Gavino, B., Ross, J., Schmidt, W. K., Hong, C., Kendall, G. V., Mohr, A., Meta, M., Genant, H., Jiang, Y., Wisner, E. R., Van Bruggen, N., Carano, R. A., Michaels, S., Grifyff, S. M., and Young, S. G. (2002) Zmpste24 deficiency in mice causes spontaneous bone fractures, muscle weakness, and a prelamin A processing defect. Proc. Natl. Acad. Sci. U.S.A. 99, 13049–13054

44. Pendás, A. M., Zhou, Z., Gadinaños, J., Freije, J. M., Wang, J., Hultenby, K., Astudillo, A., Wernerson, A., Rodríguez, F., Tryggvason, K., and López-Otin, C. (2002) Defective prelamin A processing and muscular and adipocyte alterations in Zmpste24-mutant mice. Nat. Genet. 31, 94–99

45. Fong, L. G., Nge, J. K., Lammerring, J., Vickers, T. A., Mett, C., Côté, N., Gavino, B., Qiao, X., Chang, S. Y., Young, S. R., Yang, S. H., Stewart, C. L., Lee, R. T., Bennett, C. F., Bergo, M. O., and Young, S. G. (2006) Prelamin A and lamin A appear to be dispensable in the nuclear lamina. J. Clin. Invest. 116, 743–752

46. Davies, B. S., Barnes, R. H., 2nd, Tu, Y., Ren, S., Andres, D. A., Spielmann, H. P., Lammerring, J., Wang, Y., Young, S. G., and Fong, L. G. (2010) An accumulation of non-farnesylated prelamin A causes cardiomyopathy but not progeria. Hum. Mol. Genet. 19, 2682–2694

47. Coffinier, C., Jung, H. J., Li, Z., Nobumori, C., Yun, U. J., Farber, E. A., Davies, B. S., Weinstein, M. M., Yang, S. H., Lammerring, J., Farahani, J. N., Bentolila, L. A., Fong, L. G., and Young, S. G. (2010) Direct synthesis of lamin A, bypassing prelamin A processing, causes misshapen nuclei in fibroblasts but no detectable pathology in mice. J. Biol. Chem. 285, 20818–20826
MINIREVIEW: Recent Insights into Nuclear Lamin Functions

64. Weber, K., Plessmann, U., and Traub, P. (1989) Maturation of nuclear lamin A involves a specific carboxyl-terminal trimming, which removes the polyisoprenylation site from the precursor: implications for the structure of the nuclear lamina. FEBS Lett. 257, 411–414

65. Lutz, R. J., Trujillo, M. A., Denham, K. S., Wenger, L., and Sinensky, M. (1992) Nucleoplasmic localization of prelamin A: implications for prenylation-dependent lamin A assembly into the nuclear lamina. Proc. Natl. Acad. Sci. U.S.A. 89, 3000–3004

66. Eriksson, M., Brown, W. T., Gordon, L. B., Glynn, M. W., Singer, J., Scott, L., Erdos, M. R., Robbins, C. M., Moses, T. Y., Berglund, P., Dutra, A., Pak, E., Durkin, S., Csoka, A. B., Boehnke, M., Glover, T. W., and Collins, F. S. (2003) Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. Nature 423, 293–298

67. Toth, J. I., Yang, S. H., Qiao, X., Beigneux, A. P., Gelb, M. H., Moulson, C. L., Miner, J. H., Young, S. G., and Fong, L. G. (2005) Blocking protein farnesyltransferase improves nuclear shape in fibroblasts from humans with progeroid syndromes. Proc. Natl. Acad. Sci. U.S.A. 102, 12873–12878

68. Yang, S. H., Bergo, M. O., Toth, J. I., Qiao, X., Hu, Y., Sandoval, S., Meta, M., Bendale, P., Gelb, M. H., Young, S. G., and Fong, L. G. (2005) Blocking protein farnesyltransferase improves nuclear blebbing in mouse fibroblasts with a targeted Hutchinson-Gilford progeria syndrome mutation. Proc. Natl. Acad. Sci. U.S.A. 102, 10291–10296

69. Yang, S. H., Meta, M., Qiao, X., Frost, D., Bauch, J., Coffinier, C., Majumdar, S., Bergo, M. O., Young, S. G., and Fong, L. G. (2006) Treatment with a protein farnesyltransferase inhibitor improves disease phenotypes in mice with a targeted Hutchinson-Gilford progeria syndrome mutation. J. Clin. Invest. 116, 2115–2121

70. Yang, S. H., Qiao, X., Fong, L. G., and Young, S. G. (2008) Treatment with a farnesyltransferase inhibitor improves survival in mice with a Hutchinson-Gilford progeria syndrome mutation. Biochim. Biophys. Acta 1781, 36–39

71. Yang, S. H., Andres, D. A., Spielmann, H. P., Young, S. G., and Fong, L. G. (2008) Progerin elicits disease phenotypes of progeria in mice whether or not it is farnesylated. J. Clin. Invest. 118, 3291–3300

72. Yang, S. H., Chang, S. Y., Ren, S., Wang, Y., Andres, D. A., Spielmann, H. P., Fong, L. G., and Young, S. G. (2011) Absence of progeria-like disease phenotypes in knock-in mice expressing a non-farnesylated version of progerin. Hum. Mol. Genet. 20, 436–444