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The function of lamins in the context of tissue building and maintenance

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Lamins are the major structural components of the nuclear lamina found in metazoan organisms. Extensive studies using tissue culture cells have shown that lamins are involved in a wide range of basic cell functions. This has led to the prevailing idea that a given animal cell needs at least one lamin protein for its basic proliferation and survival. However, recent studies have shown that lamins are dispensable for the proliferation and survival of mouse embryonic stem cells (ESC). In contrast to a lack of essential functions in ESCs, certain differentiated cells lacking B-type lamins exhibit increased cell cycle exit rates and enhanced senescence. In this Extra View, we discuss how studies using animal models and cell cultures have begun to reveal cell-type specific functions of lamins in tissue building and homeostasis.

Introduction

The metazoan nucleus contains type V intermediate filament proteins called lamins.[1] Depending on the organism, single or multiple lamin-coding genes express these proteins that assemble into a network underlying the inner nuclear membrane. This network interacts with inner nuclear membrane proteins and nuclear pores to form the nuclear lamina (NL). The SUN (Sad1 and UNC-84) proteins are among the inner nuclear membrane proteins that interact with lamins. The SUNs in turn bind to the outer nuclear membrane proteins called KASH (Klarsicht, ANC-1, Syne homology) through their nuclear membrane luminal domains.[2] Since both the cytoplasmic domain of the KASH proteins and some nucleoporins[3] directly interact with cytoskeletal proteins, the NL is connected to the cytoskeleton network through multiple points of contact. Within the nucleus, the NL interacts with chromatin and different nuclear proteins, including transcription factors. This extensive interaction network formed by the NL strongly suggests that it plays an important role in modulating nuclear and cytoplasmic functions.

Studies using cell-free assays or tissue culture cells that express several A- and B-type lamins have shown that lamins regulate nuclear pore assembly, DNA replication, transcription, spindle morphogenesis and cell survival.[1,4] Thus, it is generally believed that a given animal cell needs to express at least one type of lamins to proliferate and survive. However, this notion has not been rigorously tested. Whereas A- and B-type lamins differ in their C-terminal processing and prenylation,[1] the overall amino acid identities in pair-wise comparisons reveal ~50% identity. This suggests that they could share redundant functions, which complicates phenotypic analyses and assignment of functions. Additionally, although organisms such as Drosophila or *C. elegans* have fewer lamin genes than vertebrates, the maternally supplied lamin proteins and mRNA can still complicate the interpretation of lamin deletion phenotypes. In this article, we will discuss the function of lamins in light of recent findings.

Lamins are Required for Proper Development

Studies of lamins using *C. elegans*, Drosophila and mice have contributed significantly toward our understanding of these proteins in vivo. RNAi-mediated depletion of the single lamin protein (Ce-lamin) expressed from *lmn-1* gene in *C. elegans* results in defects in cell cycle progression and chromosome segregation, leading to embryonic lethality.[5] However, *C. elegans lmn-1* nulls survive to adulthood but are sterile and have reduced lifespan compared with wild-type controls.[6] The difference in the severity of phenotypes could be due to the maternally supplied Ce-lamin mRNA that is removed by RNAi at the early stage of oogenesis but not in lmn-1 null embryos derived from heterozygote mating. Nonetheless, since at least some adult worm cells should have depleted the maternally expressed Ce-lamin, these findings indicate that some animal cells may not need lamins for their survival.

Drosophila has one A- and one B-type lamin expressed from *LamC* and *LamDm0*, respectively. Whereas *LamDm0* is expressed ubiquitously, clear expression of *LamC* appears during larval stages.[7] Similar to *C. elegans*, RNAi of *LamDm0* leads to severe embryogenesis defects,[8] but *LamDm0*-null Drosophila survive to late pupal stages with a few eclosed adult flies that die within a few days.[9] One likely explanation for the discrepancy is that the maternally supplied *LamDm0* mRNA and protein could support more significant development of the *LamDm0*-null animals than the RNAi-treated flies that would only have the maternal *LamDm0* protein. Interestingly, even after *LamDm0* becomes depleted, cell proliferation appears to continue at least in certain tissues in pupal and the rare adult flies.[9] This lack of defects in cell proliferation could be due to compensation from the expression of *LamC* during larval stages. Consistent with a function of *LamC* in development, the *LamC*-null flies exhibit prepupal lethality.[10]

