

RB and Lamins in Cell Cycle Regulation and Aging

Brian K. Kennedy and Juniper K. Pennypacker

Abstract While speculation has centered on a role for nuclear lamins in tumor progression for many years, most of the diseases that have been linked to lamin mutation are dystrophic in nature, often limiting the proliferation potential of affected cells *in vivo* and *in vitro*. Nevertheless, these lamin mutations, particularly in the *LMNA* gene that encodes A-type lamins, have provided an interesting tool set to understand functions of nuclear intermediate filament proteins in cell cycle progress and various means of exit, including quiescence, senescence, and differentiation down various lineages. The picture that has emerged is complex with lamins controlling the activity of key cell cycle factors such as the retinoblastoma protein (RB) and interacting with several important signal transduction pathways. Here we describe the current state of knowledge and speculate that lamins may be intimately involved in the regulation of cell proliferation, acting at the interface between cancer and aging.

Keywords A-type lamins • B-type lamins • Retinoblastoma protein • *LMNA* gene • Lamins • Aging • Progerin • Senescence • Cancer • Cell cycle progression • Telomeres • p53

Abbreviations

ATR Ataxia telangiectasia and Rad3-related protein
ADLD Autosomal dominant leukodystrophy
CDK Cyclin-dependent kinase

B.K. Kennedy, Ph.D. (✉) • J.K. Pennypacker
The Buck Institute for Research on Aging, 8001 Redwood Boulevard, Novato, CA 94945, USA
e-mail: bkennedy@buckinstitute.org; JPennypacker@buckinstitute.org

DCM1A	Dilated cardiomyopathy type 1A
ERK	Extracellular signal-regulated kinases
HGPS	Hutchinson–Gilford Progeria syndrome
LAP2 α	Lamina-associated polypeptide 2 α
MDM2	Mouse double minute 2 homolog
ROS	Reactive oxygen species
RB	Retinoblastoma protein
SASP	Senescence-associated secretory phenotype
SIRT1	Silent mating-type information regulation 2 homolog 1
VHL	von Hippel–Lindau gene

Introduction

Since the discovery of A-type and B-type lamins as components of the nuclear lamina [1], they have been the subject of intense scrutiny regarding possible roles in a range of nuclear functions. The finding that they are targets for mutation in degenerative and progeroid diseases has further driven research in the area [2]. Partially overlapping research threads for nearly three decades have implicated lamins in the control of cell proliferation and differentiation, leading to speculation that lamins may have roles in cancer progression. One obvious connection between lamin function and cell cycle progression comes from the fact that the nuclear envelope breaks down during mitosis in mammalian cells, leading to a dissociation of the lamin intermediate filament structure that exists between the chromatin and the envelope [3]. Upon reformation of the nucleus after mitosis, the lamina also reassembles, and numerous studies have been performed to define a role for A- and B-type lamins in this process.

A full description of A- and B-type lamins is provided in other reviews. Here we provide basic facts relevant to lamin roles in cell cycle regulation and aging. All A-type lamins (lamins A and C in most settings) are encoded by the *LMNA* gene, which is targeted for mutation in a wide range of pathologies [2]. Among these, forms of dilated cardiomyopathy and muscular dystrophy are generally associated with reduced A-type lamin function and can be phenocopied by knockout of the *LMNA* locus in the mouse [4]. In contrast, dominant gain-of-function or neomorphic mutations in *LMNA* can lead to progeroid syndromes [5–7]. The most common of these is Hutchinson–Gilford Progeria syndrome (HGPS), which is most often associated with the *LMNA* G608G mutation, which is silent with respect to coding sequence but activates a cryptic splice site leading to the production of progerin, a variant of lamin A that lacks 50 amino acids in the C-terminus [6, 7]. Whether progerias are mechanistically linked to normal aging has been an ongoing debate in the aging research field for decades with no consensus yet emerging [8, 9]. Interestingly, however, alternative splicing of *LMNA* can occur in normal cells leading to low-level production of progerin, and recent studies have demonstrated progerin accumulation with organismal age or with increasing passage in cell culture [10–13].

These findings at least raise the possibility that progerin may in part promote the normal aging process.

B-type lamins, encoded by *LMNB1* and *LMNB2*, are also linked to disease states and have been implicated in cell cycle progression. Interestingly, recent studies indicate that lamin B expression may be altered as cells approach senescence [14], a topic discussed in Sects. 3 and 4. One major difference between A- and B-type lamins is their expression patterns. While B-type lamins are expressed in all cell types, A-type lamins are regulated during development and differentiation. In a mouse, for instance, A-type lamin expression is not evident until mid-gestation, when it can be detected in cells committing to different lineages [15]. This finding has led to the possibility that A-type lamins are cell commitment factors, being expressed when cells adopt certain fates and perhaps ensuring gene expression programs that define those fates. A-type lamins are also not expressed in stem cells (or at least at very low levels), a fact made particularly evident in studies aimed to generate induced pluripotent stem cells from fibroblasts of HGPS patients [16–18]. These fibroblasts have proliferation defects and altered nuclear shape but can be induced to become stem cells. Upon this transition, the cells lose A-type lamin expression (including that of progerin) and no longer display proliferation or nuclear shape abnormalities. When induced to differentiate again, they resume progerin expression and regain abnormal behavior.

A deeper role for lamins in cell cycle regulation was proposed when the discovery was made that lamin tethering of many cell cycle regulators, including c-Myc and retinoblastoma protein (RB), was important for their function [19–23]. This has stimulated investigation by many laboratories into the role of lamins in coordinating the transit through the G1 phase of the cell cycle. Lamins have also been linked to the control of DNA replication (below) and checkpoint pathways, including those involved in repair of DNA lesions [24].

If lamins control cell cycle progression and exit, then their function might be impaired during cancer progression, either through direct mutation or through other events during cancer expression that affect their activity. This theory is augmented by findings in several tumors that nuclear shape and organization are commonly altered in cancer cell lines [25, 26]. Many investigators have examined the possibility of lamin impairment in cancer progression, and, particularly with regard to A-type lamins, expression patterns often change in cancer although few mutations have been identified. This finding has led to the possibility that lamins may be used as biomarkers for cancer progression, and in many different tumor types the expression of A-type lamins or lamin B1 changes during different stages of tumor development. However, there are no clear generalizations to be made, with expression pattern changes often complex and specific to tumor type [27].

