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LINCing lamin B2 to neuronal migration

Growing evidence for cell-specific roles of B-type lamins

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Nuclear lamins are major components of the nuclear lamina, and play essential roles in supporting the nucleus and organizing nuclear structures. While a large number of clinically important mutations have been mapped to the *LMNA* gene in humans, very few mutations have been associated with the B-type lamins. We have shown that lamin B2-deficiency in mice results in severe brain abnormalities. While the early stages of forebrain development in lamin B2-deficient mice appear to be normal, cortical neurons fail to migrate and organize into proper layers within the cerebral cortex. The morphogenesis of the hippocampus and cerebellum is also severely impaired. These phenotypes are reminiscent of lissencephaly, a human brain developmental disorder characterized by an abnormal neuronal migration. Most mutations in lissencephaly patients affect cytoplasmic regulators of nuclear translocation, which is a crucial step in neuronal migration. The phenotypes of lamin B2-deficient mice suggest that lamin B2 may also play a key role in nuclear translocation. Potential mechanisms for lamin B2 involvement, which include mechanical and non-mechanical roles and participation in LINC complexes in the nuclear envelope, are discussed along with evidence that lamins B1 and B2 play distinct, cell-specific functions.

Key words: nuclear envelope, nuclear lamina, lamin B2, LINC complex, nesprin, SUN, lissencephaly, neuronal migration, cortical neurons, nuclear translocation

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Nuclear Lamins in Health and Disease

The nuclear lamina provides structural support for the nucleus and interacts with many nuclear components, including nuclear pores and chromatin.[1,2] The main components of the nuclear lamina are the lamins, a class of intermediate filament proteins found in all higher eukaryotes.[3,4] Lamins are classified into two groups: A-type lamins, which are expressed in differentiated cells and B-type lamins, which are present in all cell types including stem cells.[5,6] In mammals, the A-type lamins, predominantly lamin A and lamin C, are generated by alternative splicing of the *LMNA* transcript, whereas the somatic B-type lamins, lamin B1 and lamin B2, are encoded by two separate genes, *LMNB1* and *LMNB2*.

A-type lamins have attracted tremendous interest with the discovery that mutations in *LMNA* cause a variety of severe human genetic diseases (e.g., muscular dystrophy, cardiomyopathy, peripheral neuropathy, partial lipodystrophy), generally grouped under the term *laminopathies*.[7-9] Laminopathies are usually characterized by a late onset and often affect predominantly one tissue—skeletal and/or cardiac muscle, peripheral nerves or adipose tissue. One exception is Hutchinson-Gilford progeria syndrome (HGPS), a pediatric disorder presenting as premature aging.[10,11] Patients with HGPS typically exhibit growth retardation, osteoporosis, alopecia and eventually die from complications of occlusive cardiovascular disease.[7,8] Remarkably, however, the brain is not affected by this disease.

More than 300 human mutations have been identified in the *LMNA* gene. A large fraction of these mutations are missense mutations, but few insights have emerged between the location of a particular

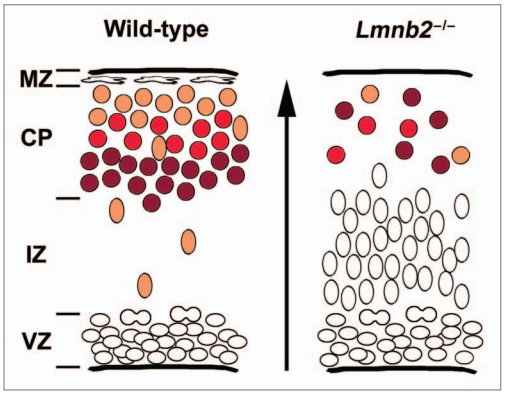

Figure 1. Neuronal migration defects in *Lmnb2* knockout mice. Comparison of the migration of cortical neurons in wild-type (left) and lamin B2-deficient (*Lmnb2*$^{-/-}$, right) brains at embryonic day 17.5. The arrow indicates the direction of migration. In wild-type brains (left), neuronal progenitors proliferate in the ventricular zone (VZ). Upon differentiation, the progenitors stop dividing and migrate across the intermediate zone (IZ) along the glial fibers. Neurons reaching the cortical plate (CP) intercalate between the marginal zone (MZ) and the neurons that arrived earlier. As a result, layers of neurons are formed, with the older neurons in the deeper layers of the cortical zone (dark red) and more recently differentiated cells (orange) located more superficially. In *Lmnb2*-deficient mice (right), most cells accumulate in the intermediate zone, and the reduced number of neurons observed in the cortical plate fail to organize into layers. Similar phenotypes are observed in other mouse models of lissencephaly.

