Published in final edited form as:

Adv Exp Med Biol. 2014 ; 773: 143–163. doi:10.1007/978-1-4899-8032-8_7.

Lamina-associated polypeptide (LAP)2 α and other LEM proteins in cancer biology

Andreas Brachner and Roland Foisner

Max F. Perutz Laboratories, Medical University Vienna, Dr. Bohr-Gasse 9, 1030 Vienna, Austria

Abstract

The LEM proteins comprise a heterogeneous family of chromatin-associated proteins that share the LEM domain, a structural motif mediating interaction with the DNA associated protein, Barrier-to-Autointegration Factor (BAF). Most of the LEM proteins are integral proteins of the inner nuclear membrane and associate with the nuclear lamina, a structural scaffold of lamin intermediate filament proteins at the nuclear periphery, which is involved in nuclear mechanical functions and (hetero-)chromatin organization. A few LEM proteins, such as Lamina-associated polypeptide (LAP)2 α and Ankyrin and LEM domain-containing protein (Ankle)1 lack transmembrane domains and localize throughout the nucleoplasm and cytoplasm, respectively. LAP2 α has been reported to regulate cell proliferation by affecting the activity of retinoblastoma protein in tissue progenitor cells and numerous studies showed upregulation of LAP2 α in cancer. Ankle1 is a nuclease likely involved in DNA damage repair pathways and single nucleotide polymorphisms in the *Ankle1* gene have been linked to increased breast and ovarian cancer risk. In this chapter we describe potential mechanisms of the involvement of LEM proteins, particularly of LAP2 α and Ankle1 in tumorigenesis and we provide evidence that LAP2 α expression may be a valuable diagnostic and prognostic marker for tumor analyses.

Keywords

LEM-domain; Lamina associated polypeptide; Retinoblastoma protein; Lamin A; cell cycle; Ankyrin and LEM domain containing; DNA repair; telomere; E2F; TMPO; Thymopoietin

Introduction

The nucleus of eukaryotic cells is surrounded by a specialized internal membrane system, the nuclear envelope [1], which is composed of two membrane sheets, the inner (INM) and outer (ONM) nuclear membranes (Fig. 1). INM and ONM merge at the sites where nuclear pore complexes are inserted into the nuclear envelope, and the ONM is continuous with the endoplasmic reticulum [2]. In metazoan organisms, the nuclear envelope also includes the nuclear lamina that underlies the INM and serves as a structural scaffold for the nucleus [3,4]. It is formed by the type V intermediate filament proteins, the A- and B-type lamins, and by a number of integral and associated proteins of the INM. The nuclear envelope, and

in particular the nuclear lamina, are involved in nuclear architecture and nuclear mechanical functions [3,5], in chromatin organization and gene regulation through tethering and silencing heterochromatic regions [6-8], and in signaling through recruiting transcription regulators, epigenetic modifier enzymes and signaling molecules to the nuclear periphery [9,10]. In view of the multitude of functions of the nuclear envelope it is not surprising that several components of the nuclear lamina have been linked to various diseases ranging from muscular dystrophies and cardiomyopathies over to lipodystrophies and systemic diseases like the premature ageing syndrome Hutchinson-Gilford progeria [11].

LEM-domain containing proteins - a prominent family of nuclear (envelope) proteins

Mass spectrometric approaches revealed that the INM of mammalian cells contains over 80 integral proteins that are expressed in a tissue specific manner [12,13]. The LAP2-Emerin-MAN1 (LEM)-domain containing proteins (Fig. 1) represent one of the best studied family of INM proteins [14]. These proteins share the LEM domain, a 40 aa long bi-helical structure motif, which mediates binding to an abundant and essential chromatin protein in metazoan species termed Barrier-to-Autointegration-Factor (BAF) [15-18]. Therefore all LEM-proteins can associate with chromatin via BAF and it is generally assumed that they are involved in tethering chromatin to the nuclear periphery during interphase [19]. Most characterized INM LEM proteins bind lamins in the lamina and link the membrane to the lamina scaffold. In addition, several LEM proteins were shown to recruit and regulate signaling molecules [20] such as Smads involved in transforming growth factor beta (TGF β) and bone morphogenetic protein (BMP) signaling [21,22], β -catenin, a transcriptional co-activator of the Wnt signaling pathway, [23], the Lmo7 transcription factor [24], the germ cell less (GCL) transcriptional repressor [25,26], and histone deacetylase 3 (HDAC3) [27].

Mammalian genomes contain seven individual genes that encode LEM-domain proteins (Fig. 1): Lamina-associated polypeptide 2 (LAP2), Emerin, MAN1, LEM2, LEMD1, Ankle1 and Ankle2 [28,14,29]. In addition, Ankle1, LAP2 and LEMD1 generate various isoforms by alternative splicing. Most LEM proteins contain either one or two transmembrane domains and are integral components of the INM. However, two isoforms of the LAP2 gene (LAP2 α and ζ) and Ankle1 lack a membrane-spanning domain and localize to the nucleoplasm and cytoplasm [14]. In this review we describe and discuss evidence that the LAP2 isoform LAP2 α and potentially other LEM proteins may be involved in cancer development or may serve as useful diagnostic and prognostic markers for some types of cancers.

LAP2 proteins in cancer

The mammalian *LAP2 (TMPO)* gene, *also known as thymopoietin*, encodes six splice isoforms (α , β , γ , δ , ϵ , ζ), all sharing a common ~180 aa long N-terminal domain including the LEM-motif (interacting with the chromatin protein BAF) and an additional LEM-like motif in the very N-terminus, which interacts with DNA directly [15] (Fig. 2). While most LAP2 isoforms differ in their up to ~300 aa long C-terminus only due to the inclusion/exclusion of small, alternatively spliced domains, the ~500 aa long LAP2 α C-terminus is encoded by a single exon unique for LAP2 α [30]. Unlike the other major LAP2 isoforms, LAP2 α 's C-terminus lacks a C-terminal transmembrane domain and folds as an extensive

four-stranded antiparallel coiled coil dimer [31] that can also form higher oligomers [32]. In addition, while the membrane bound LAP2 isoforms localize at the INM and interact primarily with B-type lamins of the peripheral lamina [33], LAP2 α specifically binds A-type lamins via its unique C-terminus [34] in the nucleoplasm [35]. Furthermore, LAP2 α 's C-terminus mediates interaction with the cell cycle regulator and tumor suppressor, retinoblastoma protein (pRb) [36,35,37]. Recent observations that LAP2 α may be involved in the regulation of pRb localization and repressor activity led to the hypothesis that LAP2 α may play a role in tumorigenesis.

Potential role of LAP2 α and A-type lamins in pRb-mediated cell cycle control

The retinoblastoma protein (pRb) is one of the three pocket proteins (pRb, p107, p130) [38], which regulate cell cycle transition from G1 to S-phase, cell cycle exit and differentiation in multicellular eukaryotes [39-42]. A plethora of data has shown that pRb is one of the major tumor suppressors by preventing cell proliferation in the absence of strong mitogenic signals, and concordantly, in the majority of tumors the pRb pathway was found deregulated [43]. However, impaired pRb functions in cancer cells are rarely linked to mutations in the *RB1* gene (except in the hereditary form of the childhood retinoblastoma disease), but are caused by defects in the expression or activity of upstream regulators or downstream effectors of pRb. Also certain human viruses, *e.g.* human papilloma virus (HPV) or cytomegalovirus (CMV) impair pRb function by expressing proteins (HPV-E7 and CMV-IE86) that bind pRb with high affinity and affect binding and activity of normal cellular pRb regulators.

In non-tumor cells pRb is regulated by post-translational modifications (Fig. 3), among which phosphorylation by cyclin D/cyclin-dependent kinase (cdk) 4 at the G1/S phase transition, and cyclin E/cdk2 during S-phase, are the best studied ones. Only hypophosphorylated pRb binds to and represses the cell cycle-activating E2F transcription factors (E2F1, E2F2, E2F3), to allow cells to efficiently exit the cell cycle. Hyperphosphorylation of pRb by mitogen-activated cyclin dependent kinases inhibits its repressor function, since E2Fs are released from the complex, leading to transcriptional activation of E2F target genes required for S-phase progression (*e.g.* cyclin E, PCNA, thymidine kinase) [44]. This basic cell cycle-dependent regulation of pRb and E2Fs is fine-tuned by a complex network of proteins with pro- and anti-proliferative activities, which feed into reinforcing and attenuating signaling loops (Fig. 3). Cell cycle entry initiated by cyclin D/cdk4-dependent pRb phosphorylation and activation of E2F1 is reinforced by a positive feedback loop through E2F-dependent upregulation of E2Fs themselves and cyclins, maintaining hyper-phosphorylated pRb during S-phase [45]. On the other hand, E2Fs activate also negative cell cycle regulators [46], which provide a negative feedback loop to prevent uncontrolled proliferation. Among others, E2F1 activates transcription of *RB1*, anti-proliferative factors like p19^{ink4d} (an inhibitor of cdk4) [47], various checkpoint and DNA repair genes (*e.g.* p73 and ATM) and pro-apoptotic genes (*e.g.* APAF1, caspases) [44], as well as the transcriptional repressor E2F7 [48] which together with E2F4-6 silence promoters of cell cycle promoting genes independently of pRb [49].