In this review, we focus on the role of A-type lamins in cell cycle progression and exit, discussing how these specific functions may relate to both cancer and aging. The answers to these questions remain unresolved, but a number of tantalizing findings have been reported in the last few years that may finally lead to the primary functions of lamins in the nucleus, as well as how they relate to disease progression, both those of a dystrophic and hyper-proliferative nature.

Cell Proliferation

The G1-to-S phase transition of the mammalian cell cycle is tightly regulated in normal cells and a primary target for dysregulation in cancer. Many of the regulatory factors have been associated with the nuclear matrix. Rather than cover a compendium of these factors, which in many cases interact with nuclear lamins, the focus of this section will be to define the phenotypic roles of nuclear lamins in cell proliferation and, wherever possible, to connect these roles to regulation of proliferative factors. In general, proliferative effects of *LMNA* mutations will be separated into those associated with reduced A-type lamin function and those associated with the expression of progeria alleles, which are either hypermorphs or neomorphs.

Lmna^{-/-} mice develop skeletal muscle dystrophy and dilated cardiomyopathy [4], succumbing between 6 and 8 weeks of age likely due to cardiac conduction defects [28]. To clarify, recent findings suggest that *Lmna*^{-/-} mice may not be true nulls for the *LMNA* locus, as a truncated allele of lamin A appears to be expressed in these mice [29]. The most likely scenario is that this mouse is actually a hypomorph, a theory supported by the phenotype of another *Lmna* disruption in a mouse that results in lethality before weaning [30] and the one known case of a homozygous nonsense mutation of *LMNA* identified in human patient who died shortly after birth [31]. For purposes of clarity and consistency, the term *Lmna*^{-/-} will still be applied to the original mouse generated by Sullivan et al. [4].

While speculation about reduced A-type lamin expression and cancer has a long history, none of the mouse models or human patients with *LMNA* mutations linked to striated and cardiac muscle have been associated with oncogenesis. However, there is strong evidence that A-type lamins regulate key factors involved in controlling the G1-to-S transition, and the most evidence exists for lamin A effects on the RB [32]. The connection between A-type lamins and RB has been examined in a variety of settings, and, while there may be differences, the general consensus is that A-type lamins are required for normal RB function.

One of the first tumor suppressors identified, loss of both copies of the *RB* gene leads to a range of different cancers including retinoblastomas and osteosarcomas [33]. More broadly, RB activity is deregulated in a wide range of tumors, generally through unchecked activity of cyclin-dependent kinases (CDKs) [34]. RB has myriad binding partners and has been ascribed to a number of functions in the nucleus [35]. Most notably, RB acts as a repressor of the transcriptional factor E2F, which controls a range of genes important for entry into S phase of the cell cycle. When hypophosphorylated and active, RB binds to E2F complexes and acts as a repressor of S-phase genes, retaining cells in G1. CDK-dependent phosphorylation promotes release of RB from E2F and cell cycle progression. Along with p53 (discussed below) and telomere regulation, the RB pathway is a major determinant of cell senescence and also plays a role in cell differentiation in multiple lineages. Finally, control of G1-dependent gene expression is but one function ascribed to RB, which is also linked to DNA replication, mitosis, and checkpoint pathways, including those initiated by DNA damage where its roles are still being fully defined [34].

Both A-type lamins and their binding partner, lamina-associated polypeptide 2 α (LAP2 α), have been reported to interact with RB [21, 36], repress E2F-dependent transcription, and promote cell cycle arrest [37]. Consistently, loss of LAP2 α or lamin A/C impairs normal cell cycle regulation leading to inappropriate S-phase entry. Mouse cells lacking A-type lamins or LAP2 α have altered cell cycle profiles with premature S-phase entry and in some contexts enhanced proliferation [38–40]. In contrast, one study in human primary fibroblasts indicated that reduced lamin A/C or LAP2 α expression led to cell cycle arrest [41]. The reason(s) for these different observations remains unknown.

In addition to promoting RB-dependent transcriptional repression of E2F target genes, A-type lamins regulate RB by at least three other mechanisms by coordination of RB phosphorylation, localization, and protein stability [39, 42]. Some aspects of control of RB protein stability are beginning to be understood. For instance, in cells lacking lamin A/C, enhanced levels of RB degradation occur through a proteasome-dependent mechanism [39]. Reduced RB levels make *Lmna*^{-/-} fibroblasts insensitive to p16^{INK4A}-mediated cell cycle arrest [38]. However, the E3 ligase responsible for RB degradation remains to be identified and appears to be independent of the MDM2 and gankyrin pathways that have been linked to RB turnover in other contexts [43]. A number of other proteins are destabilized by loss of RB, including the RB-related protein p107 [39], emerlin [44], and ATR kinase [45]. These findings raise the possibility that A-type lamins might coordinate nuclear proteasome function, and altered activity of ubiquitin ligase components has been detected in cells expressing mutant forms of lamin A [45].

Other A-type lamin functions may promote G1 maintenance. Serum stimulation of G1 arrested cells promotes ERK1/2 mitogen-activated protein kinase-dependent phosphorylation of c-Fos, leading to its association with c-Jun- and AP-1-dependent transcription [46]. Prior to stimulation, c-Fos and ERK1/2 were found to be in a complex with lamin A/C at the nuclear periphery preventing premature activation of AP-1, which occurred in *Lmna*^{-/-} fibroblasts [47, 48]. Independent studies have reported enhanced ERK1/2 activity in cells with reduced A-type lamin expression, and this has been linked to cardiac pathology in dilated cardiomyopathy type 1A (DCM1A) laminopathy patients [49]. Interestingly, a more recent study indicates that ERK1/2–lamin A/C and RB–lamin A/C complexes are mutually exclusive and finds that ERK1/2-dependent lamin A/C binding upon serum stimulation displaces RB, thereby promoting cell cycle progression [50]. If ERK1/2 levels are elevated in cycling cells, this may lead to RB dysregulation and underlie some of the altered cell cycle parameters evident in *Lmna*^{-/-} cells.

A number of reports have implicated lamins in regulation of DNA replication. For instance, early studies showed that disruption of the lamin structure impaired initiation of DNA synthesis [51–53]. In immortalized cells, lamin B was localized to intranuclear sites of late S-phase replication [54], whereas in primary fibroblasts, intranuclear A-type lamins associate with initial sites of DNA synthesis upon S-phase entry [55]. The impact of lamins on S-phase progression in mammalian cells is less clear. S phase is elongated in fibroblasts lacking A-type lamins, although this could be an indirect effect of premature S-phase entry due to defective RB function [39].