mutation and the disease phenotype.[7,12] In particular, it is unclear why mutations in a gene that is so broadly expressed would give rise to diseases affecting only certain tissues.[8] Part of the explanation could relate to abnormalities in heterochromatin organization and secondary effects on gene expression.[13,14] Many but not all disease-causing *LMNA* mutations result in abnormal nuclear shape and defective nuclear lamina,[15-17] and defects in lamins A and C cause motion-related fragility of the nuclear envelope.[18,19]

In contrast to the situation with *LMNA*, only two diseases have been linked to mutations in *LMNB1* or *LMNB2*. Duplications of the *LMNB1* gene result in an autosomal dominant leukodystrophy (ADLD), a neurodegenerative disease with widespread loss of myelin in the adult central nervous system.[20-22] Also, one study reported an increased frequency of *LMNB2* polymorphisms in patients with acquired partial lipodystrophy (Barraquer syndrome)[23]—but firm evidence for a bona fide disease association was limited.

The remarkable disparity in the frequency of disease association for the A- and B-type lamins led us to generate a mouse model for lamin B2-deficiency. Our goal was to determine if *Lmnb2* was an essential gene for development or whether it could be redundant with *Lmnb1*. Complete redundancy of *Lmnb1* and *Lmnb2* seemed unlikely, as *Lmnb1* deficiency is lethal at birth and homozygous mice displayed impaired growth and severe lung and bone defects.[24] Our analysis of *Lmnb2* knockout mice supported the notion that *Lmnb1* and *Lmnb2* have unique functions. The most striking result of our study was the discovery that lamin B2 is essential for neuronal migration in the developing brain.

Lamin B2 is Essential for Cortical Migration

Mice homozygous for the *Lmnb2* knockout allele (*Lmnb2*$^{-/-}$) appeared normal during development but died soon after birth.[25] The most dramatic phenotype was profound disorganization of the layering of the cerebral cortex, reminiscent of lissencephaly in humans.[26,27] Like lissencephaly, we found evidence of impaired neuronal migration in *Lmnb2*-deficient brains.[25] The early stages of forebrain development were normal, but defects appeared as the cortical neurons initiated their radial migration. As neuronal progenitors exit the cell cycle and start their differentiation into neurons, they leave the ventricular zone and migrate along the glial fibers to form the cortical plate[28] (**Fig. 1**). This process was abnormal in *Lmnb2*$^{-/-}$ embryos, with most neuronal cells accumulating in the intermediate zone (**Fig. 1**).[25] Birthdating experiments and marker analysis for different layers of the cortex confirmed that most neurons failed to reach their target layers (**Fig. 1**). Morphogenesis of the cerebellum and hippocampus, which also involves neuronal migration and is sometimes perturbed in lissencephaly,[26] was also profoundly abnormal in *Lmnb2*$^{-/-}$ embryos.[25]

The brain specificity of the *Lmnb2* phenotype was surprising. *LMNA* mutations in humans affect primarily mesenchymal derivatives—muscle, heart, skin, bone and adipose tissue.[8] Also, *Lmna*-deficiency results in muscular dystrophy in young mice,[29] and *Lmna* knockout heterozygous mice manifest cardiomyopathy after one year of age.[30] *Lmnb1*$^{-/-}$ mice die at birth and display severe lung and bone abnormalities and reduced growth.[24] These differences in phenotypes led us to investigate whether differences in gene expression could underlie the brain-specific phenotype in *Lmnb2* knockout mice.

