Review

Nuclear lamin functions and disease

Veronika Butin-Israeli, Stephen A. Adam, Anne E. Goldman and Robert D. Goldman

Department of Cell and Molecular Biology, Feinberg School of Medicine, Northwestern University, 303 East Chicago Avenue, Chicago, IL 60611, USA

Recent studies have shown that premature cellular senescence and normal organ development and function depend on the type V intermediate filament proteins, the lamins, which are major structural proteins of the nucleus. This review presents an up-to-date summary of the literature describing new findings on lamin functions in various cellular processes and emphasizes the relationship between the lamins and devastating diseases ranging from premature aging to cancer. Recent insights into the structure and function of the A- and B- type lamins in normal cells and their dysfunctions in diseased cells are providing novel targets for the development of new diagnostic procedures and disease intervention. We summarize these recent findings, focusing on data from mice and humans, and highlight the expanding knowledge of these proteins in both healthy and diseased cells.

Nuclear lamin structure and assembly

The nuclear lamins are the major structural proteins of the nuclear lamina, which is located in the peripheral region of the nucleus between the inner nuclear envelope membrane and chromatin. In addition, lamins are distributed throughout the nucleoplasm, but at significantly lower concentrations than at the nuclear lamina. Genetic analyses have revealed that lamin genes are highly evolutionarily conserved in metazoans, but are not found in plants or unicellular organisms [1]. The lamins are subdivided into A- and B-types, both of which belong to the type V intermediate filament protein family. Lamin A and lamin C are alternative splice variants of the *LMNA* gene [2], whereas lamin B1 and lamin B2 are derived from two different genes, *LMNB1 and LMNB2* [3]. Lamin proteins exhibit extensive sequence similarity in their N-terminal 'head', central α-helical rod and carboxy terminal 'tail' domains. The tail domains of all lamins contain a nuclear localization signal and an Ig-fold motif [1]. Lamins A, B1, and B2 are initially synthesized as precursors termed pre-lamin A, pre-lamin B1, and pre-lamin B2. The processing of these precursors into mature lamins A, B1, and B2 involves a sequential series of post-translational modifications [3], beginning with farnesylation of the cysteine residue in the C-terminal CaaX motif, followed by the subsequent cleavage of the aaX residues by specific endoproteases, such as RCE1, which cleaves lamin B1 [4] and ZMPSTE24, which cleaves lamin A [5] and then the methylation of the farnesylcysteine by isoprenylcysteine carboxyl methyltransferase (ICMT) [6]. Lamin A is further processed by the ZMPSTE24-catalyzed removal of a 15 amino acid farnesylated carboxy terminal peptide [7]. It has been suggested that the farnesylation and methylation steps may be involved in targeting lamins to the nuclear periphery and stabilizing their interactions with the inner nuclear membrane, although prelamin A processing appears to be dispensable in mice [8].

Biochemical studies have shown that purified lamins assemble into higher order filamentous structures *in vitro* [3]. This involves a multi-step process initiated by dimerization of lamin monomers and head to tail interactions of coiled-coil dimers to form protofilaments [9]. *In vitro*, these protofilaments associate laterally and ultimately lead to the formation of highly ordered paracrystalline arrays [3,9,10]. Recent evidence indicates that lamins can form both homodimers and heterodimers, suggesting that lamin filaments could assemble into protofilaments composed of both A- and B-type lamins [11]. Alternatively, it is possible that protofilaments formed from only A-type or B-type lamins could associate laterally to form mixed higher order lamin structures.

In contrast to what is known about the lamin assembly process *in vitro*, little is known about lamin assembly and structure within nuclei, although it has been suggested that the formation of a lamin network in cells is a self-organizing process [12]. Recent studies have demonstrated that the nuclear lamina in cells is composed of separate, but interacting, A-type or B-type fibrillar meshworks [13]. High-resolution confocal microscopy reveals a separation of A- and B-type lamin filaments with some sites of overlap. However, silencing the expression of individual lamin isoforms can lead to changes in and sometimes disruption of the remaining lamin network structures. This frequently leads to the formation of misshapen nuclei, suggesting that the individual lamin networks must physically interact. Furthermore, both the silencing of lamin B1 expression and the expression of some mutant forms of lamin A cause misshapen nuclei. Many of these misshapen nuclei possess nuclear envelope blebs that are enriched in enlarged lamin A/C networks, but are devoid of B-type lamins [13,14]. Surprisingly, mouse fibroblasts expressing only mature lamin A have misshapen nuclei similar to those seen in laminopathy patient fibroblasts, but the mice have no apparent defects [8].

B-type lamins in proliferation and development

The B-type lamins are expressed in most cell types independently of their differentiation states, whereas the expression of lamins A/C is thought to be restricted to differentiated cells [15]. These observations have led to the suggestion that B-type lamins may have important

Corresponding author: Butin-Israeli, V. (v-butin-israeli@northwestern.edu)
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roles in the regulation of DNA replication, cellular differentiation, cell proliferation, gene expression, developmental processes, and life span [3]. This is supported by the observation that silencing of lamin B1 or B2 expression in HeLa cells induces apoptosis [16]. Other studies on the role of B-type lamins in cell proliferation have painted a complex picture of the roles of lamins in cell proliferation. Fibroblasts prepared from mice with an insertional mutation in *Lmnb1* have misshapen nuclei, increased polyploidy, impaired differentiation and they become prematurely senescent [17]. However, conditional knockouts for *Lmnb1* and *Lmnb2* in mouse skin keratinocytes develop normally and isolated keratinocytes proliferate normally in culture [18]. Embryonic stem cells (ESCs) from different B-type lamin knockout mice have no obvious nuclear or proliferative abnormalities and only minor changes in their transcription profile in comparison to wild-type mouse ESCs [19]. In contrast to these mouse knockout studies, the silencing of lamin B1 expression in normal human diploid fibroblasts (HDFs) causes a proliferation defect and triggers rapid premature senescence [20]. Furthermore, lamin B1 protein and mRNA levels are reduced both in normal cellular senescence and in premature senescence induced by oncogenic Ras [20].