A recent study has shed light on a different aspect of replication by comparing the response of *Lmna*^{-/-} cells to forms of DNA damage-induced cell cycle arrest, finding that lamin A/C was required for restart of stalled replication forks and genome maintenance after hydroxyurea-induced replication stress [56]. While the roles of A-type and B-type lamins in DNA replication remain to be fully elaborated, this is clearly an important area for further studies.

Mitotic defects have not been reported for cells with reduced A-type lamin function. However, a recently identified novel allele of LMNA, *Lmna*^{DHE}, was identified as a spontaneous mouse mutation with a subset of progeroid phenotypes [57]. Fibroblasts heterozygous for this *Lmna* allele exhibit, in addition to reduced levels of hypophosphorylated RB, a reduction in a mitosis-specific centromere condensing subunit that depends on RB activity [58]. These alterations result in a range of chromosome segregation defects. It will be of interest to determine whether other *Lmna* disease-associated alleles lead to similar defects.

Cell Senescence: A-Type Lamins

Both A-type and B-type lamins have been linked to cell senescence, the process by which primary cells withdraw from the cell cycle in response to extended passaging, irreparable damage, or unbalanced proliferative signals. Cell senescence has typically been viewed as an impediment to cancer progression and not a driving force in aging, but recent findings paint a more complex picture [59]. Senescent cells do accumulate with age, and while they generally never reach a large percentage of the population of a tissue, recent findings indicate that they adopt an altered secretory profile, the senescence-associated secretory phenotype (SASP), that leads to paracrine release of a number of inflammatory cytokines. These cytokines may promote tissue aging and stimulate tumor development in neighboring cells. In this section, we cover links between lamins and senescence, discussing the still tenuous connections between lamins and normal aging process.

Several studies have implicated A-type lamins in cell senescence, although the phenotype is most clearly associated with the expression of progeria-associated LMNA alleles such as progerin [9]. Progerin expression, in addition to delaying cell cycle progression, brings about premature senescence in a variety of contexts [60, 61]. Lamin A is normally farnesylated at its C-terminus but only for a short time because the last 18 amino acid residues are removed in two cleavage steps. The protease that removes the farnesyl group is Zmpste24 in mice (FACE-1 in humans). In HGPS the deleted exon also removes this cleavage site so that the progerin form of lamin A is permanently farnesylated. *Zmpste24*^{-/-} cells with defective lamin A processing also exhibit enhanced levels of senescence [62, 63]. The mechanisms behind these effects remain unclear. As cells approach senescence the p16INK4A/RB and p53 pathways both become engaged, leading cells to stop proliferation and enter a permanently arrested state [59]. In addition, telomere attrition during passaging in culture drives senescence, particularly as telomere ends shorten beyond

critical thresholds, invoking DNA damage checkpoint response pathways. All three of these networks (p16INK4A/RB, p53, and telomeres) are interrelated, and progerin has been linked functionally to each.

The connection between progerin expression and RB pathway is not entirely understood presently. In one study, where *LMNA*-*progerin* alleles were expressed in a lamin A/C-deficient background, it was found that progerin restored RB stability [38]. Moreover, inactivation of the RB pathway by expression of HPV E7 failed to suppress the proliferation defects of human fibroblasts stably expressing progerin [64]. However, an analysis of global gene expression profiles in fibroblasts from HGPS patients identified the RB-E2F pathway as dysregulated [65] due in part to RB gene expression. The mechanisms underlying this effect were unknown. Interestingly, exposure of cells to farnesyl transferase inhibitors mostly restored the normal gene expression profile.

It is generally thought that *LMNA* mutations are not associated with tumors; however, two instances have been reported in progeria models. In one case, an osteosarcoma was identified in an HGPS patient [66, 67]. This is intriguing since osteosarcomas are commonly associated with *RB* mutations [68]. Interestingly, this patient expressed a smaller 35 amino acid C-terminal deletion in the C-terminus of *LMNA* and not progerin [66, 67]. It would be interesting to determine the levels of RB and activity of the RB pathway in this context. One issue possibly limiting cancer progression in progeria patients is the early progression of the disease leading to mortality for patients usually in their teens. A recent study has identified a novel late-onset progeria syndrome, *LMNA*-associated cardiocutaneous progeria, that is associated with possible cancer susceptibility [69]. This syndrome is associated with a heterozygous novel mutation in the lamin A/C coiled-coil domain that is largely uncharacterized.

The RB pathway is not the only cell cycle regulatory network that is influenced by A-type lamins. Whereas inactivation of RB did not rescue proliferation defects and premature senescence in human fibroblasts stably expressing progerin, either inactivation of p53 (by HPV E7) or expression of telomerase did [64]. Several studies have connected *LMNA* mutation to p53 engagement due to enhanced DNA damage [24], but a recent study has elaborated this connection further. In this case, depletion of lamin A/C in primary human fibroblasts led to dramatic destabilization of RB as expected; however, the cells also had proliferation defects and a senescent phenotype instead of the expected short G1 phase due to enhanced specific activation of the p53–p21 axis [70]. p53 did not display enhanced levels or activating phosphorylation, and many targets were not upregulated. Instead, a subset of targets including p21 were upregulated leading to repression of E2F targets even in the absence of normal levels of RB. Cross talk between the RB and p53 pathways is not unprecedented. Moreover, these findings suggest that the A-type lamins interact with both pathways in a nuanced manner and whether *LMNA* mutations lead to altered proliferation with early G1 cell cycle exit or reduced proliferation leading to senescence may depend on the specific nature of the *LMNA* mutation.

Another interesting recent finding has connected lamins to the p53 pathway in a different manner. In renal carcinoma cells, where genetic inactivation of the

von Hippel–Lindau (VHL) gene E3 ligase is a frequent event, progerin expression may play a role in controlling the p53 pathway [71]. p53 is not generally mutated in these tumors but is inactivated functionally. Jung et al. found that progerin was a target of VHL-mediated proteasomal degradation. Loss of VHL led to stabilization of progerin, which was otherwise bound to p14/ARF, sequestering it from MDM2 and leading in turn to p53 degradation. Thus, progerin was required for p53 inactivation in the absence of VHL. If progerin has this activity in a wide array of cell types, this finding may provide a potential link between aging and cancer:

Accumulation of progerin with aging would lead to inactivation of the p53 network, impairing its tumor suppressive and checkpoint activities. More research is needed to test this intriguing hypothesis.