How does LAP2 α fit into this complex regulatory network modulating pRb function? Both LAP2 α [36,37] and its nucleoplasmic binding partners lamin A and C (A-type lamins) [50] bind pRb directly. Several studies have revealed different mechanisms by which these proteins may affect pRb regulation (Fig. 4). LAP2 α was found to preferentially interact with hypophosphorylated pRb and is required for pRb anchorage in the nucleus [37]. LAP2 α overexpression in cells caused down-regulation of E2F-dependent reporter gene activity and repressed endogenous E2F target genes [36], suggesting that LAP2 α promotes pRb-mediated repression of target genes. Accordingly, overexpression of LAP2 α in pre-adipocytes promoted cell cycle exit and initiation of differentiation to adipocytes *in vitro* [36]. In contrast, fibroblasts derived from LAP2 α -deficient mice showed impaired pRb repressor activity, upregulated E2F/pRb target gene expression and delayed cell cycle exit upon contact inhibition. Also at the tissue and organismal level, progenitor cells in proliferative tissues showed impaired cell cycle regulation in the mouse model. Proliferating progenitors in the paw epidermis, in colon crypts and skeletal muscle were significantly upregulated, leading to epidermal hyperplasia, increased crypt length and an increased number of fiber-associated satellite cells, respectively [35]. Overall, LAP2 α seems to be important for an additional level of pRb regulation on top of the basic regulatory machinery, allowing an efficient activation of pRb repressor activity and pRb target gene repression to promote cell cycle exit (Fig. 3). Upon loss of LAP2 α , pRb activity is not lost but impaired, which may explain the observation that LAP2 α -deficient mice did not show a clearly increased incidence of cancer during their life time [35]. However, these mice have not been challenged yet with cancer promoting agents or treatments.

A-type lamins have been suggested to be required for pRb protein stabilization (Fig. 4) by preventing its proteasomal degradation [51,52]. Another study has suggested that A-type lamins form a platform allowing efficient PP2A-dependent dephosphorylation of pRb, which is required for efficient TGF β -induced cell cycle arrest of fibroblasts [53]. Yet another study reported a complex of pRb-lamin A in non-proliferating cells, keeping pRb in a hypophosphorylated state [54]. Mitogenic signal-dependent activation of MAPK signaling leads to translocation of ERK to the nucleus, where it displaces pRb from lamin A, which in turn becomes hyper-phosphorylated by cyclin/cdks. Interestingly, displacement of pRb from lamins did not require ERK's kinase activity.

Overall, these results indicate that LAP2 α and A-type lamins can activate pRb repressor activity and thereby act in an anti-proliferative manner (Figs 3 and 4). The molecular mechanisms how these proteins affect pRb activity are not yet clear. One could imagine various ways, such as stabilization of pRb protein, stable tethering of pRb to chromatin and/or promoters, preventing pRb phosphorylation or mediating efficient pRb dephosphorylation. Interestingly, lamin A has been shown to have repressive activity when artificially tethered to reporter gene promoters [55]. Furthermore, a recent study in *C. elegans* showed that a muscular dystrophy-linked lamin mutant impaired tissue-specific gene regulation during worm development [7]. Thus, lamin A may not only increase pRb-dependent gene repression, but may have more general roles maybe through recruiting epigenetic modifiers or changing overall chromatin state at promoters.

Another open question concerns the functional relationship between LAP2 α and A-type lamins in pRb-mediated gene regulation. A-type lamins are assumed to exist in 2 different sub-compartments in the nucleus: An estimated 90% of total A-type lamins localize to the nuclear envelope as a component of the nuclear lamina scaffold in a LAP2 α -independent pool, while ~10% localize throughout the nucleoplasm in a mobile and dynamic pool, most likely in association with LAP2 α [56,57,35]. It is unclear whether pRb binds preferentially to a LAP2 α - lamin complex in the nucleoplasm or to the peripheral lamina network (Fig. 4). Most studies on the role of A-type lamins in pRb-mediated cell cycle control do not discriminate between these two lamin pools, or assume, without clear experimental evidence that the peripheral nuclear lamina is involved. We favor a predominant role of nucleoplasmic lamins in the regulation of pRb-dependent gene expression for the following reasons: i) Peripheral localization of pRb, as predicted by a preferential docking of pRb to the lamina, has not been observed [58]. ii) Both knockout of LAP2 α in mice, which leads to specific loss of the nucleoplasmic lamin pool only, and total lamin A/C knockout, which affects both the peripheral and nucleoplasmic lamin A, showed the same misregulation of pRb and hyperproliferation phenotype in epidermal progenitor cells [35].

LAP2 α expression during the cell cycle and in the context of tumorigenesis

A number of studies have shown that LAP2 α is highest expressed in proliferating cells and is down-regulated upon cell cycle exit and differentiation [59,37,60,35] or is differentially expressed during the cell cycle in proliferating cells [61]. LAP2 α transcripts were also up-regulated during liver [62] and muscle regeneration *in vivo* [63,64], processes that involve transient controlled proliferation of progenitor cells. Independent studies on the LAP2 α promoter, based on chromatin immunoprecipitation and microarray techniques identified E2F1 and c-Myc [65], E2F1 and E2F4 [66], E2F3b [67] and E2F7 [68] on the LAP2 promoter, suggesting that the expression of the LAP2 gene is under direct control of major cell cycle regulators, such as E2Fs. Interestingly both, cell cycle driving (i.e. c-Myc, E2F1) and repressing transcription factors (i.e. E2F3b, E2F4, E2F7) seem to regulate the LAP2 promoter, which points to a complex feedback mechanism. From these studies it remains unclear, though, whether all LAP2 isoforms are similarly regulated. In line with its high expression in proliferating cells, LAP2 α was found to be overexpressed in various human tumor samples and cancer-derived cell lines at transcript and protein levels (examples summarized in Table 1).

Is cancer-related LAP2 α overexpression cause or consequence of proliferation?

Numerous studies found LAP2 or LAP2 α overexpressed in tumor cells (Table 1), frequently correlated with the up-regulation of tumor-relevant signaling pathways such as the NEK2- [69], Gli- [70], Notch- [71] and Estrogen- [72,73] pathways. Thus, many studies have shown a consistent correlation between active proliferation and up-regulation of LAP2 transcription during physiological processes and in a variety of cancers. These results are inconsistent with an anti-proliferative activity of LAP2 α , predicted from the studies in mice and several cell lines mentioned above. On the one hand LAP2 α seems to be up-regulated in most if not all proliferating, particularly cancer cells: on the other hand LAP2 α expression is predicted to have an anti-proliferative function. How can one solve this apparent discrepancy? Is

LAP2 α causally involved in promoting proliferation of cancer cells or is its upregulation a consequence of the high proliferation activity of these cells?

A potential causal positive relation between LAP2 α levels and proliferation is only supported by a handful of reports consistent with a pro-proliferative effect of the LAP2 α -lamin A complex. Both RNA interference-mediated knockdown of lamin A and LAP2 α caused cell cycle arrest in primary human dermal fibroblasts [58]. Furthermore muscular dystrophy-linked homozygous mutations in the *LMNA* gene in patient-derived fibroblasts, leading to loss of lamin protein expression, severely impaired cell proliferation [74]. Additionally, fibroblasts derived from Hutchinson-Gilford progeria patients expressing the very different lamin A variant progerin, lacking 50 amino acids and permanently farnesylated, caused passage-dependent proliferation defects in culture [75]. Similarly postnatal fibroblasts, but not embryonic fibroblasts, from a progeria mouse model showed proliferative arrest and cell death [76]. However in all these cases, it seems likely that the anti-proliferative effect is caused indirectly by DNA damage and/or deregulation of signaling pathways, which lead to the activation of cell cycle checkpoints. For example progeria cells have been shown to accumulate DNA damage during *in vitro* passage [75], and mouse fibroblasts from a progeria model have a defective Wnt signaling causing misregulation of extracellular matrix components [76].

Overall, it seems very likely that LAP2 α and lamin A have an anti-proliferative activity through promoting pRb repressor activity as described above. The increased LAP2 α protein levels in proliferating versus non-proliferating cells and in tumor versus normal cells may simply be a consequence of the mitogen-induced increase in E2F1 activity. We propose that in normal cells the E2F1-dependent up-regulation of LAP2 α provides a negative feedback loop that ensures efficient LAP2 α -mediated activation of pRb repressor activity causing inhibition of E2F-dependent transcription and cell cycle exit. Cancer cells acquire multiple changes impacting on the pRb and p53 checkpoint pathways. If these changes impair the pRb pathway, LAP2 α overexpression would be unable to activate the pRb-mediated negative cell cycle feedback loop. In line with this hypothesis, several studies reported that viral oncoproteins affect LAP2 expression levels via inactivation of pRb [77,78] and p53 pathways [78]. For example, expression of HPV proteins E6 and E7, which are known to inhibit p53 and pRb by direct binding [79], is linked to an upregulation of LAP2 α in cervical cancer cells [78]. Knockdown of E6 or E7 in these cells restored p53 and pRb activity, respectively, and caused down-regulation of LAP2 α . Conversely, knockdown of p53 in normal human fibroblasts increased LAP2 α levels [78]. Similarly, expression of CMV IE86, an inhibitor of pRb led to up-regulation of LAP2 levels [77], and the LAP2 promoter was shown to be regulated by the pRb-p16ink4a pathway [80] and by E2F7, which is a target of p53 [68]. Unfortunately, these studies did not look at the relationship between p53/pRb-mediated LAP2 expression control and tumorigenic behavior of cells.

Overall we conclude that LAP2 α overexpression in cancer cells is possible only upon additional changes that promote cell cycle progression, like amplification of c-myc, hyperactivity of mitogenic signaling or loss of repressive factors. This may also explain why overexpression of LAP2 α was linked to a worse patient prognosis [81,82]. LAP2 α may thus be a useful diagnostic and prognostic gene in tumorigenesis.