Similar to Drosophila, the A-type lamins encoded by the *Lmna* gene in mammals are only expressed in certain differentiated cells during development, whereas the two B-type lamins, lamin-B1 and lamin-B2, encoded by *Lmnb1* and *Lmnb2*, respectively, are expressed ubiquitously. Mice null for *Lmna* can develop and are viable but have general growth retardation and defects in cardiac and skeletal muscles, and they die by 8 weeks of age.[11] Interestingly, mice that harbor either a truncation of *Lmnb1* ($Lmnb1^{\Delta/\Delta}$, which expresses only the N-terminal half of lamin-B1 protein) or *Lmnb2* deletion ($Lmnb2^{-/-}$) can develop to birth but die shortly thereafter.[12,13] $Lmnb1^{\Delta/\Delta}$ mice exhibit defects in the lung and bone,[12] whereas $Lmnb2^{-/-}$ mice have defects in brain development in part due to defects in neuronal migration.[13,14] Thus, whereas individual B-type lamins is required for postnatal mouse survival, it remains unclear whether lamins are essential for cell proliferation, survival or differentiation.

Further analyses using Cre-recombinase-mediated tissue-specific deletion of B-type lamins show that keratinocytes and hepatocytes depleted of lamin-Bs (but still express A-type lamins) have no obvious defects.[15,16] By contrast, forebrain specific deletion of B-type lamins leads to a dramatic reduction in brain size and disorganization of the cortex.[17] Since embryonic brains express very little A-type lamins,[18] the different effects of lamin-B loss in the skin and liver vs. the brain could be due to functional compensation of lamin-B by lamin-A in the skin and liver.

Taken together, while in vivo studies have established the important functions of lamins in development, they also suggest that certain cells in an organism may not need lamins for their basic proliferation and survival. However, due to the perdurance of maternally supplied mRNA/protein (in Drosophila and *C. elegans*) and the potentially redundant functions shared between A- and B-type lamins (in Drosophila and mice), the possibility that lamins are required for cell proliferation and survival remains.

Lamins are Not Essential in Mouse Embryonic Stem Cells

To determine whether lamins are essential for many of the basic cell functions in all cells, it is necessary to delete all lamins in a given cell type and analyze the effects. To ensure complete removal of lamin proteins, we deleted both the promoters and the first exons of *Lmnb1* and *Lmnb2*.[19] Using blastocysts obtained from heterozygote mating, we derived ESCs lacking lamin-B1, lamin-B2 or both. ESCs do not express A-type lamins. Consistent with this, none of our ESCs express A-type lamins based on western blotting and qPCR analyses. Thus, our lamin-B double knockout ESCs do not express any lamins. Surprisingly, these lamin-null ESCs exhibit similar proliferation rates as the control wild-type ESCs.[19] Lamin-null ESCs also do not exhibit any increase in cell death compared with controls under standard ESC culturing conditions. There is a slight delay in prometaphase, which may indicate minor defects in spindle morphogenesis or orientation during mitosis. However, since lamin-null ESCs can be propagated up to at least 25 passages without significant differences in their karyotypes compared with controls, the minor prometaphase delay does not affect chromosome segregation in lamin-null ESCs. Thus, lamins are not essential for cell proliferation and survival in ESCs.[19] Further analyses reveal that lamin-null ESCs have indistinguishable nuclear morphology compared with controls. Both nuclear pores and nuclear envelopes have similar appearances between lamin-null and control ESCs.[19] Therefore, lamins are also not required for maintaining nuclear pore distribution and nuclear morphology in ESCs.