Recent studies have also pointed to a role for lamins in the maintenance of telomere metabolism, another activity that could be closely linked to cell senescence [72]. For instance, HGPS fibroblasts are reported to have faster rates of telomere attrition [73]. This finding does not on its own suggest a direct role for A-type lamins at telomeres; however, a number of studies have reported that telomeres associate with the nuclear matrix and more specifically with A-type lamins [74–77]. *Lmna*^{-/-} fibroblasts have shorter telomeres but no differences in telomerase activity [78]. Instead, the answer may be related to altered chromatin structure at telomeres and trace back to the reduced function of RB and its related proteins p107 and p130 [72]. Cells lacking A-type lamins exhibit a decrease in histone H4K20me3 [78], a known feature of cells lacking RB family members [79, 80]. However, the latter cells have increased telomere length, leading the authors of the lamin study to suggest that A-type lamins might be required for telomere elongation in the absence of RB family members [81, 82]. A relocalization of telomeres from peripheral to central regions of the nucleus has also been reported in *Lmna*^{-/-} cells, through at present unknown mechanisms [83].

HGPS fibroblasts have altered telomere chromatin as well, although the changes are distinct from those in *Lmna*^{-/-} cells [83, 84]. In this case, decreased H4K20me3 and increased H4K20me were found. This finding suggests that, not unexpectedly, progerin influences telomere metabolism in a manner distinct from hypomorphic mutation of *LMNA*. Recently, it was reported that progerin-induced DNA damage is localized specifically to telomeres [85]. Expression of telomerase resolves this DNA damage, and, once repaired, HGPS fibroblasts regain full potential to proliferate. It will be intriguing to see how DNA damage is restricted in the genome by progerin.

Finally, the proliferative defects leading to senescence with expression of progerin and/or unprocessed lamin A appear to extend to adult stem cell populations. Studies in mesenchymal stem cells have indicated that progerin expression leads to elevated Notch signaling, causing perturbations in stem cell differentiation and maintenance of stem cell identity [13]. In addition, adult bone marrow-derived stem cells from *Zmpste24*^{-/-} mice have decreased *SIRT1* function due to its dissociation from the nuclear matrix and leading to reduced proliferation and premature senescence [86]. This phenotype may be relevant for aging as restoration of *SIRT1* function was associated with improved stem cell function and enhanced survival. Studies in fibroblasts and other cell culture models have provided important insights

into lamin function; however, more emphasis needs to be placed on the role of lamins in adult stem cell populations, which could be central to a subset of the pathologies associated with laminopathies.

Cell Senescence: B-Type Lamins

Lamin B1 has also been tightly associated with cell senescence, with altered expression in either direction possibly having deleterious consequences [87]. Initial suggestions of altered lamin B expression came from studies of HGPS cells, where lamin B1 was found to be reduced [87]. Two virtually contemporaneous recent reports have shown that loss of lamin B1 expression is a marker for cell senescence induced by a variety of causes, including replicative exhaustion. Loss of lamin B1 expression was not dependent on many molecular inducers of senescence but was driven by activation of either the p53 or the RB pathway [88]. Changes in lamin B1 could be traced back to reduced mRNA stability, although reduced protein stability could be detected as well in mouse liver induced to senescence by irradiation. In the second study, Shimi et al. also reported loss of lamin B1 as a much needed biomarker of cell senescence [14]. Shimi et al. also examined the consequences of RNAi-mediated knockdown of lamin B1 expression, finding that this was sufficient to both slow proliferation and reduce senescence. The proliferative delay was dependent on p53, and the senescent phenotype was dependent on both p53 and RB. Yet a third very recent study has confirmed and extended the observed reduction in lamin B1 expression to senescent keratinocytes and to chronologically aged human skin tissue [89]. However, in this study enforced reduction in lamin B1 expression failed to lead to senescence. The disparities between the two studies are not known [14, 89]. Together these findings (1) indicate that loss of lamin B1 may serve as an effective biomarker of in vivo senescence and (2) suggest the existence of a complex regulatory loop connecting B-type lamins to the RB and p53 pathways.

Whereas mutations affecting the *LMNB1* coding sequence have not been reported, overexpression is linked to at least two diseases, suggesting that too much lamin B1 may be as deleterious as too little. Duplication of the *LMNB1* locus results in adult-onset autosomal dominant leukodystrophy (ADLD) [90], and lamin B1 overexpression has been detected in lymphoblasts and fibroblasts from ataxia telangiectasia patients [91]. Interestingly, lamin B1 overexpression also drives cell senescence, a phenomenon also observed in ataxia telangiectasia cells, which are rescued by restoration of normal lamin B1 expression. Induction of senescence by overexpression of lamin B1 has been repeated in a second study [89]. In this case, the senescent phenotype could be rescued by expression of telomerase or inactivation of p53, paralleling observations for progerin-induced senescence [64]. Finally, senescence induced by overexpression of lamins is not restricted to B1. Increased levels of lamin A also reduce the replicative life-span of primary human fibroblasts [92].

Several studies indicate a connection between A-type and B-type lamins in the formation of intermediate filament networks, and there appears to be an interplay between the two nuclear intermediate filament families with respect to cell

senescence. For instance, reduced expression of A-type lamins exacerbates the senescent phenotype of cells overexpressing lamin B1 [89]. In the context of senescence in normal cells, one thing that needs to be resolved is whether increased progerin levels and reduced lamin B1 expression are related. Does one family of nuclear intermediate filaments regulate the other during aging and senescence?

Whether reactive oxygen species (ROS) drive aspects of the aging process remains highly debated [93]. Both A- and B-type lamins have been linked to reactive oxygen production and sensing in recent years, and while the details remain murky, these findings represent another promising set of leads as the relationship between lamins and aging is elucidated [87]. There may be a direct connection as conserved cysteines in the C-terminal tail of lamin A have been found to be oxidized in senescent cells [94]. This led to the formation of intra- and intermolecular disulfide bonds and perturbation of the lamina. These cysteine residues may serve as a reservoir or a sensor for oxidation, as mutating the cysteines to alanine led to oxidative stress sensitivity and premature senescence. In the case of B-type lamins, a number of conflicting results have been reported. In some contexts, increased ROS has been reported to lead to elevated and reduced lamin B1 levels [14, 88, 91]. Similarly, both higher and lower levels of lamin B1 lead to reduced ROS levels [14]. Further studies with ROS and lamins will likely clarify this complex and potentially mechanistically rewarding relationship.

Conclusions

While nuclear lamins have been speculated to control cell cycle progression for decades, this area of research has exploded in recent years and many labs have investigated the effect of laminopathy-associated mutations in *LMNA* and diseases associated with *LMNB1* overexpression. These studies have linked nuclear lamins to virtually every major aspect of cell cycle progression and, more recently, cell senescence. This latter connection may be particularly interesting given that *LMNA* mutations are associated with progeria as well as the findings that both progerin and lamin B1 have altered expression with normal aging.