LAP2 α at telomeres - a link to DNA damage repair?

Several microscopy studies revealed that LAP2 α is highly dynamic and changes its localization during the cell cycle. While it localizes throughout the nucleoplasm in interphase and disperses in the cytoplasm upon nuclear envelope breakdown in prophase, it associates with (sub-)telomeric regions on chromosomes during late anaphase and telophase [56] (Fig. 5). In addition, a proteomic approach identified LAP2 α in a complex with the telomere repeat binding factor 1 (TRF1) [83], a component of the telomeric shelterin complex that protects and regulates telomeres. The physiological relevance of these findings is still unclear, but several recent observations are consistent with a potential role of LAP2 α in a DNA damage-response pathway at telomeres, which is known to be required for functional telomeres [84].

Several studies showed that lamin A is involved in DNA repair and telomere maintenance [85-87]. LAP2 α was found to associate with Werner helicase, WRN [88], a protein well-known for its role in telomere maintenance and DNA repair [89]. Both Werner helicase and LAP2 α were found in two independent studies in a complex with Ku86 [90], a key protein involved in non-homologous end joining DNA repair pathways and in telomere protection [91-93]. LAP2 α also appeared among the top hits in an interaction screen of proteins modified with Poly(ADP-ribose) scaffolds [94], which are generated by poly(ADP-ribose) polymerases (PARPs) at sites of DNA damage and serve as docking site for DNA damage signaling and repair proteins. Interestingly, the PARP tankyrase localizes to telomeres and targets TRF1 in S/G2 phase, thereby triggering the release of TRF1 from telomeres and allowing access for telomerase and telomere-processing enzymes.

Overall, LAP2 α may be involved in telomere maintenance or protection pathways. However, as LAP2 α deficient mice did not show any of the phenotypes associated with dysfunctional telomeres (*e.g.* premature aging, infertility, increased occurrence of tumors), it seems unlikely that LAP2 α is essential for telomere maintenance. Having said this, one has to take into account that telomere biology is substantially different in rodents and humans, including the broader expression of telomerase in mouse versus human cells and tissues and the about 5-10 times longer telomeres in murine *versus* human cells. Therefore it is still possible that aberrant LAP2 α function may have an impact on telomere maintenance in human cancer.

The potential relevance of other LAP2 isoforms in cancer

Two studies have reported a potential link between cancer and LAP2 β , the largest membrane-bound LAP2 isoform. LAP2 β was upregulated in various digestive tract cancers (stomach, liver, pancreas and bile duct) [95]. Knockdown of LAP2 β in cancer cells reduced — whereas ectopic expression of LAP2 β increased — cell motility, but had no effect on cell proliferation. LAP2 β knockdown also induced significant changes in gene expression [95], which is likely linked to the previously reported interaction of LAP2 β with histone deacetylase 3 (HDAC3) and its involvement in gene regulation at the nuclear envelope [96]. LAP2 β upregulation was also reported in lymphoma patient samples and in normal human lymphocytes upon mitogenic stimulation with phytohaemagglutinin [97]. Since also LAP2 α

was found upregulated in phytohaemagglutinin stimulated cells this is likely a consequence of proliferation dependent activation of the LAP2 promoter.

Links of other LEM proteins to cancer

LEMD1, a germline LEM protein is re-expressed in cancer cells

LEMD1 is a mammalian-specific LEM-protein of the INM expressed exclusively in testis as six alternatively spliced isoforms. Interestingly, LEMD1 was initially described as a component overexpressed in colorectal tumor samples [98], prostate cancer [99] and lymphoma cells [100]. Hence, LEMD1 was postulated to belong to the cancer/testis antigens [98], a group of about 40 germ line-specific genes, that are re-expressed in tumors originating from unrelated cell types [101]. However, neither the biological functions of LEMD1 nor its contribution to tumorigenesis are known.

Polymorphisms in the Ankle1 gene are linked to breast and ovarian cancer risk

In breast and ovarian cancer, female and male carriers of mutant alleles of the breast cancer associated genes BRCA1 and BRCA2 bear a dramatically increased risk to develop cancer compared to the reference population. Inherited BRCA1 and BRCA2 mutations account for approximately 5% of all cases of breast and 14% of ovarian cancers [102]. In families with inherited predisposition for breast cancer or with a combined risk for breast and ovarian cancers, the frequency of BRCA mutations is 40% and > 80%, respectively [103]. Some other cases of families with an inherited predisposition for breast cancer show no mutations in the coding sequences of BRCA1 and BRCA2. Therefore, it is assumed that other high risk breast cancer genes exist, or that a combination of genetic variants of low penetrance genes exert additive effects manifesting in a significantly increased risk to develop breast or ovarian cancer [102]. Several recently published studies employed high-throughput genomic analyses of breast and ovarian cancer patient samples aiming at the identification of loci containing such low penetrance genes that may modulate cancer risk [104-108].

Intriguingly, two single nucleotide polymorphisms (SNPs) locating at chromosomal locus 19p13.11 consistently appeared in all of these studies showing a statistically significant link to breast cancer susceptibility. These SNPs are localized within the coding sequence of the gene encoding Ankyrin and LEM-domain containing protein 1 (Ankle1) and lead to amino acid changes within the polypeptide. Ankle1 is a conserved gene in metazoan species encoding an unusual LEM protein described in two recent studies in *C. elegans* and mammalian cells [109,110]. Ankle1 lacks a transmembrane domain and shuttles between the nucleoplasm and cytoplasm in human cells [109]. Intriguingly, Ankle1 contains a GIY-YIG-type endonuclease domain, which was shown to cleave DNA *in vitro* and *in vivo* [109,110]. While Ankle1 overexpression in mammalian cells activates DNA damage response pathways, a *C. elegans* strain carrying a point mutation in the *lem-3* gene — the *C. elegans* ortholog of Ankle1 — was hypersensitive towards DNA damaging agents. Altogether, these studies suggest that Ankle1 may be an enzyme involved in DNA repair pathways.

Considering that the vast majority of mutations predisposing carriers to breast cancer were identified in genes involved in DNA damage signaling and repair (e.g. BRCA1, BRCA2,

Rad51, Chk2, ATM, p53), the endonuclease Ankle1 may indeed be a relevant factor for tumorigenesis.

Acknowledgements

We thank Andreas Gajewski and Thomas Dechat, MFPL, Vienna, for generously providing immunofluorescence images shown in Fig. 5. Work in the authors' laboratory was supported by grants from the Austrian Science Research Fund (FWF P22569-B09 and P23805-B20) to RF and from the "Herzfelder'sche Familienstiftung" to AB.

Abbreviations

CMV	cytomegalovirus
HPV	human papilloma virus
INM	inner nuclear membrane
ONM	outer nuclear membrane
PARP	poly(ADP-ribose) polymerase
SNP	single nucleotide polymorphism

References

1. Wilson KL, Dawson SC. Evolution: functional evolution of nuclear structure. *J Cell Biol.* 2011; 195(2):171–181. doi:jcb.201103171 [pii] 10.1083/jcb.201103171. [PubMed: 22006947]
2. Mekhail K, Moazed D. The nuclear envelope in genome organization, expression and stability. *Nat Rev Mol Cell Biol.* 2010; 11(5):317–328. doi:nrm2894 [pii] 10.1038/nrm2894. [PubMed: 20414256]
3. Dechat T, Pflieger K, Sengupta K, Shimi T, Shumaker DK, Solimando L, Goldman RD. Nuclear lamins: major factors in the structural organization and function of the nucleus and chromatin. *Genes Dev.* 2008; 22(7):832–853. doi:22/7/832 [pii] 10.1101/gad.1652708. [PubMed: 18381888]
4. Parnai VK. Role of nuclear lamins in nuclear organization, cellular signaling, and inherited diseases. *Int Rev Cell Mol Biol.* 2008; 266:157–206. doi:S1937-6448(07)66004-3 [pii] 10.1016/S1937-6448(07)66004-3. [PubMed: 18544494]
5. Dahl KN, Ribeiro AJ, Lammerding J. Nuclear shape, mechanics, and mechanotransduction. *Circ Res.* 2008; 102(11):1307–1318. doi:102/11/1307 [pii] 10.1161/CIRCRESAHA.108.173989. [PubMed: 18535268]
6. Kind J, van Steensel B. Genome-nuclear lamina interactions and gene regulation. *Curr Opin Cell Biol.* 2010; 22(3):320–325. doi:S0955-0674(10)00054-2 [pii] 10.1016/j.ceb.2010.04.002. [PubMed: 20444586]
7. Mattout A, Pike BL, Towbin BD, Bank EM, Gonzalez-Sandoval A, Stadler MB, Meister P, Gruenbaum Y, Gasser SM. An EDMD mutation in *C. elegans* lamin blocks muscle-specific gene relocation and compromises muscle integrity. *Curr Biol.* 2011; 21(19):1603–1614. doi:S0960-9822(11)00936-5 [pii] 10.1016/j.cub.2011.08.030. [PubMed: 21962710]
8. Solovei I, Wang AS, Thanisch K, Schmidt CS, Krebs S, Zwerger M, Cohen TV, Devys D, Foisner R, Peichl L, Herrmann H, Blum H, Engelkamp D, Stewart CL, Leonhardt H, Joffe B. LBR and Lamin A/C Sequentially Tether Peripheral Heterochromatin and Inversely Regulate Differentiation. *Cell.* 2013; 152(3):584–598. doi:S0092-8674(13)00012-3 [pii] 10.1016/j.cell.2013.01.009. [PubMed: 23374351]
9. Andres V, Gonzalez JM. Role of A-type lamins in signaling, transcription, and chromatin organization. *J Cell Biol.* 2009; 187(7):945–957. doi:jcb.200904124 [pii] 10.1083/jcb.200904124. [PubMed: 20038676]