Extensive studies have shown that lamins can regulate gene expression through their direct binding to chromatin.[20-24] By mapping lamin-B binding to chromatin using the Dam-ID (DNA adenine methyltransferase IDentification) technique, a strong correlation between lamin-B binding and gene silencing has been reported in reference 25. Lamin-null ESCs have allowed us to test whether this correlation reflects a general role of lamin-B in repressing its bound genes. Using microarray and Dam-ID analyses, we show that whereas lamin-B binding to genes is correlated with their lack of expression, such binding does not have a general role in repressing the bound genes in ESCs.[19]

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B-type Lamins are Not Essential for Initiating Lineage Specification but are Required for Postnatal Survival in Mice

In addition to no requirement of lamins in the proliferation and survival in ESCs, we found that lamin-null ESCs can also undergo lineage specification in vitro. Indeed, trophectoderm cells differentiated from lamin-null ESCs upregulate their lineage markers with similar efficiencies as those from control ESCs. Since the expression of lineage-specific proteins occur before lamin-A protein, it appears that lamins are not required for lineage specification of ESCs.[19]

Strikingly, mice harboring germline deletions of both lamin-B1 and -B2 can develop to birth with grossly normal body plans, heartbeats and paw-pinching responses.[19] Thus B-type lamins are not required for lineage specification and further differentiation of different tissues and organs. However, since A-type lamins begin to express from embryonic (E) day 12 in certain embryonic tissues,[26] they could compensate for the loss of B-type lamins in these tissues during development. Such compensation coupled with the lack of functions of lamins in lineage specification and early organogenesis could explain why lamin-B-null mice can develop to birth. To precisely determine the requirement of lamins in development, it is necessary to remove all three lamin genes in the germline.

Nonetheless, analyzing mice null for B-type lamins has yielded important information regarding the functions of these proteins. Although lamin-B1 and -B2 double knockout (DKO, *Lmnb1*$^{-/-}$*Lmnb2*$^{-/-}$) mice can develop to birth, all pups fail to breathe and die soon after. Starting from E13.5, *Lmnb1*$^{-/-}$*Lmnb2*$^{-/-}$ mice exhibit significantly lower body weights than control littermates. *Lmnb1*$^{-/-}$*Lmnb2*$^{-/-}$ mice also exhibit microcephaly, defects in lungs, and extremely thin diaphragm muscles. Poor phrenic nerve innervation in the diaphragm and defects in the lung could explain why the newborn *Lmnb1*$^{-/-}$*Lmnb2*$^{-/-}$ pups are unable to breathe.[19]

Previous analyses have shown that *Lmnb1*$^{\Delta/\Delta}$ or *Lmnb2*$^{-/-}$ mice also die soon after birth.[12,13] Consistently, we found that our *Lmnb1*$^{-/-}$ or *Lmnb2*$^{-/-}$ newborn pups also fail to breathe. Interestingly, compared with *Lmnb1*$^{-/-}$ mice, *Lmnb2*$^{-/-}$ mice have a better-developed lung. However, both phrenic nerve innervation and the diaphragm muscle are defective in *Lmnb1*$^{-/-}$ or *Lmnb2*$^{-/-}$ mice, which alone could contribute to the failure to breathe in lamin-B single knockout mice.[19]

B-type Lamins are Required for Proper Cellular Organization in Several Organs

Although our understanding of the role of B-types lamins in mice is still at its infancy, studies of both the germline and conditional knockout mice strongly suggest that they are required for proper cellular organization of many organs examined thus far. Among the examined organs, the role of lamin-B in the brain has been studied in most detail.

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Lamin-B in neuronal migration. Consistent with a role of lamin-B2 in neuronal migration reported previously in reference 13, our studies of the brain in the setting of conventional lamin-B1 and -B2 DKO mice showed that although these proteins are not essential for the formation of different neurons as judged by neuronal marker staining, neurons fail to migrate to their proper positions in the brain.[19] Tissue specific DKO of lamin-B1 and -B2 in the forebrain showed similar neuronal migration defects, which demonstrates a brain specific function of lamin-B in neuronal migration during development.[17] However, since the migration assay used in these studies is based on BrdU immunohistochemistry to date the birth and final positions of neurons, how lamin-Bs contribute toward neuronal migration remains unclear.