However, several big questions remain to be resolved: Does altered lamin expression promote tumor progression? Are lamins important regulators of the aging process? With respect to cancer, an increasing number of studies have linked altered expression of both A-type and B-type to different tumors, but the relationships are complex and causal links are generally lacking. It is critical to resolve these issues in more detail to determine for which tumors lamins might be effective biomarkers and perhaps more importantly to understand why changes in lamin expression may promote tumorigenesis.

With respect to aging, the findings are certainly becoming more intriguing. That *LMNA* mutations cause HGPS is not sufficient to ascribe A-type lamins a role in normal aging. That progerin is expressed in aging and/or senescent cells is also not sufficient, but together the data certainly justify further analysis of lamin roles in the

normal aging process. To provide convincing evidence, it will be necessary to manipulate A-type (or B-type) lamins in a manner that leads to enhanced organismal longevity. For instance, it would be informative to apply technologies developed to reduce progerin expression in HGPS models to wild-type mice to determine whether suppression of progerin in this context leads to longer life-span. Experiments such as these will begin to answer the critical questions surrounding aging and lamins.

Progress in understanding disease-relevant functions of lamins has escalated dramatically in recent years, and the next few years will without a doubt provide exciting new findings relevant to cancer and aging. Perhaps the most exciting aspect of the field is that researchers are beginning to understand the roles of lamins at the mechanistic level. Further progress on this front will likely yield effective therapeutic approaches for treatment of laminopathies and, importantly, an increasingly elegant understanding of the organization of the mammalian nucleus.

Acknowledgements Lamin-related research in the lab of B.K.K. is supported by a grant from the National Institute of Aging (R01 AG024287).

References

1. Gerace L, Blum A, Blobel G (1978) Immunocytochemical localization of the major polypeptides of the nuclear pore complex-lamina fraction. Interphase and mitotic distribution. *J Cell Biol* 79(2 Pt 1):546–566
2. Schreiber KH, Kennedy BK (2013) When lamins go bad: nuclear structure and disease. *Cell* 152(6):1365–1375
3. Gerace L, Blobel G (1980) the nuclear envelope lamina is reversibly depolymerized during mitosis. *Cell* 19:277–287
4. Sullivan T, Escalante-Alcalde D, Bhatt H, Anver M, Bhat N, Nagashima K, Stewart CL, Burke B (1999) Loss of A-type lamin expression compromises nuclear envelope integrity leading to muscular dystrophy. *J Cell Biol* 147:913–920
5. Cao H, Hegele RA (2003) LMNA is mutated in Hutchinson-Gilford progeria (MIM 176670) but not in Wiedemann-Rautenstrauch progeroid syndrome (MIM 264090). *J Hum Genet* 48:271–274
6. De Sandre-Giovannoli A, Bernard R, Cau P, Navarro C, Amiel J, Boccaccio I, Lyonnet S, Stewart CL, Munnich A, Le Merrer M, Levy N (2003) Lamin A truncation in Hutchinson-Gilford progeria. *Science* 300:2055
7. Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, Erdos MR, Robbins CM, Moses TY, Berglund P, Dutra A, Pak E, Durkin S, Csoka AB, Boehnke M, Glover TW, Collins FS (2003) Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature* 423:293–298
8. Burtner CR, Kennedy BK (2010) Progeria syndromes and ageing: what is the connection? *Nat Rev Mol Cell Biol* 11(8):567–578
9. Reddy S, Comai L (2012) Lamin A, farnesylation and aging. *Exp Cell Res* 318(1):1–7
10. Verdy C, Branka JE, Mekideche N (2011) Quantitative assessment of lactate and progerin production in normal human cutaneous cells during normal ageing: effect of an Alaria esculenta extract. *Int J Cosmet Sci* 33(5):462–466
11. McClintock D, Ratner D, Lokuge M, Owens DM, Gordon LB, Collins FS, Djabali K (2007) The mutant form of lamin A that causes Hutchinson-Gilford progeria is a biomarker of cellular aging in human skin. *PLoS One* 2(12):e1269