10. Heessen S, Fornerod M. The inner nuclear envelope as a transcription factor resting place. *EMBO Rep.* 2007; 8(10):914–919. doi:7401075 [pii] 10.1038/sj.embor.7401075. [PubMed: 17906672]
11. Worman HJ. Nuclear lamins and laminopathies. *J Pathol.* 2012; 226(2):316–325. doi:10.1002/path.2999. [PubMed: 21953297]
12. Korfali N, Wilkie GS, Swanson SK, Srsen V, de Las Heras J, Batrakou DG, Malik P, Zuleger N, Kerr AR, Florens L, Schirmer EC. The nuclear envelope proteome differs notably between tissues. *Nucleus.* 2012; 3(6):552–564. doi:22257 [pii] 10.4161/nucl.22257. [PubMed: 22990521]
13. Schirmer EC, Florens L, Guan T, Yates JR 3rd, Gerace L. Nuclear membrane proteins with potential disease links found by subtractive proteomics. *Science.* 2003; 301(5638):1380–1382. doi:10.1126/science.1088176 301/5638/1380 [pii]. [PubMed: 12958361]
14. Brachner A, Foisner R. Evolvement of LEM proteins as chromatin tethers at the nuclear periphery. *Biochem Soc Trans.* 2011; 39(6):1735–1741. doi:BST20110724 [pii] 10.1042/BST20110724. [PubMed: 22103517]
15. Cai M, Huang Y, Ghirlando R, Wilson KL, Craigie R, Clore GM. Solution structure of the constant region of nuclear envelope protein LAP2 reveals two LEM-domain structures: one binds BAF and the other binds DNA. *EMBO J.* 2001; 20(16):4399–4407. doi:10.1093/emboj/20.16.4399. [PubMed: 11500367]
16. Shumaker DK, Lee KK, Tanhehco YC, Craigie R, Wilson KL. LAP2 binds to BAF.DNA complexes: requirement for the LEM domain and modulation by variable regions. *EMBO J.* 2001; 20(7):1754–1764. doi:10.1093/emboj/20.7.1754. [PubMed: 11285238]
17. Lin F, Blake DL, Callebaut I, Skerjanc IS, Holmer L, McBurney MW, Paulin-Levasseur M, Worman HJ. MAN1, an inner nuclear membrane protein that shares the LEM domain with lamina-associated polypeptide 2 and emerin. *J Biol Chem.* 2000; 275(7):4840–4847. [PubMed: 10671519]
18. Cai M, Huang Y, Suh JY, Louis JM, Ghirlando R, Craigie R, Clore GM. Solution NMR structure of the barrier-to-autointegration factor-Emerin complex. *J Biol Chem.* 2007; 282(19):14525–14535. doi:M700576200 [pii] 10.1074/jbc.M700576200. [PubMed: 17355960]
19. Wilson KL, Foisner R. Lamin-binding Proteins. *Cold Spring Harb Perspect Biol.* 2010; 2(4):a000554. doi:cshperspect.a000554 [pii] 10.1101/cshperspect.a000554. [PubMed: 20452940]
20. Wilson KL, Berk JM. The nuclear envelope at a glance. *J Cell Sci.* 2010; 123(Pt 12):1973–1978. doi:123/12/1973 [pii] 10.1242/jcs.019042. [PubMed: 20519579]
21. Pan D, Estevez-Salmeron LD, Stroschein SL, Zhu X, He J, Zhou S, Luo K. The integral inner nuclear membrane protein MAN1 physically interacts with the R-Smad proteins to repress signaling by the transforming growth factor- β superfamily of cytokines. *J Biol Chem.* 2005; 280(16):15992–16001. doi:M411234200 [pii] 10.1074/jbc.M411234200. [PubMed: 15647271]
22. Lin F, Morrison JM, Wu W, Worman HJ. MAN1, an integral protein of the inner nuclear membrane, binds Smad2 and Smad3 and antagonizes transforming growth factor- β signaling. *Hum Mol Genet.* 2005; 14(3):437–445. doi:ddi040 [pii] 10.1093/hmg/ddi040. [PubMed: 15601644]
23. Markiewicz E, Tilgner K, Barker N, van de Wetering M, Clevers H, Dorobek M, Hausmanowa-Petrusewicz I, Ramaekers FC, Broers JL, Blankesteyn WM, Salpingidou G, Wilson RG, Ellis JA, Hutchison CJ. The inner nuclear membrane protein emerin regulates beta-catenin activity by restricting its accumulation in the nucleus. *EMBO J.* 2006; 25(14):3275–3285. doi:7601230 [pii] 10.1038/sj.emboj.7601230. [PubMed: 16858403]
24. Dedeic Z, Cetera M, Cohen TV, Holaska JM. Emerin inhibits Lmo7 binding to the Pax3 and MyoD promoters and expression of myoblast proliferation genes. *J Cell Sci.* 2011; 124(Pt 10):1691–1702. doi:jcs.080259 [pii] 10.1242/jcs.080259. [PubMed: 21525034]
25. Holaska JM, Lee KK, Kowalski AK, Wilson KL. Transcriptional repressor germ cell-less (GCL) and barrier to autointegration factor (BAF) compete for binding to emerin in vitro. *J Biol Chem.* 2003; 278(9):6969–6975. doi:10.1074/jbc.M208811200 M208811200 [pii]. [PubMed: 12493765]
26. Nili E, Cojocaru GS, Kalma Y, Ginsberg D, Copeland NG, Gilbert DJ, Jenkins NA, Berger R, Shalkai S, Amariglio N, Brok-Simoni F, Simon AJ, Rechavi G. Nuclear membrane protein LAP2 β mediates transcriptional repression alone and together with its binding partner GCL (germ-cell-less). *J Cell Sci.* 2001; 114(Pt 18):3297–3307. [PubMed: 11591818]

27. Demmerle J, Koch AJ, Holaska JM. The nuclear envelope protein emerin binds directly to histone deacetylase 3 (HDAC3) and activates HDAC3 activity. *J Biol Chem.* 2012; 287(26):22080–22088. doi:M111.325308 [pii] 10.1074/jbc.M111.325308. [PubMed: 22570481]
28. Wagner N, Krohne G. LEM-Domain proteins: new insights into lamin-interacting proteins. *Int Rev Cytol.* 2007; 261:1–46. doi:S0074-7696(07)61001-8 [pii] 10.1016/S0074-7696(07)61001-8. [PubMed: 17560279]
29. Lee KK, Wilson KL. All in the family: evidence for four new LEM-domain proteins Lem2 (NET-25), Lem3, Lem4 and Lem5 in the human genome. *Symp Soc Exp Biol.* 2004; (56):329–339. [PubMed: 15565891]
30. Harris CA, Andryuk PJ, Cline SW, Mathew S, Siekierka JJ, Goldstein G. Structure and mapping of the human thymopoietin (TMPO) gene and relationship of human TMPO beta to rat lamin-associated polypeptide 2. *Genomics.* 1995; 28(2):198–205. doi:S0888-7543(85)71131-7 [pii] 10.1006/geno.1995.1131. [PubMed: 8530026]
31. Bradley CM, Jones S, Huang Y, Suzuki Y, Kvaratskhelia M, Hickman AB, Craigie R, Dyda F. Structural basis for dimerization of LAP2alpha, a component of the nuclear lamina. *Structure.* 2007; 15(6):643–653. doi:S0969-2126(07)00174-8 [pii] 10.1016/j.str.2007.04.007. [PubMed: 17562312]
32. Snyers L, Vlcek S, Dechat T, Skegro D, Korbei B, Gajewski A, Mayans O, Schofer C, Foisner R. Lamina-associated polypeptide 2-alpha forms homo-trimers via its C terminus, and oligomerization is unaffected by a disease-causing mutation. *J Biol Chem.* 2007; 282(9):6308–6315. doi:M605782200 [pii] 10.1074/jbc.M605782200. [PubMed: 17213199]
33. Foisner R, Gerace L. Integral membrane proteins of the nuclear envelope interact with lamins and chromosomes, and binding is modulated by mitotic phosphorylation. *Cell.* 1993; 73(7):1267–1279. doi:0092-8674(93)90355-T [pii]. [PubMed: 8324822]
34. Dechat T, Korbei B, Vaughan OA, Vlcek S, Hutchison CJ, Foisner R. Lamina-associated polypeptide 2alpha binds intranuclear A-type lamins. *J Cell Sci.* 2000; 113(Pt 19):3473–3484. [PubMed: 10984438]
35. Naetar N, Korbei B, Kozlov S, Kerenyi MA, Dorner D, Kral R, Gotic I, Fuchs P, Cohen TV, Bittner R, Stewart CL, Foisner R. Loss of nucleoplasmic LAP2alpha-lamin A complexes causes erythroid and epidermal progenitor hyperproliferation. *Nat Cell Biol.* 2008; 10(11):1341–1348. doi:ncb1793 [pii] 10.1038/ncb1793. [PubMed: 18849980]
36. Dorner D, Vlcek S, Foeger N, Gajewski A, Makolm C, Gotzmann J, Hutchison CJ, Foisner R. Lamina-associated polypeptide 2alpha regulates cell cycle progression and differentiation via the retinoblastoma-E2F pathway. *J Cell Biol.* 2006; 173(1):83–93. doi:jcb.200511149 [pii] 10.1083/jcb.200511149. [PubMed: 16606692]
37. Markiewicz E, Dechat T, Foisner R, Quinlan RA, Hutchison CJ. Lamin A/C binding protein LAP2alpha is required for nuclear anchorage of retinoblastoma protein. *Mol Biol Cell.* 2002; 13(12):4401–4413. doi:10.1091/mbc.E02-07-0450. [PubMed: 12475961]
38. Grana X, Garriga J, Mayol X. Role of the retinoblastoma protein family, pRB, p107 and p130 in the negative control of cell growth. *Oncogene.* 1998; 17(25):3365–3383. doi:10.1038/sj.onc.1202575. [PubMed: 9916999]
39. Poznic M. Retinoblastoma protein: a central processing unit. *J Biosci.* 2009; 34(2):305–312. [PubMed: 19550046]
40. Zhu L. Tumour suppressor retinoblastoma protein Rb: a transcriptional regulator. *Eur J Cancer.* 2005; 41(16):2415–2427. doi:S0959-8049(05)00707-0 [pii] 10.1016/j.ejca.2005.08.009. [PubMed: 16209920]
41. Bartek J, Bartkova J, Lukas J. The retinoblastoma protein pathway and the restriction point. *Curr Opin Cell Biol.* 1996; 8(6):805–814. doi:S0955-0674(96)80081-0 [pii]. [PubMed: 8939678]
42. Weinberg RA. The retinoblastoma protein and cell cycle control. *Cell.* 1995; 81(3):323–330. doi:0092-8674(95)90385-2 [pii]. [PubMed: 7736585]
43. Malumbres M, Barbacid M. To cycle or not to cycle: a critical decision in cancer. *Nat Rev Cancer.* 2001; 1(3):222–231. doi:10.1038/35106065. [PubMed: 11902577]

