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Minireview

Velcro in the nuclear envelope: LBR and LAPs

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Abstract The nuclear envelope is crucial for the functional organization of the nucleus. Lamin B receptor (LBR) and several lamina-associated proteins (LAPs), residing in the inner membrane, provide attachment sites for chromatin and the nuclear lamina. LAPs and LAP-related proteins are members of a growing family of proteins, whose genes are expressed in a tissue and development specific manner, opening the opportunity for a complex regulation of membrane-chromatin and membrane-lamina interactions. Post-translational modifications of LBR and LAPs are likely to modulate their binding to lamins and chromatin, interactions that need to be dynamic to accommodate nuclear growth in interphase and nuclear envelope disassembly in mitosis. Accumulation of proteins in the inner nuclear membrane is believed to depend on their retention mediated by the interaction with nuclear components such as chromatin and lamins.

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Key words: Nuclear envelope; Nuclear lamina; Chromatin; Lamin B receptor; Lamina-associated protein

1. Introduction

The nuclear envelope (NE), separating the nucleoplasm from the cytoplasm, is organized into four domains: the inner and outer nuclear membrane, the perinuclear space and the nuclear lamina [1,2]. The outer nuclear membrane, studded with ribosomes, is continuous with the endoplasmic reticulum (ER) and similar to the ER in protein composition [1,2]. By contrast, the unique molecular make up of the inner nuclear membrane reflects its distinct functions. Located between the inner and outer nuclear membrane, the perinuclear space is continuous with the ER lumen, enabling molecules to diffuse between these compartments (Fig. 1). The inner and outer nuclear membranes fuse at nuclear pore complexes; it is here that nucleocytoplasmic trafficking of soluble macromolecules takes place [1,2].

Lining the inner nuclear membrane of higher eukaryotes, the nuclear lamina supplies the nucleus with structural support [1–3]. Lamins, members of the intermediate filament family of proteins, are the lamina's major building blocks; they form a meshwork of filaments, providing a skeletal framework and attachment sites for chromatin. Nuclear lamins can be divided into two groups, with B-type lamins being present in all mammalian cells. In contrast, A-type lamins (lamin A and C are alternatively spliced variants of the same gene) are restricted to differentiated cells [1–3]. A- and B-type lamins bind directly to polypeptides of the inner nuclear membrane (Table 1). Lamin B receptor (LBR) and an increasing number of lamina-associated proteins (LAPs), all but one integral proteins of the inner nuclear membrane (see below), are key players in these associations [4–8]. In addition to A- and B-type lamins, other constituents of the nuclear lamina have been identified [9,10]. The function of these components including their possible interaction with the NE has yet to be defined.

The proper organization of the nucleus relies on the association of the inner nuclear membrane with the nuclear lamina or chromatin; such binding reactions need to be dynamic as the nuclear envelope disassembles at the onset of mitosis and grows during interphase. In the following, we will discuss the key players for these interactions, LBR and LAPs.

2. LBR

LBR, so far the best characterized protein of the inner nuclear membrane, participates in multiple binding reactions. As a protein of 637 amino acid residues in chicken [11], LBR contains a nucleoplasmic N-terminal part of approximately 210 residues that is organized into two globular domains (amino acid residues 1–60 and 105–210, Fig. 2), separated by a hinge region. The nucleoplasmic portion is followed by eight predicted transmembrane segments and a hydrophilic C-terminal tail. LBR's first transmembrane region is sufficient to target β-galactosidase to the inner nuclear membrane [12].

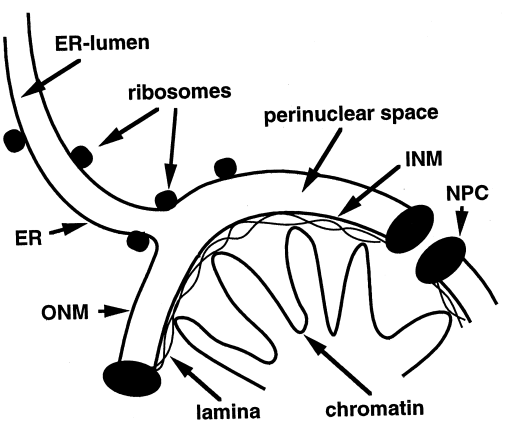

Fig. 1. Organization of the nuclear envelope. A schematic representation for the organization of the nuclear envelope and its relationship to the ER is shown. INM, inner nuclear membrane; ONM, outer nuclear membrane; NPC, nuclear pore complex.