12. Scaffidi P, Misteli T (2006) Lamin A-dependent nuclear defects in human aging. *Science* 312(5776):1059–1063
13. Scaffidi P, Misteli T (2008) Lamin A-dependent misregulation of adult stem cells associated with accelerated ageing. *Nat Cell Biol* 10(4):452–459
14. Shimi T, Butin-Israeli V, Adam SA, Hamanaka RB, Goldman AE, Lucas CA, Shumaker DK, Kosak ST, Chandel NS, Goldman RD (2011) The role of nuclear lamin B1 in cell proliferation and senescence. *Genes Dev* 25(24):2579–2593
15. Rober RA, Weber K, Osborn M (1989) Differential timing of nuclear lamin A/C expression in the various organs of the mouse embryo and the young animal: a developmental study. *Development* 105:365–378
16. Ho JC, Zhou T, Lai WH, Huang Y, Chan YC, Li X, Wong NL, Li Y, Au KW, Guo D, Xu J, Siu CW, Pei D, Tse HF, Esteban MA (2011) Generation of induced pluripotent stem cell lines from 3 distinct laminopathies bearing heterogeneous mutations in lamin A/C. *Aging (Albany NY)* 3(4):380–390
17. Zhang J, Lian Q, Zhu G, Zhou F, Sui L, Tan C, Mutalif RA, Navasankari R, Zhang Y, Tse HF, Stewart CL, Colman A (2011) A human iPSC model of Hutchinson Gilford progeria reveals vascular smooth muscle and mesenchymal stem cell defects. *Cell Stem Cell* 8(1):31–45
18. Liu GH, Barkho BZ, Ruiz S, Diep D, Qu J, Yang SL, Panopoulos AD, Suzuki K, Kurian L, Walsh C, Thompson J, Boue S, Fung HL, Sancho-Martinez I, Zhang K, Yates J 3rd, Izpisua Belmonte JC (2011) Recapitulation of premature ageing with iPSCs from Hutchinson-Gilford progeria syndrome. *Nature* 472(7342):221–225
19. Eisenman RN, Tachibana CY, Abrams HD, Hann SR (1985) V-myc- and c-myc-encoded proteins are associated with the nuclear matrix. *Mol Cell Biol* 5(1):114–126
20. Mancini MA, Shan B, Nickerson JA, Penman S, Lee WH (1994) The retinoblastoma gene product is a cell cycle-dependent, nuclear matrix-associated protein. *Proc Natl Acad Sci U S A* 91(1):418–422
21. Ozaki T, Saijo M, Murakami K, Enomoto H, Taya Y, Sakiyama S (1994) Complex formation between Lamin A and the retinoblastoma gene product: identification of the domain on Lamin A required for its interaction. *Oncogene* 9:2649–2653
22. Templeton DJ, Park SH, Lanier L, Weinberg RA (1991) Nonfunctional mutants of the retinoblastoma protein are characterized by defects in phosphorylation, viral oncoprotein association, and nuclear tethering. *Proc Natl Acad Sci U S A* 88:3033–3037
23. Mittnacht S, Weinberg RA (1991) G1/S phosphorylation of the retinoblastoma protein is associated with altered affinity for the nuclear compartment. *Cell* 65:381–393
24. Redwood AB, Gonzalez-Suarez I, Gonzalo S (2011) Regulating the levels of key factors in cell cycle and DNA repair: new pathways revealed by lamins. *Cell Cycle* 10(21):3652–3657
25. Zink D, Fischer AH, Nickerson JA (2004) Nuclear structure in cancer cells. *Nat Rev Cancer* 4(9):677–687
26. Foster CR, Przyborski SA, Wilson RG, Hutchison CJ (2010) Lamins as cancer biomarkers. *Biochem Soc Trans* 38(Pt 1):297–300
27. Butin-Israeli V, Adam SA, Goldman AE, Goldman RD (2012) Nuclear lamin functions and disease. *Trends Genet* 28(9):464–471
28. Nikolova V, Leimena C, McMahon AC, Tan JC, Chandar S, Jogia D, Kesteven SH, Michalick J, Otway R, Verheyen F, Rainer S, Stewart CL, Martin D, Feneley MP, Fatkin D (2004) Defects in nuclear structure and function promote dilated cardiomyopathy in lamin A/C-deficient mice. *J Clin Invest* 113(3):357–369
29. Jahn D, Schramm S, Schnolzer M, Heilmann CJ, de Koster CG, Schutz W, Benavente R, Alsheimer M (2012) A truncated lamin A in the *Lmna*^{-/-} mouse line: implications for the understanding of laminopathies. *Nucleus* 3(5):463–474
30. Kubben N, Voncken JW, Konings G, van Weeghel M, van den Hoogenhof MM, Gijbels M, van Erk A, Schoonderwoerd K, van den Bosch B, Dahlmans V, Calis C, Houten SM, Misteli T, Pinto YM (2011) Post-natal myogenic and adipogenic developmental: defects and metabolic impairment upon loss of A-type lamins. *Nucleus* 2(3):195–207

31. van Engelen BG, Muchir A, Hutchison CJ, van der Kooij AJ, Bonne G, Lammens M (2005) The lethal phenotype of a homozygous nonsense mutation in the lamin A/C gene. *Neurology* 64(2):374–376
32. Boban M, Braun J, Foisner R (2010) Lamins: ‘structure goes cycling’. *Biochem Soc Trans* 38(Pt 1):301–306
33. Friend SH, Bernards R, Rogelj S, Weinberg RA, Rapaport JM, Albert DM, Dryja TP (1986) A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. *Nature* 323(6089):643–646
34. Dick FA, Rubin SM (2013) Molecular mechanisms underlying RB protein function. *Nat Rev Mol Cell Biol* 14(5):297–306
35. Morris EJ, Dyson N (2001) Retinoblastoma protein partners. *Adv Cancer Res* 82:1–54
36. Markiewicz E, Dechat T, Foisner R, Quinlan RA, Hutchison CJ (2002) Lamin A/C binding protein LAP2a is required for nuclear anchorage of retinoblastoma protein. *Mol Biol Cell* 13:4401–4413
37. Dorner D, Vlcek S, Foeger N, Gajewski A, Makolm C, Gotzmann J, Hutchison CJ, Foisner R (2006) Lamina-associated polypeptide 2alpha regulates cell cycle progression and differentiation via the retinoblastoma-E2F pathway. *J Cell Biol* 173(1):83–93
38. Nitta RT, Jameson SA, Kudlow BA, Conlan LA, Kennedy BK (2006) Stabilization of the retinoblastoma protein by A-type nuclear lamins is required for INK4A-mediated cell cycle arrest. *Mol Cell Biol* 26:5360–5372
39. Johnson BR, Nitta RT, Frock RL, Mounkes L, Barbie DA, Stewart CL, Harlow E, Kennedy BK (2004) A-type lamins regulate retinoblastoma protein function by promoting subnuclear localization and preventing proteasomal degradation. *Proc Natl Acad Sci U S A* 101:9677–9682
40. Naeger LK, Goodwin EC, Hwang ES, DeFilippis RA, Zhang H, DiMaio D (1999) Bovine papillomavirus E2 protein activates a complex growth-inhibitory program in p53 negative HT-3 cervical carcinoma cells that includes repression of cyclin A and cdc25A phosphatase genes and accumulation of hypophosphorylated retinoblastoma protein. *Cell Growth Differ* 10(6):413–422
41. Pekovic V, Harborth J, Broers JL, Ramaekers FC, van Engelen B, Lammens M, von Zglinicki T, Foisner R, Hutchison C, Markiewicz E (2007) Nucleoplasmic LAP2{alpha}-lamin A complexes are required to maintain a proliferative state in human fibroblasts. *J Cell Biol* 176(2):163–172
42. Van Berlo JH, Voncken JW, Kubben N, Broers JL, Duisters R, van Leeuwen RE, Crijns HJ, Ramaekers FC, Hutchison CJ, Pinto YM (2005) A-type lamins are essential for TGF-beta1 induced PP2A to dephosphorylate transcription factors. *Hum Mol Genet* 14(19):2839–2849
43. Nitta RT, Smith CL, Kennedy BK (2007) Evidence that proteasome-dependent degradation of the retinoblastoma protein in cells lacking A-type lamins occurs independently of gankyrin and MDM2. *PLoS One* 2(9):e963
44. Muchir A, Massart C, van Engelen BG, Lammens M, Bonne G, Worman HJ (2006) Proteasome-mediated degradation of integral inner nuclear membrane protein emerin in fibroblasts lacking A-type lamins. *Biochem Biophys Res Commun* 351(4):1011–1017
45. Muralikrishna B, Chaturvedi P, Sinha K, Parnaik VK (2012) Lamin misexpression upregulates three distinct ubiquitin ligase systems that degrade ATR kinase in HeLa cells. *Mol Cell Biochem* 365(1–2):323–332
46. Verde P, Casalino L, Talotta F, Yaniv M, Weitzman JB (2007) Deciphering AP-1 function in tumorigenesis: fra-ternizing on target promoters. *Cell Cycle* 6(21):2633–2639
47. Ivorra C, Kubicek M, Gonzalez JM, Sanz-Gonzalez SM, Alvarez-Barrientos A, O’Connor JE, Burke B, Andres V (2006) A mechanism of AP-1 suppression through interaction of c-Fos with lamin A/C. *Genes Dev* 20(3):307–320
48. Gonzalez JM, Navarro-Puche A, Casar B, Crespo P, Andres V (2008) Fast regulation of AP-1 activity through interaction of lamin A/C, ERK1/2, and c-Fos at the nuclear envelope. *J Cell Biol* 183(4):653–666