As described in the introduction, the NL is connected to the cytoskeleton through KASH and SUN proteins. Disrupting any lamin protein could interrupt the connection between the nucleus and the cytoskeleton,[27] which would hinder cell migration. Indeed, studies of *Lmnb1*$^{\Delta/\Delta}$ mouse embryonic fibroblasts (MEFs) have shown an increased nuclear spinning as compared with wild-type MEFs,[28] suggesting that the nuclei are not connected to the cytoskeleton properly. Additionally, *Lmna*$^{-/-}$ MEFs have migration defects, which can be explained by the disrupted connection between the cytoskeleton and the nucleus.[29,30] Further studies employing live imaging techniques should help to better define the role of lamin-B in neuronal migration.

Lamin-B in cell survival and proliferation during brain development. Analyzing the cerebral cortex of *Lmnb1*$^{-/-}$*Lmnb2*$^{-/-}$, *Lmnb1*$^{-/-}$, *Lmnb1*$^{\Delta/\Delta}$ and *Lmnb2*$^{-/-}$ mice showed that B-type lamins are required for protecting both neural progenitor cells (NPC) and neurons from apoptosis.[17,19] *Lmnb1*$^{-/-}$*Lmnb2*$^{-/-}$ mice exhibit the strongest apoptosis phenotype followed by *Lmnb1*$^{-/-}$ and *Lmnb2*$^{-/-}$ mice. Thus, lamin-B1 appears to make a bigger contribution toward cell survival than lamin-B2.[19] Based on analyses of *Lmnb1*$^{-/-}$*Lmnb2*$^{-/-}$ mice using BrdU/Ki67 double labeling, the NPCs in the cerebral cortex exhibit increased rates of cell cycle exit compared with controls,[19] which is consistent with the reduced number of Sox2 positive NPCs in *Lmnb1*$^{\Delta/\Delta}$ mice as judged by Ki67/Sox2 double staining.[17] Consistently, studies using different human primary fibroblasts showed that varying the amounts of lamin-B alters the proliferation capacity of these cells.[31,32] Thus, although lamins are not required for ESC survival or proliferation, B-type lamins are needed either directly or indirectly in preventing certain differentiated cells from apoptosis and/or modulating their proliferation potential.

Lamin-B in nuclear morphology of neurons. Although we did not observe a gross defect in nuclear morphology such as nuclear blubs in neurons of our *Lmnb1*$^{-/-}$, *Lmnb2*$^{-/-}$ or *Lmnb1*$^{-/-}$*Lmnb2*$^{-/-}$ mice,[19] another study has shown several nuclear defects in various mutant settings.[17] Neurons in *Lmnb1*$^{\Delta/\Delta}$ brains exhibit nuclear blebs and asymmetric distribution of lamin-B2 compared with controls. Conversely, lamin-B1 distribution in lamin-B2-null neurons (in both the conventional and forebrain-specific-knockout mice) appears normal, but the nuclei are more elongated than controls. The difference between the two studies could be due to different knockout strategies and/or strain background. Nonetheless, the defects in nuclear