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Abbreviations: EDMD, Emery-Dreifuss muscular dystrophy; ER, endoplasmic reticulum; FRAP, fluorescence recovery after photobleaching; GFP, green fluorescent protein; INM, inner nuclear membrane; LAP, lamina-associated protein; LBR, lamin B receptor; NE, nuclear envelope; NLS, nuclear localization sequence; NPC, nuclear pore complex; ONM, outer nuclear membrane

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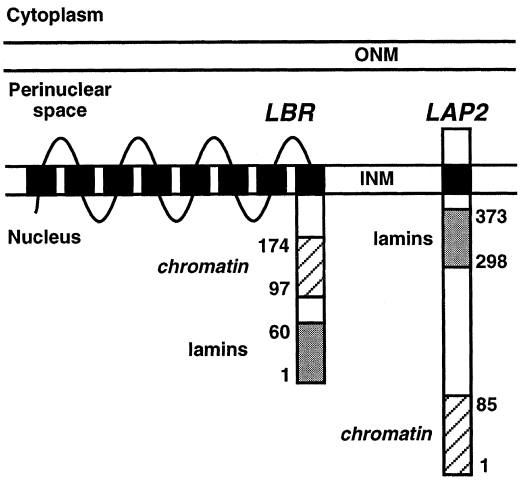

Fig. 2. Topology of LBR and LAP2-beta. The organization of LBR and LAP2-beta within the nuclear envelope is illustrated. Protein segments proposed to be involved in chromatin association are cross-hatched and lamin binding sites are depicted in gray. Predicted transmembrane segments are shown in black. Numbers refer to the positions of amino acid residues. See text for details. INM and ONM denote the inner and outer nuclear membrane, respectively.

Several human autoantibodies against LBR's first globular domain are also anti-idiotype antibodies to lamin B, suggesting this part of LBR to participate in interactions with the lamina [13,14]. However, more direct experimental evidence is needed to substantiate this finding and to determine whether LBR's first N-terminal domain is sufficient for lamin B binding or requires additional segments of the protein. LBR's isolated hinge region, rich in basic and proline residues, binds double-stranded DNA in vitro [15]. Since intact LBR does not bind naked DNA [16], the significance of this interaction is unclear. In contrast, LBR's association with chromatin mediated by heterochromatin protein HP1 seems more physiologically relevant [15,16]. Specifically the N-terminal portion of LBR's second globular domain was shown to bind HP1's chromo shadow domain ([15]; Fig. 2, amino acid residues 97–174). It has been speculated that at the end of mitosis LBR's binding to HP1 is involved in vesicle targeting to the surface of chromosomes [17].

In avian erythrocytes, LBR is part of a larger protein complex located in the inner nuclear membrane; this complex contains several components including an LBR kinase (RS-kinase), lamin B and a small integral membrane protein, p18 [18]. In vitro, p18 binds directly to LBR and B-type lamins, with p18's binding to LBR being stronger than its association with lamin B [18]. p18, a protein equally distributed between the inner and outer nuclear membrane, is predominantly found in avian erythrocytes, but is of low abundance or absent in other avian tissues. This implies a tissue-specific role for p18, possibly as a modulator of NE-lamina interactions mediated by the LBR-complex.

LBR's hydrophobic region shows sequence similarities with yeast sterol C-14 reductase, an enzyme missing LBR's N-terminal nucleoplasmic part that is involved in binding to chromatin and lamins (reviewed in [1,3]). When expressed in *Saccharomyces cerevisiae*, an organism without lamins, chicken LBR localizes to the nuclear envelope [19]; possibly via its binding to chromatin. Furthermore, human LBR, when synthesized in *S. cerevisiae*, exhibits sterol C14 reductase activity. This enzyme is involved in the synthesis of zymosterol, a cholesterol precursor [20]. Although speculative at this point, one could envision LBR, as a multifunctional protein, also to participate in the biosynthesis of steroids and/or the regulation of genes involved in steroid metabolism.