44. Bracken AP, Ciro M, Cocito A, Helin K. E2F target genes: unraveling the biology. *Trends Biochem Sci.* 2004; 29(8):409–417. doi:S0968-0004(04)00151-3 [pii] 10.1016/j.tibs.2004.06.006. [PubMed: 15362224]
45. Wong JV, Dong P, Nevins JR, Mathey-Prevot B, You L. Network calisthenics: control of E2F dynamics in cell cycle entry. *Cell Cycle.* 2011; 10(18):3086–3094. doi:17350 [pii]. [PubMed: 21900750]
46. Polager S, Ginsberg D. E2F - at the crossroads of life and death. *Trends Cell Biol.* 2008; 18(11): 528–535. doi:S0962-8924(08)00214-6 [pii] 10.1016/j.tcb.2008.08.003. [PubMed: 18805009]
47. Carcagno AL, Marazita MC, Ogara MF, Ceruti JM, Sonzogni SV, Scassa ME, Giono LE, Canepa ET. E2F1-mediated upregulation of p19INK4d determines its periodic expression during cell cycle and regulates cellular proliferation. *PLoS One.* 2011; 6(7):e21938. doi:10.1371/journal.pone.0021938 PONE-D-11-06188 [pii]. [PubMed: 21765927]
48. Lammens T, Li J, Leone G, De Veylder L. Atypical E2Fs: new players in the E2F transcription factor family. *Trends Cell Biol.* 2009; 19(3):111–118. doi:S0962-8924(09)00026-9 [pii] 10.1016/j.tcb.2009.01.002. [PubMed: 19201609]
49. Chen HZ, Tsai SY, Leone G. Emerging roles of E2Fs in cancer: an exit from cell cycle control. *Nat Rev Cancer.* 2009; 9(11):785–797. doi:nrc2696 [pii] 10.1038/nrc2696. [PubMed: 19851314]
50. Ozaki T, Saijo M, Murakami K, Enomoto H, Taya Y, Sakiyama S. Complex formation between lamin A and the retinoblastoma gene product: identification of the domain on lamin A required for its interaction. *Oncogene.* 1994; 9(9):2649–2653. [PubMed: 8058329]
51. Johnson BR, Nitta RT, Frock RL, Mounkes L, Barbie DA, Stewart CL, Harlow E, Kennedy BK. A-type lamins regulate retinoblastoma protein function by promoting subnuclear localization and preventing proteasomal degradation. *Proc Natl Acad Sci U S A.* 2004; 101(26):9677–9682. doi: 10.1073/pnas.0403250101 0403250101 [pii]. [PubMed: 15210943]
52. Nitta RT, Jameson SA, Kudlow BA, Conlan LA, Kennedy BK. Stabilization of the retinoblastoma protein by A-type nuclear lamins is required for INK4A-mediated cell cycle arrest. *Molecular and cellular biology.* 2006; 26(14):5360–5372. doi:26/14/5360 [pii] 10.1128/MCB.02464-05. [PubMed: 16809772]
53. Van Berlo JH, Voncken JW, Kubben N, Broers JL, Duisters R, van Leeuwen RE, Crijns HJ, Ramaekers FC, Hutchison CJ, Pinto YM. A-type lamins are essential for TGF-beta1 induced PP2A to dephosphorylate transcription factors. *Hum Mol Genet.* 2005; 14(19):2839–2849. doi:ddi316 [pii] 10.1093/hmg/ddi316. [PubMed: 16115815]
54. Rodriguez J, Calvo F, Gonzalez JM, Casar B, Andres V, Crespo P. ERK1/2 MAP kinases promote cell cycle entry by rapid, kinase-independent disruption of retinoblastoma-lamin A complexes. *J Cell Biol.* 2010; 191(5):967–979. doi:jcb.201004067 [pii] 10.1083/jcb.201004067. [PubMed: 21115804]
55. Lee DC, Welton KL, Smith ED, Kennedy BK. A-type nuclear lamins act as transcriptional repressors when targeted to promoters. *Exp Cell Res.* 2009; 315(6):996–1007. doi:S0014-4827(09)00014-7 [pii] 10.1016/j.yexcr.2009.01.003. [PubMed: 19272320]
56. Dechat T, Gajewski A, Korbei B, Gerlich D, Daigle N, Haraguchi T, Furukawa K, Ellenberg J, Foisner R. LAP2alpha and BAF transiently localize to telomeres and specific regions on chromatin during nuclear assembly. *J Cell Sci.* 2004; 117(Pt 25):6117–6128. doi:jcs.01529 [pii] 10.1242/jcs.01529. [PubMed: 15546916]
57. Moir RD, Yoon M, Khuon S, Goldman RD. Nuclear lamins A and B1: different pathways of assembly during nuclear envelope formation in living cells. *J Cell Biol.* 2000; 151(6):1155–1168. [PubMed: 11121432]
58. Pekovic V, Harborth J, Broers JL, Ramaekers FC, van Engelen B, Lammens M, von Zglinicki T, Foisner R, Hutchison C, Markiewicz E. Nucleoplasmic LAP2alpha-lamin A complexes are required to maintain a proliferative state in human fibroblasts. *J Cell Biol.* 2007; 176(2):163–172. doi:jcb.200606139 [pii] 10.1083/jcb.200606139. [PubMed: 17227891]
59. Gotic I, Schmidt WM, Biadasiewicz K, Leschnik M, Spilka R, Braun J, Stewart CL, Foisner R. Loss of LAP2 alpha delays satellite cell differentiation and affects postnatal fiber-type determination. *Stem Cells.* 2010; 28(3):480–488. doi:10.1002/stem.292. [PubMed: 20039368]