Although the mechanisms by which lamin B1 regulates cell proliferation are unknown, some insights come from the findings that the senescence induced by silencing lamin B1 expression requires activation of the p53 and Rb pathways and is independent of both telomere dysfunction and accumulation of DNA damage. Surprisingly, lamin B1 silencing also causes a transient decrease in mitochondrial reactive oxygen species (ROS) through activation of the p53 pathway and upregulation of various antioxidant genes including SOD1/2. This decrease in ROS level appears to be responsible for the cellular proliferation defects in lamin B1 silenced cells. Furthermore, overexpression of lamin B1 in HDFs increases their proliferation rate and extends their lifespan [20]. Together these experiments suggest that lamin B1 plays an important role in regulating HDF proliferation [20]. Interestingly, another study has recently shown that lamin B1 levels are increased when HDFs are induced to become senescent by oxidative stress or oncogenic Ras [21]. By contrast, silencing of lamin B1 expression in mouse fibroblasts [22] causes an increase in ROS levels, possibly reflecting differences in the susceptibility to oxidative stress between human and mouse fibroblasts [23]. The discrepancies in lamin B1 expression levels detected during senescence among these studies remains to be resolved.

Surprisingly, neither lamin B1 nor B2 are required to complete embryogenesis in mice; however, the mice die immediately after birth. Lamin B1 null mice die from respiratory failure due to poorly developed diaphragms and lungs with smaller alveoli. These mice also have bone abnormalities, microcephaly and undeveloped cerebral cortices [19,24,25]. Interestingly, *Lmnb2* null mice are born with significantly fewer organ abnormalities, but development of the cerebral cortex and cerebellum are severely impaired due to the defective migration of neurons from the ventricular zone to the cortical plate [19,24,25].The importance of the B-type lamins in brain development is further emphasized in mice carrying forebrain specific conditional knockout alleles for *Lmnb1* and *Lmnb2* [25]. These double knockouts exhibit even more severely disorganized cortical structures [25]. Although the specific roles played by the B-type lamins in normal mouse brain development remain unknown, it has been suggested that a normal nuclear lamina composition is required for proper mitotic spindle orientation in neural progenitor cells, nuclear elongation in neurons, neuronal migration and the organization of different brain compartments [18,19,24–26]. Thus, these recent findings suggest that the B-type lamins are essential for the development of specific tissues and organs such as brain and lung, but may not be required in general for cellular proliferation or differentiation.

Lamin B2 may also have cytoplasmic functions. Recently, lamin B2 was identified as a locally translated protein in *Xenopus* retinal ganglion cell axons [27]. Remarkably, lamin B2-depleted axons exhibit mitochondrial dysfunction, defects in axonal transport, and axonal degradation. The importance of B-type lamins in neuronal tissues is underscored by the observation that the expression of prelamin A is very low or nonexistent in the neurons and glia cells of mouse brain [28]. The expression of prelamin A, lamin A, and the major lamin A mutant causing progeria, appear to be specifically downregulated by miR-9, a brain specific microRNA. These findings may ultimately explain the absence of central nervous system pathologies in HGPS patients.

Lamin B associated disorders

Disease causing mutations in the human *LMNB1* and *LMNB2* genes are extremely rare. The most extensively studied of these, adult-onset autosomal dominant leukodystrophy (ADLD), is caused by duplication of *LMNB1* [29]. The pathology of this disease includes slow degeneration of myelin in the central nervous system followed by pyramidal signs, ataxia, and impaired cardiovascular reflexes due to the absence of sympathetic nerve functions [30–32]. In most cases of ADLD, increased expression of lamin B1 has been detected in peripheral leukocytes [31]. Increased lamin B1 expression has also been detected in a variant of ADLD where neither gene copy number defects nor point mutations in *LMNB1* are found. It appears that a mutation in an *LMNB1* regulatory sequence is responsible for this phenotype [33]. At the cellular level, overexpression of lamin B1 creates disorganization of inner nuclear membrane proteins and chromatin. Additionally, myelin gene expression is downregulated and myelin proteins become mislocalized in ADLD brains. The microRNA *miR-23* appears to be a negative regulator of lamin B1 expression and may be important in this disease pathology [34]. Lamin B1 over expression is also seen in ataxia–telangiectasia (A–T) and the normalization of its expression level reduces nuclear shape defects and the premature senescence of patients' cells [21]. Interestingly, overexpression of the *Drosophila* lamin B1 ortholog, Dm0, induces a degenerative phenotype in the cells of the eye, neuronal death, and shortened lifespan [35]. These findings emphasize the importance of determining the mechanisms involved in the regulation of lamin B1 expression and its specific functions in different species and cell types.

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