49. Muchir A, Wu W, Worman HJ (2010) Mitogen-activated protein kinase inhibitor regulation of heart function and fibrosis in cardiomyopathy caused by lamin A/C gene mutation. *Trends Cardiovasc Med* 20(7):217–221
50. Rodriguez J, Calvo F, Gonzalez JM, Casar B, Andres V, Crespo P (2010) ERK1/2 MAP kinases promote cell cycle entry by rapid, kinase-independent disruption of retinoblastoma-lamin A complexes. *J Cell Biol* 191(5):967–979
51. Ellis DJ, Jenkins H, Whitfield WG, Hutchison CJ (1997) GST-lamin fusion proteins act as dominant negative mutants in *Xenopus* egg extract and reveal the function of the lamina in DNA replication. *J Cell Sci* 110:2507–2518
52. Spann TP, Moir RD, Goldman AE, Stick R, Goldman RD (1997) Disruption of nuclear lamin organization alters the distribution of replication factors and inhibits DNA synthesis. *J Cell Biol* 136:1201–1212
53. Moir RD, Spann TP, Herrmann H, Goldman RD (2000) Disruption of nuclear lamin organization blocks the elongation phase of DNA replication. *J Cell Biol* 149:1179–1192
54. Moir RD, Spann TP, Goldman RD (1994) Dynamic properties of nuclear lamins: lamin B is associated with sites of DNA replication. *J Cell Biol* 125:1201–1212
55. Kennedy BK, Barbie DA, Classon M, Dyson N, Harlow E (2000) Nuclear organization of DNA replication in primary mammalian cells. *Genes Dev* 14:2855–2868
56. Singh M, Hunt CR, Pandita RK, Kumar R, Yang CR, Horikoshi N, Bachoo R, Serag S, Story MD, Shay JW, Powell SN, Gupta A, Jeffery J, Pandita S, Chen BP, Deckbar D, Lobrich M, Yang Q, Khanna KK, Worman HJ, Pandita TK (2013) Lamin A/C depletion enhances DNA damage-induced stalled replication fork arrest. *Mol Cell Biol* 33(6):1210–1222
57. Odgren PR, Pratt CH, Mackay CA, Mason-Savas A, Curtain M, Shopland L, Ichicki T, Sundberg JP, Donahue LR (2010) Disheveled hair and ear (Dhe), a spontaneous mouse *Lmna* mutation modeling human laminopathies. *PLoS One* 5(4):e9959
58. Pratt CH, Curtain M, Donahue LR, Shopland LS (2011) Mitotic defects lead to pervasive aneuploidy and accompany loss of RB1 activity in mouse *Lmna*Dhe dermal fibroblasts. *PLoS One* 6(3):e18065
59. Campisi J (2013) Aging, cellular senescence, and cancer. *Annu Rev Physiol* 75:685–705
60. Dechat T, Shimi T, Adam SA, Rusinol AE, Andres DA, Spielmann HP, Sinensky MS, Goldman RD (2007) Alterations in mitosis and cell cycle progression caused by a mutant lamin A known to accelerate human aging. *Proc Natl Acad Sci U S A* 104(12):4955–4960
61. Cao K, Capell BC, Erdos MR, Djabali K, Collins FS (2007) A lamin A protein isoform overexpressed in Hutchinson-Gilford progeria syndrome interferes with mitosis in progeria and normal cells. *Proc Natl Acad Sci U S A* 104(12):4949–4954
62. Liu B, Wang J, Chan KM, Tjia WM, Deng W, Guan X, Huang JD, Li KM, Chau PY, Chen DJ, Pei D, Pendas AM, Cadinanos J, Lopez-Otin C, Tse HF, Hutchison C, Chen J, Cao Y, Cheah KS, Tryggvason K, Zhou Z (2005) Genomic instability in laminopathy-based premature aging. *Nat Med* 11(7):780–785
63. Varela I, Cadinanos J, Pendas AM, Gutierrez-Fernandez A, Folgueras AR, Sanchez LM, Zhou Z, Rodriguez FJ, Stewart CL, Vega JA, Tryggvason K, Freije JM, Lopez-Otin C (2005) Accelerated ageing in mice deficient in *Zmpste24* protease is linked to p53 signalling activation. *Nature* 437(7058):564–568
64. Kudlow BA, Stanfel MN, Burtner CR, Johnston ED, Kennedy BK (2008) Suppression of proliferative defects associated with processing-defective lamin A mutants by hTERT or inactivation of p53. *Mol Biol Cell* 19(12):5238–5248
65. Marji J, O'Donoghue SI, McClintock D, Satagopam VP, Schneider R, Ratner D, Worman HJ, Gordon LB, Djabali K (2010) Defective lamin A-Rb signaling in Hutchinson-Gilford progeria syndrome and reversal by farnesyltransferase inhibition. *PLoS One* 5(6):e11132
66. King CR, Lemmer J, Campbell JR, Atkins AR (1978) Osteosarcoma in a patient with Hutchinson-Gilford progeria. *J Med Genet* 15(6):481–484
67. Shalev SA, De Sandre-Giovannoli A, Shani AA, Levy N (2007) An association of Hutchinson-Gilford progeria and malignancy. *Am J Med Genet A* 143A(16):1821–1826