60. Markiewicz E, Ledran M, Hutchison CJ. Remodelling of the nuclear lamina and nucleoskeleton is required for skeletal muscle differentiation in vitro. *J Cell Sci.* 2005; 118(Pt 2):409–420. doi: 118/2/409 [pii] 10.1242/jcs.01630. [PubMed: 15654018]
61. Whitfield ML, Sherlock G, Saldanha AJ, Murray JI, Ball CA, Alexander KE, Matese JC, Perou CM, Hurt MM, Brown PO, Botstein D. Identification of genes periodically expressed in the human cell cycle and their expression in tumors. *Mol Biol Cell.* 2002; 13(6):1977–2000. doi:10.1091/mbc.02-02-0030. [PubMed: 12058064]
62. Dong HM, Xu CS. Analysis of the relevance of e2fs and their target genes with rat liver regeneration. *Indian J Gastroenterol.* 2008; 27(1):31–32. [PubMed: 18541936]
63. Melcon G, Kozlov S, Cutler DA, Sullivan T, Hernandez L, Zhao P, Mitchell S, Nader G, Bakay M, Rottman JN, Hoffman EP, Stewart CL. Loss of emerin at the nuclear envelope disrupts the Rb1/E2F and MyoD pathways during muscle regeneration. *Hum Mol Genet.* 2006; 15(4):637–651. doi:ddi479 [pii] 10.1093/hmg/ddi479. [PubMed: 16403804]
64. Bakay M, Wang Z, Melcon G, Schiltz L, Xuan J, Zhao P, Sartorelli V, Seo J, Pegoraro E, Angelini C, Shneiderman B, Escolar D, Chen YW, Winokur ST, Pachman LM, Fan C, Mandler R, Nevo Y, Gordon E, Zhu Y, Dong Y, Wang Y, Hoffman EP. Nuclear envelope dystrophies show a transcriptional fingerprint suggesting disruption of Rb-MyoD pathways in muscle regeneration. *Brain.* 2006; 129(Pt 4):996–1013. doi:awl023 [pii] 10.1093/brain/awl023. [PubMed: 16478798]
65. Li Z, Van Calcar S, Qu C, Cavenee WK, Zhang MQ, Ren B. A global transcriptional regulatory role for c-Myc in Burkitt's lymphoma cells. *Proc Natl Acad Sci U S A.* 2003; 100(14):8164–8169. doi:10.1073/pnas.1332764100 1332764100 [pii]. [PubMed: 12808131]
66. Ren B, Cam H, Takahashi Y, Volkert T, Terragni J, Young RA, Dynlacht BD. E2F integrates cell cycle progression with DNA repair, replication, and G(2)/M checkpoints. *Genes Dev.* 2002; 16(2):245–256. doi:10.1101/gad.949802. [PubMed: 11799067]
67. Asp P, Acosta-Alvear D, Tsikitis M, van Oevelen C, Dynlacht BD. E2f3b plays an essential role in myogenic differentiation through isoform-specific gene regulation. *Genes Dev.* 2009; 23(1):37–53. doi:23/1/37 [pii] 10.1101/gad.1727309. [PubMed: 19136625]
68. Westendorp B, Mokry M, Groot Koerkamp MJ, Holstege FC, Cuppen E, de Bruin A. E2F7 represses a network of oscillating cell cycle genes to control S-phase progression. *Nucleic Acids Res.* 2012; 40(8):3511–3523. doi:gkr1203 [pii] 10.1093/nar/gkr1203. [PubMed: 22180533]
69. Zhou W, Yang Y, Xia J, Wang H, Salama ME, Xiong W, Xu H, Shetty S, Chen T, Zeng Z, Shi L, Zangari M, Miles R, Bearss D, Tricot G, Zhan F. NEK2 Induces Drug Resistance Mainly through Activation of Efflux Drug Pumps and Is Associated with Poor Prognosis in Myeloma and Other Cancers. *Cancer Cell.* 2013; 23(1):48–62. doi:S1535-6108(12)00514-4 [pii] 10.1016/j.ccr.2012.12.001. [PubMed: 23328480]
70. Shi T, Mazumdar T, Devecchio J, Duan ZH, Agyeman A, Aziz M, Houghton JA. cDNA microarray gene expression profiling of hedgehog signaling pathway inhibition in human colon cancer cells. *PLoS One.* 2010; 5(10) doi:10.1371/journal.pone.0013054.
71. Viatour P, Ehmer U, Saddic LA, Dorrell C, Andersen JB, Lin C, Zmoos AF, Mazur PK, Schaffer BE, Ostermeier A, Vogel H, Sylvester KG, Thorgeirsson SS, Grompe M, Sage J. Notch signaling inhibits hepatocellular carcinoma following inactivation of the RB pathway. *J Exp Med.* 2011; 208(10):1963–1976. doi:jem.20110198 [pii] 10.1084/jem.20110198. [PubMed: 21875955]
72. Moudgil VK, Dinda S, Khattree N, Jhanwar S, Alban P, Hurd C. Hormonal regulation of tumor suppressor proteins in breast cancer cells. *J Steroid Biochem Mol Biol.* 2001; 76(1-5):105–117. doi:S0960076000001515 [pii]. [PubMed: 11384868]
73. Buterin T, Koch C, Naegeli H. Convergent transcriptional profiles induced by endogenous estrogen and distinct xenoestrogens in breast cancer cells. *Carcinogenesis.* 2006; 27(8):1567–1578. doi:bgi339 [pii] 10.1093/carcin/bgi339. [PubMed: 16474171]
74. Muchir A, van Engelen BG, Lammens M, Mislou JM, McNally E, Schwartz K, Bonne G. Nuclear envelope alterations in fibroblasts from LGMD1B patients carrying nonsense Y259X heterozygous or homozygous mutation in lamin A/C gene. *Exp Cell Res.* 2003; 291(2):352–362. doi:S0014482703003902 [pii]. [PubMed: 14644157]
75. Goldman RD, Shumaker DK, Erdos MR, Eriksson M, Goldman AE, Gordon LB, Gruenbaum Y, Khuon S, Mendez M, Varga R, Collins FS. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci U S A.*

- A. 2004; 101(24):8963–8968. doi:10.1073/pnas.0402943101 0402943101 [pii]. [PubMed: 15184648]
76. Hernandez L, Roux KJ, Wong ES, Mounkes LC, Mutalif R, Navasankari R, Rai B, Cool S, Jeong JW, Wang H, Lee HS, Kozlov S, Grunert M, Keeble T, Jones CM, Meta MD, Young SG, Daar IO, Burke B, Perantoni AO, Stewart CL. Functional coupling between the extracellular matrix and nuclear lamina by Wnt signaling in progeria. *Dev Cell*. 2010; 19(3):413–425. doi:S1534-5807(10)00388-6 [pii] 10.1016/j.devcel.2010.08.013. [PubMed: 20833363]
 77. Song YJ, Stinski MF. Effect of the human cytomegalovirus IE86 protein on expression of E2F-responsive genes: a DNA microarray analysis. *Proc Natl Acad Sci U S A*. 2002; 99(5):2836–2841. doi:10.1073/pnas.052010099 052010099 [pii]. [PubMed: 11867723]
 78. Ward MC, van der Watt PJ, Tzoneva G, Leaner VD. Deregulated LAP2alpha expression in cervical cancer associates with aberrant E2F and p53 activities. *IUBMB Life*. 2011; 63(11):1018–1026. doi:10.1002/iub.528. [PubMed: 21990273]
 79. Munger K, Scheffner M, Huibregtse JM, Howley PM. Interactions of HPV E6 and E7 oncoproteins with tumour suppressor gene products. *Cancer Surv*. 1992; 12:197–217. [PubMed: 1322242]
 80. Vernell R, Helin K, Muller H. Identification of target genes of the p16INK4A-pRB-E2F pathway. *J Biol Chem*. 2003; 278(46):46124–46137. doi:10.1074/jbc.M304930200 M304930200 [pii]. [PubMed: 12923195]
 81. Gentles AJ, Alizadeh AA, Lee SI, Myklebust JH, Shachaf CM, Shahbaba B, Levy R, Koller D, Plevritis SK. A pluripotency signature predicts histologic transformation and influences survival in follicular lymphoma patients. *Blood*. 2009; 114(15):3158–3166. doi:10.1182/blood-2009-02-202465 [pii] 10.1182/blood-2009-02-202465. [PubMed: 19636063]
 82. Agnelli L, Forcato M, Ferrari F, Tuana G, Todoerti K, Walker BA, Morgan GJ, Lombardi L, Biciato S, Neri A. The reconstruction of transcriptional networks reveals critical genes with implications for clinical outcome of multiple myeloma. *Clin Cancer Res*. 2011; 17(23):7402–7412. doi:1078-0432.CCR-11-0596 [pii] 10.1158/1078-0432.CCR-11-0596. [PubMed: 21890453]
 83. Crabbe L, Cesare AJ, Kasuboski JM, Fitzpatrick JA, Karlseder J. Human Telomeres Are Tethered to the Nuclear Envelope during Postmitotic Nuclear Assembly. *Cell Rep*. 2012; 2(6):1521–1529. doi:S2211-1247(12)00416-0 [pii] 10.1016/j.celrep.2012.11.019. [PubMed: 23260663]
 84. Verdun RE, Crabbe L, Hagblom C, Karlseder J. Functional human telomeres are recognized as DNA damage in G2 of the cell cycle. *Mol Cell*. 2005; 20(4):551–561. doi:S1097-2765(05)01645-X [pii] 10.1016/j.molcel.2005.09.024. [PubMed: 16307919]
 85. Redwood AB, Perkins SM, Vanderwaal RP, Feng Z, Biehl KJ, Gonzalez-Suarez I, Morgado-Palacin L, Shi W, Sage J, Roti-Roti JL, Stewart CL, Zhang J, Gonzalo S. A dual role for A-type lamins in DNA double-strand break repair. *Cell Cycle*. 2011; 10(15):2549–2560. doi:16531 [pii]. [PubMed: 21701264]
 86. Gonzalez-Suarez I, Redwood AB, Perkins SM, Vermolen B, Lichtensztejin D, Grotzky DA, Morgado-Palacin L, Gapud EJ, Sleckman BP, Sullivan T, Sage J, Stewart CL, Mai S, Gonzalo S. Novel roles for A-type lamins in telomere biology and the DNA damage response pathway. *EMBO J*. 2009; 28(16):2414–2427. doi:emboj2009196 [pii] 10.1038/emboj.2009.196. [PubMed: 19629036]
 87. Huang S, Risques RA, Martin GM, Rabinovitch PS, Oshima J. Accelerated telomere shortening and replicative senescence in human fibroblasts overexpressing mutant and wild-type lamin A. *Exp Cell Res*. 2008; 314(1):82–91. doi:S0014-4827(07)00390-4 [pii] 10.1016/j.yexcr.2007.08.004. [PubMed: 17870066]
 88. Lachapelle S, Gagne JP, Garand C, Desbiens M, Coulombe Y, Bohr VA, Hendzel MJ, Masson JY, Poirier GG, Lebel M. Proteome-wide identification of WRN-interacting proteins in untreated and nuclease-treated samples. *J Proteome Res*. 2011; 10(3):1216–1227. doi:10.1021/pr100990s. [PubMed: 21210717]
 89. Kudlow BA, Kennedy BK, Monnat RJ Jr. Werner and Hutchinson-Gilford progeria syndromes: mechanistic basis of human progeroid diseases. *Nat Rev Mol Cell Biol*. 2007; 8(5):394–404. doi:nrm2161 [pii] 10.1038/nrm2161. [PubMed: 17450177]
 90. Sand-Dejmek J, Adelmant G, Sobhian B, Calkins AS, Marto J, Iglehart DJ, Lazaro JB. Concordant and opposite roles of DNA-PK and the “facilitator of chromatin transcription” (FACT) in DNA