In most previous studies, the two B-type lamins were not distinguished from each other and were assumed to be expressed in all cells.[5,31] Röber et al.[31] documented lamin B expression in all mouse tissues, whereas lamin A/C expression was confined to differentiating tissues starting at embryonic day 12, with a later onset in the brain (postnatal day 5). But interestingly, tissue specificity for lamin B1 and lamin B2 expression has been reported in a few studies.[32,33] Broers et al.[32] found that lamin B2 is expressed in most human adult tissues, while lamin B1 expression was more restricted to epithelia (of note, this survey did not include brain). Takamori et al.[33] reported that lamin A/C, lamin B1 and lamin B2 were differentially expressed in the adult rat brain, and that the composition of the nuclear lamina varies during neuronal differentiation in the adult dentate gyrus and subventricular zone. We searched for differences in the expression patterns of lamins B1 and B2 in the developing mouse cortex. We found that both lamin B1 and lamin B2 were present in neuronal progenitors and differentiated neurons in wild-type embryos,

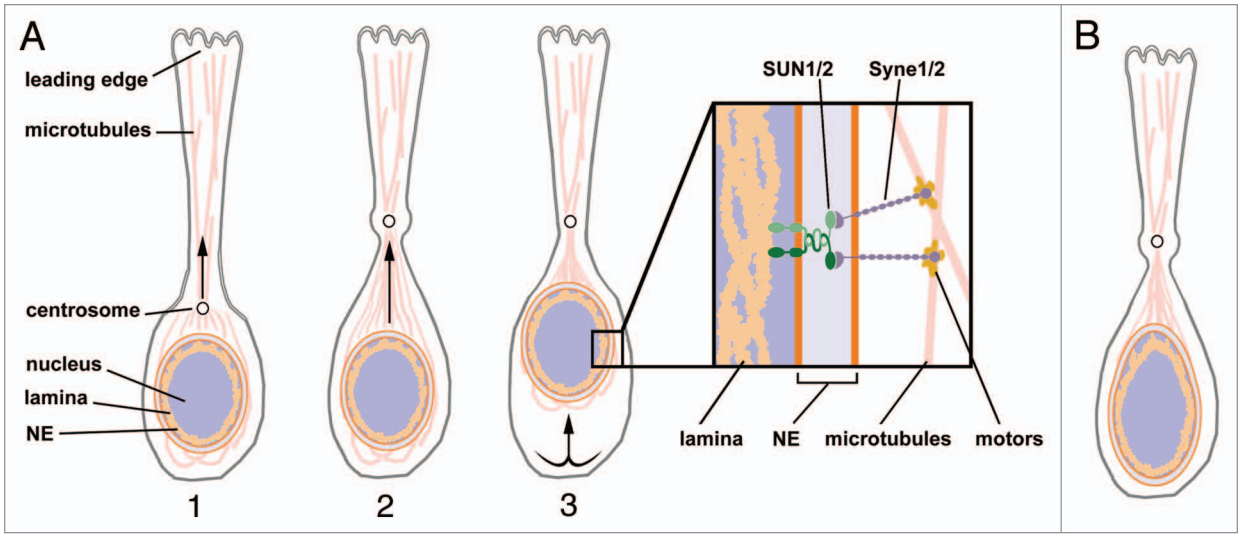

Figure 2. Nuclear movement during neuronal migration. (A) Nuclear translocation during neuronal migration in a wild-type neuron. Neuronal progression is achieved by the succession of three steps. (1) After extension of the leading process, the centrosome positioned in front of the nucleus is pulled in the direction of the leading edge. (2) The nucleus moves toward the centrosome by contraction of the microtubules. (3) The trailing process retracts, and as a result the whole neuron is moved forward. This sequence is repeated many times during cortical migration. Box: Model for a LINC complex spanning the neuron nuclear envelope, based on the similarities between phenotypes in *Lmnb2*, *Syne*-1/2 and *Sun*1/2 mutant mice. A complex involving lamin B2, SUN1/2 and Syne1/2 proteins might provide anchoring of the nucleus to the network of microtubules. Syne1/2 interaction with the microtubules is mediated by binding to motors that move along the microtubules.[38] (B) A possible mechanism for defective neuronal migration in the setting of lamin B2 deficiency. Lamin B2 deficiency might impair the mechanical properties of nuclei in neurons, and an increase in nuclear deformability could prevent nuclear translocation and adversely affect neuronal migration. NE, nuclear envelope.

at the same developmental stage affected in *Lmnb2* mutants.[25] However, we noted wide variation between cell types in the level of *Lmnb2* expression (detected with a *lacZ* reporter gene inserted at the ATG of *Lmnb2)*.[25] During brain development, *Lmnb2* was strongly expressed in neuronal progenitors in the ventricular zone; at later stages and in newborns, the ß-galactosidase activity was detected in the upper layers of the cortex, hippocampus, cerebellum and olfactory bulbs.[25] All of these structures develop rapidly, with neuronal migration playing an important role in their morphogenesis. This observation supports the concept that lamin B2 is required for neuronal migration, and that lamin B1 cannot compensate for the loss of lamin B2 in the developing brain.