The N-terminal region of rat LBR (amino acid residues 1–89) was shown to bind nucleoplasmin's nuclear localization sequence (NLS) [21], and it was proposed that LBR is used as a temporary anchor for nuclear proteins. At present, it seems unlikely that LBR plays a role in nucleocytoplasmic transport of proteins. Nevertheless, binding the NLS of lamin B or chromatin-associated proteins may contribute to LBR's association with the lamina or chromatin.

3. LAPs and related proteins

Thymopoietin, a polypeptide of 49 amino acid residues, was identified as a component that induces T-cell differentiation ([22], and references therein). Thymopoietin is most likely a proteolytic product of the N-terminal portion of LAP2-related proteins; the significance of its action on T-cell differentiation is not clear. Since LAP2's role in lamina interactions is well established, we will follow the nomenclature recently introduced for members of the LAP2 family [4]: in this review LAP2/thymopoietin beta is referred to as LAP2-beta, and all other LAP2-related proteins are named accordingly.

Except for LAP2-alpha (see below) members of the LAP1 and LAP2 families are predicted to be type II integral membrane proteins with their single membrane-spanning region close to the C-terminus. Three different isoforms of LAP1, named LAP1A, -B and -C, are presumably alternatively spliced transcripts of the same gene (Table 1). Binding of chromatin can be demonstrated for all three isoforms in vitro; however, binding requires a linker protein(s), likely to be provided by nuclear membranes [6]. In vitro, LAP1A and -B associate with lamins A, C and B1, with LAP1A having the

Table 1
Proteins of the inner nuclear membrane, interactions with lamins, chromatin, other factors and phosphorylation

Protein/alternative name	Lamins	Binding to chromatin	Other factors	Phosphorylation
LBR/p58	B-type in vitro and in vivo	Yes, HP1 as binding partner	Components of LBR-complex: p18.p34/p32	RS-kinase, cdc2
p18	B-type lamins	?	LBR	?
LAP1A	All lamin types in vitro	Yes, linker required	–	Mitotic kinase(s)
LAP1B	All lamin types in vitro	Yes, linker required	–	Mitotic kinase(s)
LAP1C	Complexed with B-type lamins in vivo	Yes, linker required	–	Mitotic kinase(s)
LAP2-beta	B-type lamins	Yes	–	Mitotic kinase(s)

The association of integral proteins of the inner nuclear membrane with lamins, chromatin or other nuclear components is listed. Kinases that phosphorylate these membrane proteins are shown.

higher affinity for lamins. In contrast, LAP1C does not bind lamins in these experiments [6]. Nevertheless, as a component of a larger protein complex in vivo, LAP1C associates with a protein kinase and B-type lamins [18], though a direct LAP1C-lamin B interaction has not been demonstrated. LAP1 containing complexes are distinct from those harboring LAP2-beta or LBR, and it was proposed that different complexes occupy separate territories in the inner nuclear membrane [23].

LAP1 isotypes, as well as nuclear lamins, are differentially expressed during development, LAP1C being present both in non-differentiated and differentiated cells, whereas LAP1A and -B are abundant in differentiated cells only [7]. These data suggest that the controlled expression of LAP1 isoforms and lamins may modulate the nuclear organization in a developmentally regulated fashion. Since lamins A/C are preferentially synthesized in differentiated cells, it is tempting to speculate that LAP1A and -B may play a role in the association with A-type lamins.

LAP2-beta, the best characterized member of the LAP2 family, binds lamin B1 in vitro, with low affinities for lamin A and C [6]. LAP2-beta's chromatin association does not require a linker protein [6]; both its lamin binding site (residues 298–373) and chromatin attachment region have been located within the N-terminal nucleoplasmic portion [24]. Using in vitro binding assays and the yeast two-hybrid screen the rod domain of lamin B1 was demonstrated to interact with LAP2-beta's N-terminal portion [25].