- repair, apoptosis and necrosis after cisplatin. *Mol Cancer*. 2011; 10:74. doi:1476-4598-10-74 [pii] 10.1186/1476-4598-10-74. [PubMed: 21679440]
91. Jaco I, Munoz P, Blasco MA. Role of human Ku86 in telomere length maintenance and telomere capping. *Cancer Res*. 2004; 64(20):7271–7278. doi:64/20/7271 [pii] 10.1158/0008-5472.CAN-04-1381. [PubMed: 15492246]
 92. Wang Y, Ghosh G, Hendrickson EA. Ku86 represses lethal telomere deletion events in human somatic cells. *Proc Natl Acad Sci U S A*. 2009; 106(30):12430–12435. doi:10.1073/pnas.0903362106. [PubMed: 19581589]
 93. Myung K, Ghosh G, Fattah FJ, Li G, Kim H, Dutia A, Pak E, Smith S, Hendrickson EA. Regulation of telomere length and suppression of genomic instability in human somatic cells by Ku86. *Molecular and cellular biology*. 2004; 24(11):5050–5059. doi:10.1128/MCB.24.11.5050-5059.2004. [PubMed: 15143195]
 94. Gagne JP, Pic E, Isabelle M, Krietsch J, Ethier C, Paquet E, Kelly I, Boutin M, Moon KM, Foster LJ, Poirier GG. Quantitative proteomics profiling of the poly(ADP-ribose)-related response to genotoxic stress. *Nucleic Acids Res*. 2012; 40(16):7788–7805. doi:gks486 [pii] 10.1093/nar/gks486. [PubMed: 22669911]
 95. Kim HJ, Hwang SH, Han ME, Baek S, Sim HE, Yoon S, Baek SY, Kim BS, Kim JH, Kim SY, Oh SO. LAP2 is widely overexpressed in diverse digestive tract cancers and regulates motility of cancer cells. *PLoS One*. 2012; 7(6):e39482. doi:10.1371/journal.pone.0039482 PONE-D-11-17540 [pii]. [PubMed: 22745766]
 96. Somech R, Shaklai S, Geller O, Amariglio N, Simon AJ, Rechavi G, Gal-Yam EN. The nuclear-envelope protein and transcriptional repressor LAP2beta interacts with HDAC3 at the nuclear periphery, and induces histone H4 deacetylation. *J Cell Sci*. 2005; 118(Pt 17):4017–4025. doi: 118/17/4017 [pii] 10.1242/jcs.02521. [PubMed: 16129885]
 97. Somech R, Gal-Yam EN, Shaklai S, Geller O, Amariglio N, Rechavi G, Simon AJ. Enhanced expression of the nuclear envelope LAP2 transcriptional repressors in normal and malignant activated lymphocytes. *Ann Hematol*. 2007; 86(6):393–401. doi:10.1007/s00277-007-0275-9. [PubMed: 17364180]
 98. Yuki D, Lin YM, Fujii Y, Nakamura Y, Furukawa Y. Isolation of LEM domain-containing 1, a novel testis-specific gene expressed in colorectal cancers. *Oncol Rep*. 2004; 12(2):275–280. [PubMed: 15254688]
 99. Ghafouri-Fard S, Ousati Ashtiani Z, Sabah Golian B, Hasheminasab SM, Modarressi MH. Expression of two testis-specific genes, SPATA19 and LEMD1, in prostate cancer. *Arch Med Res*. 2010; 41(3):195–200. doi:S0188-4409(10)00075-5 [pii] 10.1016/j.arcmed.2010.04.003. [PubMed: 20682177]
 100. Matsuyama H, Suzuki HI, Nishimori H, Noguchi M, Yao T, Komatsu N, Mano H, Sugimoto K, Miyazono K. miR-135b mediates NPM-ALK-driven oncogenicity and renders IL-17-producing immunophenotype to anaplastic large cell lymphoma. *Blood*. 2011; 118(26):6881–6892. doi:blood-2011-05-354654 [pii] 10.1182/blood-2011-05-354654. [PubMed: 22042699]
 101. Simpson AJ, Caballero OL, Jungbluth A, Chen YT, Old LJ. Cancer/testis antigens, gametogenesis and cancer. *Nat Rev Cancer*. 2005; 5(8):615–625. doi:nrc1669 [pii] 10.1038/nrc1669. [PubMed: 16034368]
 102. Berliner JL, Fay AM. Risk assessment and genetic counseling for hereditary breast and ovarian cancer: recommendations of the National Society of Genetic Counselors. *Journal of genetic counseling*. 2007; 16(3):241–260. doi:10.1007/s10897-007-9090-7. [PubMed: 17508274]
 103. Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struwing J, Arason A, Scherneck S, Peto J, Rebbeck TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynch H, Ponder BA, Gayther SA, Zelada-Hedman M, et al. The Breast Cancer Linkage Consortium. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. *Am J Hum Genet*. 1998; 62(3):676–689. doi:S0002-9297(07)63848-8 [pii]. [PubMed: 9497246]
 104. Stevens KN, Vachon CM, Lee AM, Slager S, Lesnick T, Olswold C, Fasching PA, Miron P, Eccles D, Carpenter JE, Godwin AK, Ambrosone C, Winqvist R, Brauch H, Schmidt MK, Cox A, Cross SS, Sawyer E, Hartmann A, Beckmann MW, Schulz-Wendtland R, Ekici AB, Tapper WJ, Gerty SM, Durcan L, Graham N, Hein R, Nickels S, Flesch-Janys D, Heinz J, Sinn HP,

- Konstantopoulou I, Fostira F, Pectasides D, Dimopoulos AM, Fountzilas G, Clarke CL, Balleine R, Olson JE, Fredericksen Z, Diasio RB, Pathak H, Ross E, Weaver J, Rudiger T, Forsti A, Dunnebie T, Ademuyiwa F, Kulkarni S, Pylkas K, Jukkola-Vuorinen A, Ko YD, Van Limbergen E, Janssen H, Peto J, Fletcher O, Giles GG, Baglietto L, Verhoef S, Tomlinson I, Kosma VM, Beesley J, Greco D, Blomqvist C, Irwanto A, Liu J, Blows FM, Dawson SJ, Margolin S, Mannermaa A, Martin NG, Montgomery GW, Lambrechts D, dos Santos Silva I, Severi G, Hamann U, Pharoah P, Easton DF, Chang-Claude J, Yannoukakos D, Nevanlinna H, Wang X, Couch FJ. Common breast cancer susceptibility loci are associated with triple-negative breast cancer. *Cancer Res.* 2011; 71(19):6240–6249. doi:0008-5472.CAN-11-1266 [pii] 10.1158/0008-5472.CAN-11-1266. [PubMed: 21844186]
105. Chen F, Chen GK, Millikan RC, John EM, Ambrosone CB, Bernstein L, Zheng W, Hu JJ, Ziegler RG, Deming SL, Bandera EV, Nyante S, Palmer JR, Rebbeck TR, Ingles SA, Press MF, Rodriguez-Gil JL, Chanock SJ, Le Marchand L, Kolonel LN, Henderson BE, Stram DO, Haiman CA. Fine-mapping of breast cancer susceptibility loci characterizes genetic risk in African Americans. *Hum Mol Genet.* 2011; 20(22):4491–4503. doi:ddr367 [pii] 10.1093/hmg/ddr367. [PubMed: 21852243]
106. Zhang B, Beeghly-Fadiel A, Long J, Zheng W. Genetic variants associated with breast-cancer risk: comprehensive research synopsis, meta-analysis, and epidemiological evidence. *Lancet Oncol.* 2011; 12(5):477–488. doi:S1470-2045(11)70076-6 [pii] 10.1016/S1470-2045(11)70076-6. [PubMed: 21514219]
107. Antoniou AC, Wang X, Fredericksen ZS, McGuffog L, Tarrell R, Sinilnikova OM, Healey S, Morrison J, Kartsonaki C, Lesnick T, Ghoussaini M, Barrowdale D, Peock S, Cook M, Oliver C, Frost D, Eccles D, Evans DG, Eeles R, Izatt L, Chu C, Douglas F, Paterson J, Stoppa-Lyonnet D, Houdayer C, Mazoyer S, Giraud S, Lasset C, Remenieras A, Caron O, Hardouin A, Berthet P, Hogervorst FB, Rookus MA, Jager A, van den Ouweland A, Hoogerbrugge N, van der Luijt RB, Meijers-Heijboer H, Gomez Garcia EB, Devilee P, Vreeswijk MP, Lubinski J, Jakubowska A, Gronwald J, Huzarski T, Byrski T, Gorski B, Cybulski C, Spurdle AB, Holland H, Goldgar DE, John EM, Hopper JL, Southey M, Buys SS, Daly MB, Terry MB, Schmutzler RK, Wappenschmidt B, Engel C, Meindl A, Preisler-Adams S, Arnold N, Niederacher D, Sutter C, Domchek SM, Nathanson KL, Rebbeck T, Blum JL, Piedmonte M, Rodriguez GC, Wakeley K, Boggess JF, Basil J, Blank SV, Friedman E, Kaufman B, Laitman Y, Milgrom R, Andrulis IL, Glendon G, Ozcelik H, Kirchhoff T, Vijai J, Gaudet MM, Altshuler D, Guiducci C, Loman N, Harbst K, Rantala J, Ehrencrona H, Gerdes AM, Thomassen M, Sunde L, Peterlongo P, Manoukian S, Bonanni B, Viel A, Radice P, Caldes T, de la Hoya M, Singer CF, Fink-Retter A, Greene MH, Mai PL, Loud JT, Guidugli L, Lindor NM, Hansen TV, Nielsen FC, Blanco I, Lazaro C, Garber J, Ramus SJ, Gayther SA, Phelan C, Narod S, Szabo CI, Benitez J, Osorio A, Nevanlinna H, Heikkinen T, Caligo MA, Beattie MS, Hamann U, Godwin AK, Montagna M, Casella C, Neuhausen SL, Karlan BY, Tung N, Toland AE, Weitzel J, Olopade O, Simard J, Soucy P, Rubinstein WS, Arason A, Rennert G, Martin NG, Montgomery GW, Chang-Claude J, Flesch-Janys D, Brauch H, Severi G, Baglietto L, Cox A, Cross SS, Miron P, Gerty SM, Tapper W, Yannoukakos D, Fountzilas G, Fasching PA, Beckmann MW, Dos Santos Silva I, Peto J, Lambrechts D, Paridaens R, Rudiger T, Forsti A, Winqvist R, Pylkas K, Diasio RB, Lee AM, Eckel-Passow J, Vachon C, Blows F, Driver K, Dunning A, Pharoah PP, Offit K, Pankratz VS, Hakonarson H, Chenevix-Trench G, Easton DF, Couch FJ. A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. *Nat Genet.* 2010; 42(10):885–892. doi:ng.669 [pii] 10.1038/ng.669. [PubMed: 20852631]
108. Bolton KL, Tyrer J, Song H, Ramus SJ, Notaridou M, Jones C, Sher T, Gentry-Maharaj A, Wozniak E, Tsai YY, Weidhaas J, Paik D, Van Den Berg DJ, Stram DO, Pearce CL, Wu AH, Brewster W, Anton-Culver H, Ziogas A, Narod SA, Levine DA, Kaye SB, Brown R, Paul J, Flanagan J, Sieh W, McGuire V, Whittemore AS, Campbell I, Gore ME, Lissowska J, Yang HP, Medrek K, Gronwald J, Lubinski J, Jakubowska A, Le ND, Cook LS, Kelemen LE, Brook-Wilson A, Massuger LF, Kiemeny LA, Aben KK, van Altena AM, Houlston R, Tomlinson I, Palmieri RT, Moorman PG, Schildkraut J, Iversen ES, Phelan C, Vierkant RA, Cunningham JM, Goode EL, Fridley BL, Kruger-Kjaer S, Blaeke J, Hogdall E, Hogdall C, Gross J, Karlan BY, Ness RB, Edwards RP, Odunsi K, Moyisch KB, Baker JA, Modugno F, Heikkinen T, Butzow R, Nevanlinna H, Leminen A, Bogdanova N, Anttonenkov N, Doerk T, Hillemanns P, Durst M,