Nuclear Translocation, a Crucial Step in Neuronal Migration

Neuronal migration is essential for the patterning of the cerebral cortex. While the brain continues to develop after birth, a crucial step in patterning occurs at mid-gestation, with successive waves of neurons migrating from the ventricular zone to the cortical plate. Neurons that differentiate at the same time migrate together and stop at the same level in the cortical plate (**Fig. 1**). The final position of a neuron is a strong determinant for its maturation and the establishment of neuronal connections later within the cortex. As a result, the consequences of defective neuronal migration are quite severe, as illustrated by the pathology in lissencephaly.[26,27]

Timing is critical during neuronal migration and neurons move rapidly. To reach their destination, neurons move forward by multiple cycles of "nuclear translocation" in which the nucleus is pulled toward the centrosome by dynein, a minus-end directed motor moving along microtubules.[34] Dynein is tightly regulated by cytoplasmic proteins, such as LIS1, NDE1 and NDEL1. Perturbations of those regulators impair neuronal migration and result in lissencephaly phenotypes.[35,36] But until now, no nuclear protein, and in particular no component of the nuclear lamina, had been implicated in this process. The similarity in phenotypes observed in lissencephaly and lamin B2-deficient mice strongly suggested a role for lamin B2 in anchoring the nucleus to the microtubule network during neuronal migration. However, the localization of lamin B2 inside the nucleus strongly suggests that molecular partners would be required to link lamin B2 to cytoplasmic proteins. Obvious candidates are the LINC complexes that connect the nuclear compartment and cytoskeleton.

From the Fly Eye to the Mouse Brain: LINC Complexes and Nuclear Anchoring

LINC complexes LInk the Nucleus to the Cytoskeleton and are conserved from Drosophila and *C. elegans* to mammals.[37-39] The central elements of a LINC complex are a KASH transmembrane protein in the outer nuclear membrane and a SUN protein in the inner nuclear membrane; the two proteins interact in the perinuclear space through their KASH and SUN domains (**Fig. 2A** and box). On the cytoplasmic side, KASH proteins interact with elements of the cytoskeleton (including actin, microtubules and intermediate filaments). On the nucleoplasmic side, SUN proteins are known to bind to lamins and other nuclear components. Thus far, the

only documented interaction of SUN1/2 with lamin proteins in mammalian cells involves lamin A.[39] Two major functions of the LINC complex are nuclear anchoring and nuclear migration. In mammals, research on KASH and SUN proteins has focused largely on their role in muscle differentiation, since *SYNE1* and *SYNE2*—encoding the KASH domain proteins Syne-1/Nesprin 1 and Syne-2/Nesprin 2—are both associated with muscular dystrophy.[40] Mouse studies have revealed that Syne-1/2 and Sun1/2 are required for nuclear anchoring in myocytes.[41,42]

The importance of mammalian LINC complexes is not restricted to muscle cells. Mutations in *SYNE1* have been shown to cause cerebellar ataxia in humans.[43] Recently, Zhang et al.[44] have obtained direct evidence for LINC function in the brain by reassessing the perinatal lethality of *Sun1/Sun2* double mutant mice and of mice expressing truncated forms of Syne-1 and Syne-2. They showed that the loss of both SUN1 and SUN2 or the deletion of the KASH domain in both Syne-1/Nesprin 1 and Syne-2/Nesprin 2, resulted in severe defects in neurogenesis and neuronal migration.[44] In addition, Zhang et al.[44] showed that SUN1 and SUN2 proteins form a complex with Syne-2/Nesprin 2 and play redundant functions in anchoring the nucleus to the centrosome in glial cells.