The precise location of sequences contributing to LAP2-beta's chromatin binding, however, is at present controversial. It was reported that residues 1–85 of LAP2-beta fused to glutathione *S*-transferase support the interaction with chromatin in vitro [24]. In contrast, other data indicate that the N-terminal 187 amino acid residues, present in all LAP2-isoforms described to date, are not sufficient to bind chromatin [4]. The reasons for this discrepancy are presently not understood, however, it is conceivable that chromatin binding is stabilized by additional sequences in LAP2-related proteins. LAP2-beta's residues 244–296, which were shown to bind DNA in vitro, may be involved in these interactions [26].

In vitro reconstituted vesicles lacking LAP2 proteins were shown to bind efficiently to chromatin, whereas removal of LBR prevented chromatin binding of vesicles [16]. Thus LAP2-beta may not be the major chromatin binding partner located in the inner nuclear membrane, with LBR providing the bulk of attachment sites [16]. An essential physiological role, however, can be assigned to LAP2-beta, whose lamina interaction is required for nuclear growth following mitosis [27]. LAP2-beta's lamin-binding fragment, when injected into HeLa cells during early G1-phase, inhibits the increase of nuclear volume and entry into S-phase, suggesting the interaction between LAP2-beta and lamins to control the growth of interphase nuclei and thereby indirectly the progression into S-phase [27].

Proteins of the LAP2 family include at least three major members which have been identified by Western blotting [4,28,29]; LAP2-beta and gamma contain segments predicted to span the nuclear membrane once (Figs. 2 and 3). No such hydrophobic segment is present in LAP2-alpha, consistent with its nuclear localization but lack of membrane association [4,30]. On the basis of mRNAs isolated from mouse [31], additional isoforms of LAP2 can be predicted (Fig. 3). This

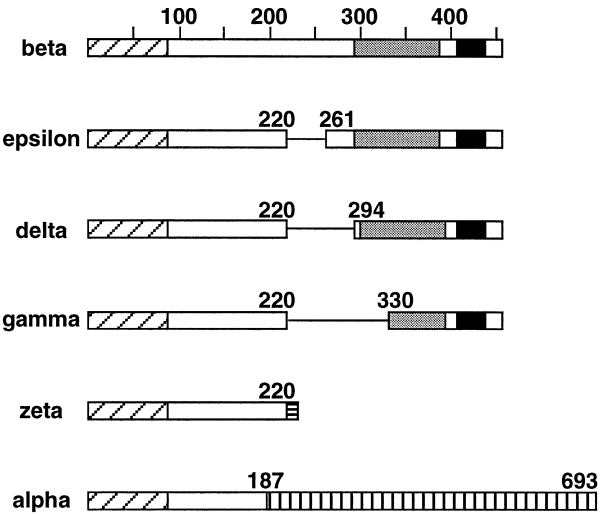

Fig. 3. Members of the LAP2 family of proteins. The synthesis of LAP2-beta, -gamma and -alpha has been demonstrated in different organisms. On the basis of mRNAs isolated from mouse, LAP2-epsilon, -delta and -zeta can be predicted. Numbers on top of the figure denote the positions of amino acid residues. The cross-hatched portions indicate that the N-terminal segment is likely to be involved, but possibly not sufficient for chromatin binding. The lamin binding region is shown in gray and the predicted single membrane-spanning segment in black. The striped segments for LAP2-zeta and LAP2-alpha represent the unique five C-terminal amino acid residues of LAP2-zeta and the large C-terminal portion of LAP2-alpha, respectively. For LAP2-epsilon, -delta and -gamma the line indicates protein segments that are missing when aligned with LAP2-beta.

hypothesis is in line with the presence of more than three LAP2-related proteins in rat tissues detected by Western blotting with antibodies against the N-terminal region of LAP2-beta [29]. All members of the LAP2 protein family described so far share their N-terminal 187 residues, thus carrying the region likely to participate in chromatin binding [4,28]. LAP2-beta, -epsilon and -delta contain the protein segment sufficient for lamin binding, whereas this portion is missing in part or completely for LAP2-gamma, -zeta and -alpha (Fig. 3).