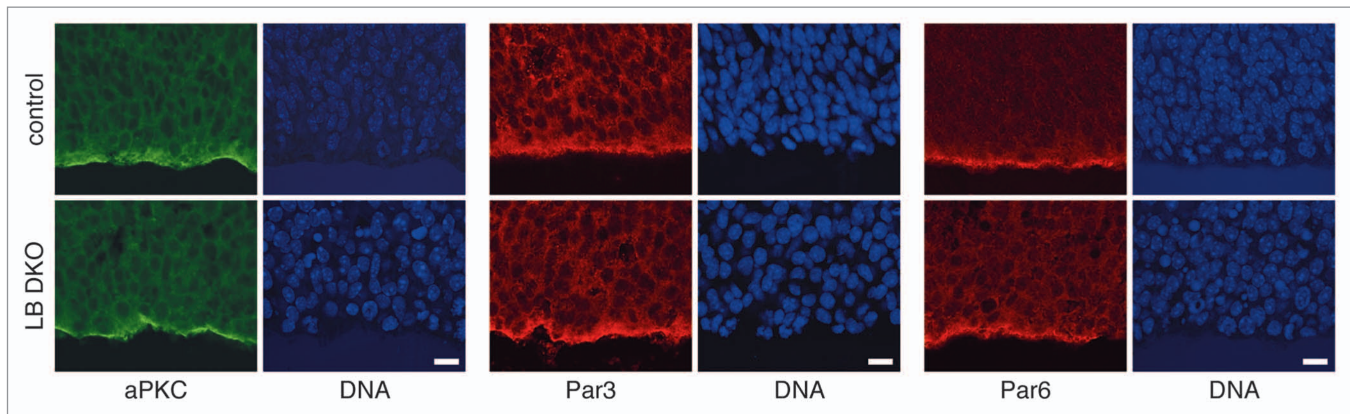

Figure 1. The E14.5 cerebral cortices of control and *Lmnb1*$^{-/-}$*Lmnb2*$^{-/-}$ (LB DKO) mice were labeled by antibodies to aPKC, Par3 or Par6. The nuclei were counterstained using Hoechst dye. Both control and lamin-B-null cortices exhibit similar enrichment of the three polarity proteins to the apical surface. Scale bars 10 μm.

morphology in neurons contrast with the lack of a requirement of lamins in maintaining nuclear morphology in ESCs.[19] ESCs have significantly less cytoplasm and a very rudimentary cytoskeletal organization compared with neurons. If an important function of lamins in the NL is to physically withstand cytoskeletal forces exerted on the nucleus, the minimal cytoskeletal structure and cytoplasm could explain why lamins are dispensable in ESCs.

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Lamin-B in spindle orientation in NPCs. We found that NPCs in the cerebral cortex of *Lmnb1*$^{-/-}$, *Lmnb2*$^{-/-}$ and *Lmnb1*$^{-/-}$*Lmnb2*$^{-/-}$ mice all exhibited defects in spindle orientation.[19] How does lamin-B regulate spindle orientation in NPCs? Lamin-B could indirectly affect spindle orientation by disrupting cell polarity in NPCs. However, immuno-staining revealed similar apical localization of polarity proteins such as aPKC, Par3 and Par6 in both lamin-B DKO and control cerebral cortices (**Fig. 1**). Thus, the spindle orientation defects are unlikely due to cell polarity defects in NPCs. Studies in HeLa cells, Xenopus egg extracts and Drosophila early embryos have shown that B-type lamins help to maintain mitotic spindle morphology as part of the spindle matrix or spindle envelope that is associated with spindle microtubules.[33-36] Thus, lamin-B knockout NPCs may fail to maintain proper spindle morphology, which in turn leads to defects in spindle orientation. Dynein is also required for spindle orientation in NPCs. Since dynein regulates the assembly of the lamin-B-containing spindle envelope,[34] it is possible that lamin-B functions downstream of the dynein pathway to regulate spindle orientation in NPCs.

We note that although ESCs lacking all lamins have normal overall proliferation rates compared with controls, the time lamin-null ESCs spend in prometaphase/metaphase appears slightly longer than wild-type cells. It is possible that a minor morphology defect in spindles in the absence of lamins contribute toward this slight delay. However, since proper orientation of cell division planes is not required for ESC proliferation, such minor defects could be tolerated in ESCs. By contrast, proper spindle orientation has been implicated in controlling symmetric or asymmetric divisions of NPCs.[37] The spindle orientation defects observed in lamin-B deficient NPCs could contribute toward their increased rate of cell cycle exit and reduced cell numbers. Studies using conditional knockout mice should help to better define how the role of lamin-B in mitosis contributes to brain development.