The striking similarities in brain phenotypes between the *Sun1/2*-deficient mice, the *Syne-1/2* mutants and our *Lmnb2*$^{-/-}$ mice suggest the existence of a neuronal LINC complex linking lamin B2 to the microtubule network (**Fig. 2A**). As noted earlier, only lamin A has been reported to interact with SUN1/2 in mammalian cells,[39] but Drosophila B-type lamin has been described as an element of a LINC complex required for eye development.[45,46] Nuclear migration is essential for photoreceptor differentiation in the fly, and a failure of the nucleus to reach an apical position results in abnormal eye development. Patterson et al.[45] showed that this process depends on a connection between centrosome and nucleus, and that this connection requires Lamin Dm0 (the Drosophila B-type lamin) and Klarsicht, a founder protein of the KASH family.[45] Further studies have shown that the interaction of Klarsicht with Lamin Dm0 is mediated by the SUN protein Klaroid.[46]

These studies in Drosophila support the hypothesis that mammalian lamin B2 might be part of a LINC complex. However, until a direct interaction between lamin B2 and one of the SUN proteins is demonstrated, other mechanisms and molecular partners cannot be excluded.

Perturbations of Nuclear Lamina and Altered Nuclear Mechanics

Another model to explain the *Lmnb2* neuronal phenotype could involve impaired nuclear mechanics (**Fig. 2B**). Several *LMNA* mutations affect the stiffness of the nuclear envelope.[17,18] Lamin B1 deficiency does not perturb the nuclear mechanics in fibroblasts,[18] but nevertheless causes severe nuclear shape abnormalities.[24] Also, the nuclei of lamin B1-deficient fibroblasts spin inside the cell, a striking phenotype that almost certainly indicates a defect in nucleus anchoring.[47] (It is not known whether this finding is specific for cultured fibroblasts, nor whether the nuclei of lamin B2-deficient fibroblasts spin).

Taken together, these observations might help to explain the sensitivity of neurons to an absence of lamin B2. Several studies have reported that migrating neurons display irregular nuclear shape,[48,49] most likely a consequence of the substantial deformation forces that accompany neuronal migration. It seems possible that lamin B2 might play a key role in supporting nuclear shape, and the absence of lamin B2 might result in increased deformability of the nucleus (**Fig. 2B**). Increased deformability of the lamina might significantly delay the migration of neurons, resulting in disorganized cortical layers. This model remains to be tested.

Defining Specific Functions for Lamin B1 and Lamin B2

B-type lamins are commonly considered as a single entity, but the analysis of *Lmnb1* and *Lmnb2* mutant mice has proven otherwise. Although both *Lmnb1* and *Lmnb2* mutants die soon after birth, *Lmnb2*-deficient embryos were normal in size, and the lungs and bones developed normally[25]-in contrast to the *Lmnb1* knockout phenotype.[24] It is unknown if the brain is affected by *Lmnb1* deficiency, but the reduced size of the head of *Lmnb1* mutants provides a hint that brain pathology might exist. Studies with cultured cells also support distinct functions for lamin B1 and lamin B2. Vergnes et al.[24] found that *Lmnb1*-deficient embryonic fibroblasts displayed severe abnormalities of the nuclear envelope with numerous blebs,[24] while *Lmnb2*-deficient fibroblasts have a normal nuclear morphology.[24,25] In addition, lamin B1-deficient fibroblasts develop severe polyploidy, exhibit slow growth and enter senescence prematurely.[24] These defects could relate to the proposed role of lamin B1 in mitotic spindle assembly.[50] In contrast, lamin B2-deficient fibroblasts have a normal chromosome count and proliferate normally.[25] These phenotypic differences support the idea that *Lmnb1* and *Lmnb2* play unique functions in mammals. However, additional studies will be required to understand specific functions of these two lamins and to identify binding partners in different tissues.

Concluding Remarks and Perspectives

Studies of human mutations and a variety of mutant mouse models have greatly expanded our understanding of the A-type lamins, although more work is needed to understand why different mutations in *LMNA* cause different disease phenotypes. By comparison, B-type lamins have been neglected. The finding of neuronal migration defects in lamin B2-deficient mice promises to change this situation, and should energize efforts to better understand the functions of both lamin B1 and lamin B2. We hope that future efforts will involve human geneticists, as we strongly suspect that "*LMNB2* diseases" exist in humans. If the mouse is a useful guide, *LMNB2* mutations will likely be uncovered in human patients with neurodevelopmental disorders, and not with the spectrum of diseases typically associated with *LMNA* mutations.

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