With an antibody specific to its unique C-terminal portion, LAP2-alpha has recently been analyzed in some detail [4,28]. During interphase the protein is nucleoplasmic, possibly associated with the lamina-nuclear matrix framework [4]. Specific phosphorylation during mitosis alters the distribution of LAP2-alpha, and it was found to associate with spindle poles and to concentrate between chromosomes during telophase, possibly linking chromosomes during this late stage of mitosis [4].

LAP2 proteins show tissue-specific expression, with LAP2-beta's gene being selectively expressed in highly proliferative tissues [29]. This is consistent with the model that synthesis of different LAP2 variants modulates NE-lamina and NE-chromatin interactions to accommodate the specific needs of a particular tissue. Support for this hypothesis comes from changes in the nuclear organization during spermiogenesis [28]. Specifically, the localization of LAP2 related proteins (possibly including LAP2-beta, -alpha and -gamma) is altered gradually from the entire nuclear periphery to only one spot at the posterior pole of the nucleus. Simultaneously, LAP2-gamma and LAP2-beta disappear, leaving only LAP2-alpha to be detectable in the mature sperm. Accompanying changes for LAP2 proteins, lamin B1 first becomes concentrated at the

posterior pole of the nucleus and finally disappears in mature sperm cells [28]. These studies, for the first time, show that the presence of members of the LAP2 family and lamins is coordinated during differentiation.

Furthermore, expression of LAP2 family members is developmentally regulated in *Xenopus*. LAP2-beta is not detectable in oocytes or during early stages of development up to the beginning of the gastrula stage; it appears to be the only member expressed in *Xenopus* somatic cells (M. Paulin-Levasseur and G. Krohne, personal communication).

A distant relative of the LAP2 family, the Emery-Dreifuss muscular dystrophy (EDMD) protein or emerin, has been localized to the nuclear envelope [32]. Similarity of emerin with LAP2-beta is restricted to 39 amino acid residues in the N-terminal domain and the last 34 residues in the C-terminal portion [33]. Emerin, which is phosphorylated in a cell-cycle specific fashion, contains two non-overlapping sequences involved in its targeting to the NE [33]. Mutations in the 34-kDa protein may result in EDMD, a disease associated with muscle wasting, contractures and cardiomyopathy [34]. Although wild-type emerin is expressed in several tissues, defects in EDMD patients are primarily detected in skeletal and heart muscle cells [34]. Since emerin is also associated with desmosomes and fasciae adherentes in cardiomyocytes, it was proposed to play a heart-specific role in cell adhesion, which could explain some of the defects seen in EDMD patients [35]. As of yet, emerin's functions in the nucleus are not defined. However, the ubiquitous localization to the nuclear envelope and emerin's colocalization with A-type and B-type lamins in intranuclear foci suggest interactions with the nuclear lamina [36].

Additional members of the LAP2 family are likely to be identified in the future. Using human autoimmune antibodies, several proteins were described that associate with the nuclear envelope/nuclear lamina [37]. These antibodies recognize LAP2-alpha, -beta and -gamma and a novel protein, termed MAN1. MAN1 localizes to the nuclear envelope when expressed in transiently transfected cells and represents a new candidate protein that may interact with the nuclear lamina and/or chromatin (M. Paulin-Levasseur and H.J. Worman, personal communication).

4. Regulation of LBR's and LAP's interactions by phosphorylation

NE-lamina interactions have to undergo dynamic changes, including nuclear envelope disassembly during mitosis and nuclear growth in G1-phase. Phosphorylation of NE components by cdc2 and presumably other kinases is critical for NE fragmentation [1]. Both LBR and LAPs are targets for different protein kinases in vitro and in vivo [6,32,38,39]. RS-kinase (a kinase that phosphorylates arginine-serine motifs, which are abundant in splicing factors) and cdc2 phosphorylate LBR during mitosis [39]. Phosphorylation by RS-kinase controls LBR's interaction with other subunits of the LBR complex and was proposed to modulate the interaction with chromatin [39,40]. Phosphorylation by cdc2, however, does not prevent LBR's binding to lamin B in vitro, and other data indicate that it is rather dephosphorylation of LBR that weakens its interaction with lamin B [38]. Since LBR and lamin B remain associated with the same membrane vesicles during mitosis [41], a disruption of lamin B-LBR complexes may not be required. LBR's release from chromatin, however, was proposed to involve phosphorylation of a cdc2-site close to its HP1-binding region [15]. Modification of this site may liberate LBR from chromosomes at the onset of mitosis [15].