The role of lamin-B in other organs. Besides the brain, published studies have analyzed the effect of lamin-B deletions in the lung, bone, diaphragm, liver and skin.[12,15,16,19] While *Lmnb1*$^{\Delta/\Delta}$ mice exhibit bone defects,[12] both *Lmnb1*$^{\Delta/\Delta}$ and *Lmnb1*$^{-/-}$ mice also exhibit defects in the diaphragm and the lung.[12,19] Although the lung of *Lmnb2*$^{-/-}$ mice appears grossly normal,[13,19] our further analyses revealed a clear difference in lung airway epithelial cell organization between *Lmnb2*$^{-/-}$ and control mice, suggesting that mouse lungs need both lamin-B1 and -B2 for proper functions (**Fig. 2**).

Among the analyzed tissues/organs that have been published, both the skin and liver do not appear to require B-type lamins.[15,16] Conditional deletion of lamin-B1 and -B2 in the proliferating basal cells of the epidermis showed that B-type lamins are not required for keratinocyte proliferation or the development of skins and hairs in mice. Similarly albumin-Cre-mediated conditional deletion of B-type lamins in postnatal mouse hepatocytes also did not cause obvious defects in the liver. However, the embryonic keratinocytes and postnatal hepatocytes express abundant lamin-A, it is therefore possible that A-type lamins can compensate for the function of lamin-Bs in these cells. Previous studies have shown the lack of A-type lamin expression in several embryonic tissues such as the liver, lung and several cell types in the hematopoietic system.[26,38,39] Therefore, it is possible that embryonic deletion of B-type lamins would lead to defects in these embryonic organs. With the availability of both germline and conditional lamin-B knockout mice, it is now possible to establish the role of B-type lamins in different organ/tissues.

Taken together, although mice without B-type lamins develop to birth, published studies suggest that these lamins are required for proper cellular organization and/or proper function of multiple organs examined so far. Considering that the amino acid identity shared between