- Runnebaum I, Thompson PJ, Carney ME, Goodman MT, Lurie G, Wang-Gohrke S, Hein R, Chang-Claude J, Rossing MA, Cushing-Haugen KL, Doherty J, Chen C, Rafnar T, Besenbacher S, Sulem P, Stefansson K, Birrer MJ, Terry KL, Hernandez D, Cramer DW, Vergote I, Amant F, Lambrechts D, Despiere E, Fasching PA, Beckmann MW, Thiel FC, Ekici AB, Chen X, Johnatty SE, Webb PM, Beesley J, Chanock S, Garcia-Closas M, Sellers T, Easton DF, Berchuck A, Chenevix-Trench G, Pharoah PD, Gayther SA. Common variants at 19p13 are associated with susceptibility to ovarian cancer. *Nat Genet.* 2010; 42(10):880–884. doi:ng.666 [pii] 10.1038/ng.666. [PubMed: 20852633]
109. Brachner A, Braun J, Ghodgaonkar M, Castor D, Zlopasa L, Ehrlich V, Jiricny J, Gotzmann J, Knasmuller S, Foisner R. The endonuclease Ankle1 requires its LEM and GIY-YIG motifs for DNA cleavage in vivo. *J Cell Sci.* 2012; 125(Pt 4):1048–1057. doi:jcs.098392 [pii] 10.1242/jcs.098392. [PubMed: 22399800]
110. Dittrich CM, Kratz K, Sandoel A, Gruenbaum Y, Jiricny J, Hengartner MO. LEM-3 - A LEM domain containing nuclease involved in the DNA damage response in *C. elegans*. *PLoS One.* 2012; 7(2):e24555. doi:10.1371/journal.pone.0024555 PONE-D-11-14963 [pii]. [PubMed: 22383942]
111. Rosty C, Sheffer M, Tsafir D, Stransky N, Tsafir I, Peter M, de Cremoux P, de La Rochefordiere A, Salmon R, Dorval T, Thierry JP, Couturier J, Radvanyi F, Domany E, Sastre-Garau X. Identification of a proliferation gene cluster associated with HPV E6/E7 expression level and viral DNA load in invasive cervical carcinoma. *Oncogene.* 2005; 24(47):7094–7104. doi:1208854 [pii] 10.1038/sj.onc.1208854. [PubMed: 16007141]
112. Futschik M. Gene Expression Profiling of Metastatic and Nonmetastatic Colorectal Cancer Cell Lines. *Genome Letters.* 2002; (1):26–34.
113. Ohuchida K, Mizumoto K, Ishikawa N, Fujii K, Konomi H, Nagai E, Yamaguchi K, Tsuneyoshi M, Tanaka M. The role of S100A6 in pancreatic cancer development and its clinical implication as a diagnostic marker and therapeutic target. *Clin Cancer Res.* 2005; 11(21):7785–7793. doi: 11/21/7785 [pii] 10.1158/1078-0432.CCR-05-0714. [PubMed: 16278400]
114. Kang W, Tong JH, Chan AW, Lee TL, Lung RW, Leung PP, So KK, Wu K, Fan D, Yu J, Sung JJ, To KF. Yes-associated protein 1 exhibits oncogenic property in gastric cancer and its nuclear accumulation associates with poor prognosis. *Clin Cancer Res.* 2011; 17(8):2130–2139. doi: 1078-0432.CCR-10-2467 [pii] 10.1158/1078-0432.CCR-10-2467. [PubMed: 21346147]
115. Yokota N, Mainprize TG, Taylor MD, Kohata T, Loreto M, Ueda S, Dura W, Grajkowska W, Kuo JS, Rutka JT. Identification of differentially expressed and developmentally regulated genes in medulloblastoma using suppression subtraction hybridization. *Oncogene.* 2004; 23(19):3444–3453. doi:10.1038/sj.onc.1207475 1207475 [pii]. [PubMed: 15064731]
116. Parise P, Finocchiaro G, Masciadri B, Quarto M, Francois S, Mancuso F, Muller H. Lap2alpha expression is controlled by E2F and deregulated in various human tumors. *Cell Cycle.* 2006; 5(12):1331–1341. doi:2833 [pii]. [PubMed: 16760672]

Figure 1.
Schematic overview of the mammalian LEM-protein family. Protein localization and domains are indicated.

Figure 2. LAP2α, lamin A/C and pRb interact directly and may form a trimeric complex. Domain organization of human LAP2α and pRb and interaction domains are shown.

Figure 3.

The pRb/E2F pathway regulates cell cycle progression. The scheme depicts major upstream regulators of pRb and downstream effectors, as well as important pro-proliferative and anti-proliferative feedback mechanisms upon transition from a resting (G0) to a proliferating state and during G1 to S-phase progression. The potential role of nucleoplasmic LAP2α-lamin A/C complexes in the pRb regulatory network is indicated.

Figure 4.

Hypothetical model of the functions of the peripheral lamina and the nucleoplasmic LAP2 α -lamin A/C complex in the regulation of the pRb/E2F pathway in non-proliferating and proliferating cells. In arrested cells the lamina may tether and stabilize hypophosphorylated pRb and serve as platform for efficient PP2A-dependent dephosphorylation of phospho-pRb. The nucleoplasmic LAP2 α -lamin A/C complex activates repressor activity of pRb leading to E2F target gene repression. In proliferating cells, ERK may release pRb from the lamina, favoring its cdk-mediated phosphorylation. LAP2 α -lamin A/C complexes dissociate from phospho-Rb, allowing E2F activation and E2F target gene expression.

Figure 5.

LAP2α transiently localizes to telomeric regions during late anaphase-telophase (top) and is detected on the chromosome tips in metaphase spreads (bottom). Confocal fluorescence images showing the localization of ectopic, fluorescently tagged LAP2α and Histone 2B (upper panel) or stained for LAP2α and DNA (courtesy of T. Dechat and A. Gajewski, MFPL). Bars, 5μm. Arrow indicates localization of YFP-LAP2α at chromosome tips in late anaphase. Right panel shows a hypothetical involvement of LAP2α in telomere stability based on recently reported protein interactions. See text for details.

Table 1
Tumors and tumor derived cell lines, which show upregulated LAP2 expression

Cancer samples and cell lines with upregulated LAP2 expression	Reference
cervix carcinoma; human	[78,111]
colorectal cancer cell lines; human	[112]
colon cancer; human	[70]
hepatocellular carcinoma; TKO mice	[71]
breast cancer cell line (MCF7); human	[73]
myeloma; human	[69]
pancreatic cancer; human	[113]
gastric cancer; human	[114]
medulloblastoma; human	[115]
lymphoma; human	[81,97]
larynx, stomach, colon, lymphoma, sarcoma; human	[116]