68. Wadayama B, Toguchida J, Shimizu T, Ishizaki K, Sasaki MS, Kotoura Y, Yamamuro T (1994) Mutation spectrum of the retinoblastoma gene in osteosarcomas. *Cancer Res* 54(11):3042–3048
69. Kane MS, Lindsay ME, Judge DP, Barrowman J, Ap Rhys C, Simonson L, Dietz HC, Michaelis S (2013) LMNA-associated cardiocutaneous progeria: an inherited autosomal dominant premature aging syndrome with late onset. *Am J Med Genet A* 161(7):1599–1611
70. Moiseeva O, Bourdeau V, Vernier M, Dabauvalle MC, Ferbeyre G (2011) Retinoblastoma-independent regulation of cell proliferation and senescence by the p53-p21 axis in lamin A/C-depleted cells. *Aging Cell* 10(5):789–797
71. Jung YS, Lee SJ, Lee SH, Chung JY, Jung YJ, Hwang SH, Ha NC, Park BJ (2013) Loss of VHL promotes progerin expression, leading to impaired p14/ARF function and suppression of p53 activity. *Cell Cycle* 12(14)
72. Gonzalez-Suarez I, Gonzalo S (2010) Nurturing the genome: A-type lamins preserve genomic stability. *Nucleus* 1(2):129–135
73. Allsopp RC, Vaziri H, Patterson C, Goldstein S, Younglai EV, Futcher AB, Greider CW, Harley CB (1992) Telomere length predicts replicative capacity of human fibroblasts. *Proc Natl Acad Sci U S A* 89(21):10114–10118
74. Shoeman RL, Wadle S, Scherbarth A, Traub P (1988) The binding in vitro of the intermediate filament protein vimentin to synthetic oligonucleotides containing telomere sequences. *J Biol Chem* 263(35):18744–18749
75. de Lange T (1992) Human telomeres are attached to the nuclear matrix. *EMBO J* 11(2):717–724
76. Luderus ME, van Steensel B, Chong L, Sibon OC, Cremers FF, de Lange T (1996) Structure, subnuclear distribution, and nuclear matrix association of the mammalian telomeric complex. *J Cell Biol* 135(4):867–881
77. Raz V, Vermolen BJ, Garini Y, Onderwater JJ, Mommaas-Kienhuis MA, Koster AJ, Young IT, Tanke H, Dirks RW (2008) The nuclear lamina promotes telomere aggregation and centromere peripheral localization during senescence of human mesenchymal stem cells. *J Cell Sci* 121(Pt 24):4018–4028
78. Gonzalez-Suarez I, Redwood AB, Perkins SM, Vermolen B, Lichtensztein D, Grotzky DA, Morgado-Palacin L, Gapud EJ, Sleckman BP, Sullivan T, Sage J, Stewart CL, Mai S, Gonzalo S (2009) Novel roles for A-type lamins in telomere biology and the DNA damage response pathway. *EMBO J* 28(16):2414–2427
79. Gonzalo S, Garcia-Cao M, Fraga MF, Schotta G, Peters AH, Cotter SE, Eguia R, Dean DC, Esteller M, Jenuwein T, Blasco MA (2005) Role of the RB1 family in stabilizing histone methylation at constitutive heterochromatin. *Nat Cell Biol* 7(4):420–428
80. Gonzalo S, Blasco MA (2005) Role of Rb family in the epigenetic definition of chromatin. *Cell Cycle* 4(6):752–755
81. Benetti R, Gonzalo S, Jaco I, Schotta G, Klatt P, Jenuwein T, Blasco MA (2007) Suv4-20h deficiency results in telomere elongation and derepression of telomere recombination. *J Cell Biol* 178(6):925–936
82. Garcia-Cao M, O'Sullivan R, Peters AH, Jenuwein T, Blasco MA (2004) Epigenetic regulation of telomere length in mammalian cells by the Suv39h1 and Suv39h2 histone methyltransferases. *Nat Genet* 36(1):94–99
83. Gonzalez-Suarez I, Redwood AB, Gonzalo S (2009) Loss of A-type lamins and genomic instability. *Cell Cycle* 8(23):3860–3865
84. Shumaker DK, Dechat T, Kohlmaier A, Adam SA, Bozovsky MR, Erdos MR, Eriksson M, Goldman AE, Khuon S, Collins FS, Jenuwein T, Goldman RD (2006) Mutant nuclear lamin A leads to progressive alterations of epigenetic control in premature aging. *Proc Natl Acad Sci U S A* 103(23):8703–8708
85. Benson EK, Lee SW, Aaronson SA (2010) Role of progerin-induced telomere dysfunction in HGPS premature cellular senescence. *J Cell Sci* 123(Pt 15):2605–2612
86. Liu B, Ghosh S, Yang X, Zheng H, Liu X, Wang Z, Jin G, Zheng B, Kennedy BK, Suh Y, Kaerberlein M, Tryggvason K, Zhou Z (2012) Resveratrol rescues SIRT1-dependent adult stem cell decline and alleviates progeroid features in laminopathy-based progeria. *Cell Metab* 16(6):738–750

87. Barascu A, Le Chalony C, Pennarun G, Genet D, Zaarour N, Bertrand P (2012) Oxidative stress alters nuclear shape through lamins dysregulation: a route to senescence. *Nucleus* 3(5):411–417
88. Freund A, Laberge RM, Demaria M, Campisi J (2012) Lamin B1 loss is a senescence-associated biomarker. *Mol Biol Cell* 23(11):2066–2075
89. Dreesen O, Chojnowski A, Ong PF, Zhao TY, Common JE, Lunny D, Lane EB, Lee SJ, Vardy LA, Stewart CL, Colman A (2013) Lamin B1 fluctuations have differential effects on cellular proliferation and senescence. *J Cell Biol* 200(5):605–617
90. Padiath QS, Saigoh K, Schiffmann R, Asahara H, Yamada T, Koeppen A, Hogan K, Ptacek LJ, Fu YH (2006) Lamin B1 duplications cause autosomal dominant leukodystrophy. *Nat Genet* 38(10):1114–1123
91. Barascu A, Le Chalony C, Pennarun G, Genet D, Imam N, Lopez B, Bertrand P (2012) Oxidative stress induces an ATM-independent senescence pathway through p38 MAPK-mediated lamin B1 accumulation. *EMBO J* 31(5):1080–1094
92. Candelario J, Sudhakar S, Navarro S, Reddy S, Comai L (2008) Perturbation of wild-type lamin A metabolism results in a progeroid phenotype. *Aging Cell* 7(3):355–367
93. Harman D (1956) Aging: a theory based on free radical and radiation chemistry. *J Gerontol* 11:298–300
94. Pekovic V, Gibbs-Seymour I, Markiewicz E, Alzoghaibi F, Benham AM, Edwards R, Wenhert M, von Zglinicki T, Hutchison CJ (2011) Conserved cysteine residues in the mammalian lamin A tail are essential for cellular responses to ROS generation. *Aging Cell* 10(6):1067–1079