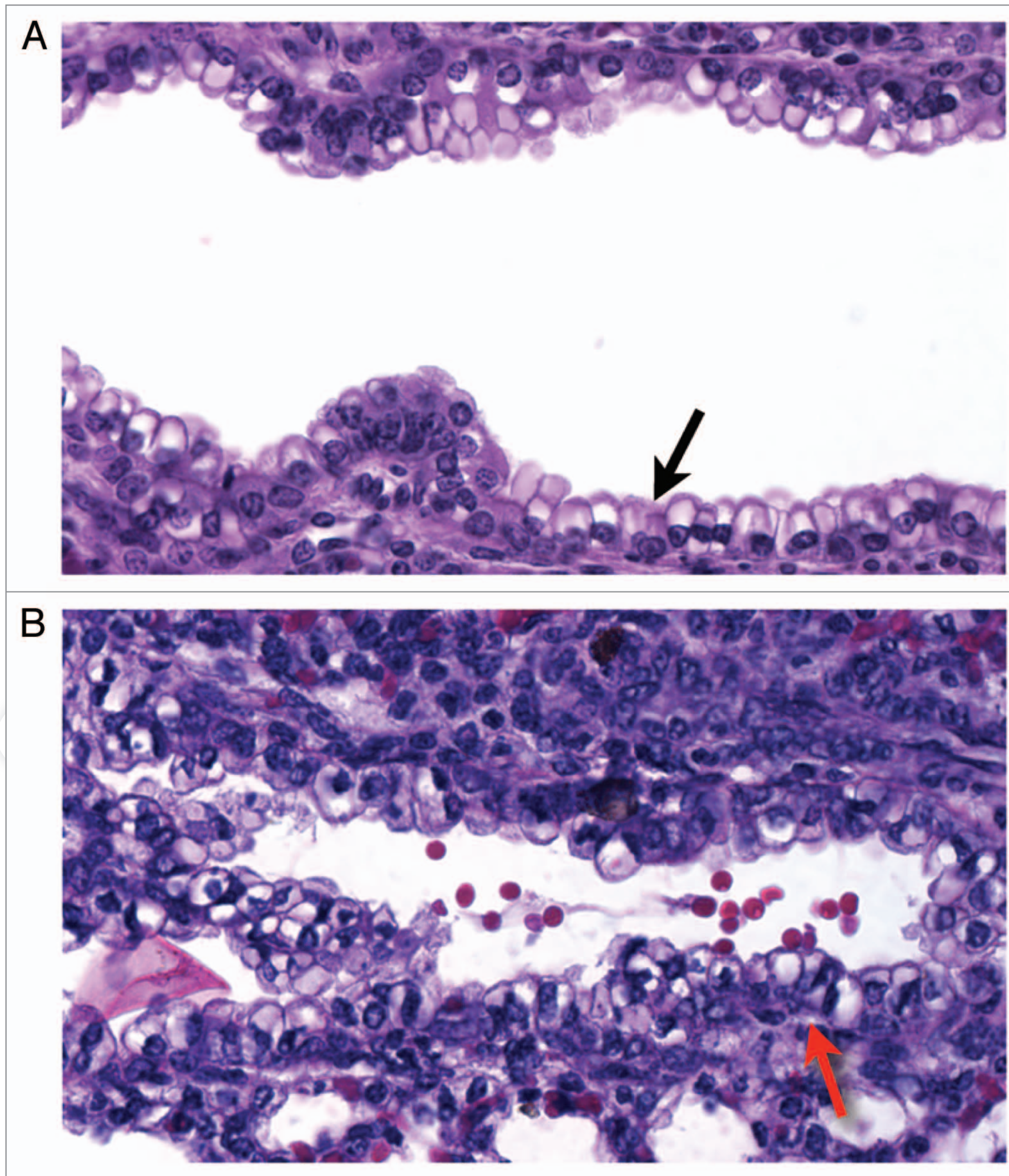

Figure 2. Hematoxylin and eosin (H&E) staining of control and *Lmnb2*$^{-/-}$ lungs at postnatal day 0 (P0). Whereas the control mouse lung (A) displays an ordered airway epithelial layer with nuclei positioned basally (black arrow), the *Lmnb2*$^{-/-}$ mouse lung (B) has a disorganized airway epithelial layer with odd shaped nuclei (red arrow).

B-type lamins is similar to that between A- and B-type lamins, it remains possible that functional compensations from A-type lamins have allowed the prenatal development of mice lacking B-type lamins. Clearly further studies are required to clarify the role of A- and B-type lamins in different organs during development and tissue homeostasis.

Conclusions and Perspectives

We have shown that lamins are not essential for many basic cell functions including proliferation and survival in ESCs. However, studies in mice show that B-type lamins do play a role in promoting cell proliferation and survival in NPCs and neurons in the embryonic brain that express no or very little A-type lamins. B-type lamins are also required for proper spindle orientation in NPCs and cell migration in neurons. The differential requirements of lamins in pluripotent ESCs vs. NPCs and neurons in mice suggest that these proteins are required in the differentiated cells in the context of tissue building. The NL is connected to the cytoskeleton through multiple points of interaction. Since different cell types need different cytoskeletal structures for tissue building, it is possible that the loss of lamins has different phenotypes depending on how each cell type uses lamins to connect the nucleus to the cytoskeleton. Therefore, it is important to study lamins' functions in different cell types both in vitro and in vivo.

Using Dam-ID and gene expression analyses, we demonstrate that although lamin-B binds to many genes, such binding is not generally required to regulate gene

expression in ESCs or as ESCs undergo lineage specification. However, it remains possible that lamin-B directly regulates a subset of its bound genes in cell type-specific manner. Additionally, lamin-B may indirectly regulate gene expression by helping to establish or stabilize three dimensional genome organization and/or epigenetic modifications, which could be important for differentiated cells to engage in proper tissue building. Considering the interaction between lamins and the cyto-skeleton, further study of lamins will shed light on how the NL senses and couples forces generated during cell and tissue morphogenesis to the refinement of genome organization during development and tissue homeostasis. Understanding the functions of lamins in the context of tissue building and maintenance should also help to unveil the mechanisms that mediate various human diseases caused by mutations in lamins and aging-associated tissue deterioration.[1]

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