A clearer picture has emerged for LAP2-beta, whose phosphorylation by mitotic kinases abolishes binding to lamin B in vitro and presumably in vivo [6]. In vivo, LAP2-alpha becomes hyperphosphorylated during mitosis coinciding with its higher solubility [4]. LAP2-alpha's phosphorylation could regulate its association with chromosomes, thereby controlling early steps of post-mitotic NE-assembly [4]. As for LAP1, in vitro phosphorylation is not sufficient to disrupt binding to lamins, and dissociation of LAP1/lamin complexes may require the simultaneous phosphorylation of lamins [6].

Taken together, several lines of evidence point to phosphorylation/dephosphorylation as the key to control NE-lamina interactions during mitosis. It is now important to determine how these interactions are modulated during interphase to accommodate nuclear growth.

5. Targeting of LBR to the inner nuclear membrane

More recent studies have focused on mechanisms that localize proteins to the inner nuclear membrane, with LBR as a model to analyze these processes. LBR's N-terminal nucleoplasmic portion is sufficient to target a soluble protein to the nucleus [42] suggesting the presence of an NLS. Furthermore, LBR's N-terminal region can locate a membrane protein to the nuclear envelope, whereas fusing an NLS to a membrane protein is insufficient for NE accumulation [42]. An additional inner membrane targeting signal resides in LBR's C-terminal domain, located within the first transmembrane segment [12,42]. Results from these studies are consistent with the idea that LBR is retained in the nucleus due to its interactions with nuclear components [12,42]. This model was recently tested in living COS-7 cells expressing the nucleoplasmic domain and the first membrane-spanning segment of LBR fused to green fluorescent protein (LBR-GFP) [43]. Fluorescence recovery after photobleaching (FRAP) was carried out to determine the mobility of fusion proteins in the ER and in the nuclear envelope [43]. In interphase cells, LBR-GFP located in the NE is practically immobile, whereas LBR-GFP in the ER displays high mobility. In mitotic cells, the entire LBR-GFP pool regains mobility, but becomes immobilized again when located in the newly formed NE at the end of mitosis. These data support the hypothesis that LBR, once in the inner nuclear membrane, is retained due to restriction of its movement, a mechanism termed 'interaction trap' [43]. LBR's binding to lamins and chromatin is likely the main cause for its immobilization. However, with the LBR-GFP fusion used for FRAP, interactions of LBR's first membrane-spanning segment with binding partners, at present not identified, may also contribute to the 'interaction trap' [12,42].

As proposed for LBR [43] and for LAP2-beta [8,24,25] the 'interaction trap' may be a general mechanism to sort proteins to the inner nuclear membrane where they become immobilized as a result of their association with nuclear components. One testable prediction of this model is that interfering with these interactions mobilizes LBR and LAPs again, thereby permitting their 'free' distribution between the nuclear envelope and the ER.

6. Conclusions

Several proteins located in the inner nuclear membrane participate in binding to the nuclear lamina or chromatin. These interactions can be regulated on different levels: for LAPs, this includes expression of distinct isoforms in a tissue-specific or developmentally regulated manner. As components of larger protein complexes, LAPs as well as LBR may create territories in the NE, thus generating subdomains in the inner nuclear membrane which could differ in their interactions with lamins and chromatin. Furthermore, phosphorylation or other modifications of LAPs and LBR may directly modulate their affinities for the nuclear lamina and for chromatin. Future experiments will now have to assign physiological consequences to the controlled expression of LAPs and the post-translational modifications of LAPs and LBR.

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