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Nuclear envelope and nuclear matrix: interactions and dynamics

S. Vlcek, T. Dechat and R. Foisner*

Department of Biochemistry and Molecular Cell Biology, Vienna Biocenter, University of Vienna, Dr Bohrgasse 9, 1030 Vienna (Austria), Fax + 43 1 4277 52854, e-mail: foisner@abc.univie.ac.at

Abstract. The peripheral nuclear lamina is located near the nuclear inner membrane and consists of lamin filaments and integral membrane proteins, including the lamin B receptor and various isoforms of lamina-associated polypeptides (LAP) 1 and 2. Several nuclear membrane proteins also interact with chromatin proteins BAF and Hp1. Lamins in the nuclear interior associate with at least one soluble (non-membrane-bound) LAP2 isoform named LAP2α. The internal lamins, together with Tpr-based filaments that connect to nuclear pore complexes, are proposed to be major structural elements of the internal nuclear matrix. We describe the structural links between the peripheral lamina and the internal nuclear matrix that are thought to be mediated by LAP2 family members, filament protein Tpr and nucleoporin Nup153. These findings are discussed in relation to human diseases that arise from mutations in nuclear lamina proteins.

Key words. Barrier-to-autointegration factor; cell cycle; chromatin structure; heterochromatin protein 1; lamin B receptor; lamina-associated polypeptide; lamins; nuclear matrix; nuclear pore complex; Tpr; transcriptional regulation.

Introduction

The nucleus of eukaryotic cells is a complex, highly organized structure responsible for essential functions, including DNA replication, RNA transcription, RNA processing and ribosome assembly. A structural framework within the nucleus, referred to as the nuclear matrix or nucleoskeleton [1], is proposed to organize activities such as replication and transcription, and to organize chromatin within the nucleus. The components and molecular organization of the nuclear matrix are not very well understood. Biochemically, the nuclear matrix is defined as the components that remain insoluble after extraction of nuclei with non-ionic detergents, salt and nucleases. The analysis and visualization of the nuclear matrix has always been hampered by the bulky chromatin mass, and it remains uncertain whether the nucleoskeleton is made of continuous, interconnected filamentous structures, or several discrete elements.

The best-characterized part of the nuclear matrix is the nuclear envelope (NE), which enwraps chromatin. The NE consists of the outer (ONM) and inner (INM) nuclear membranes, nuclear pore complexes (NPCs), and the peripheral nuclear lamina located near the INM. The term lamina includes the lamins plus numerous integral and peripheral proteins of the inner membrane [2], which are all highly resistant to extraction by detergent and high salt and are thus defined as components of the nuclear matrix. There is increasing evidence that lamins and specific lamin-binding proteins also extend throughout the interior of the nucleus [3]. In this review, we describe the structural and functional links between the peripheral lamina and the internal nuclear matrix. We will focus on three types of proteins: Lamina-associated polypeptide 2 (LAP2) family members (which are found in a variety of complexes with lamins at the NE and in the nuclear interior), proposed filament protein Tpr (which attaches to NPCs) and nucleoporin Nup153 (which interacts with both lamins and NPCs). We describe the dynamics of these proteins during the cell cycle, and their potential functions in chromatin organization, gene regulation, and cell cycle progression.

* Corresponding author.

Components and molecular interactions in the peripheral nuclear lamina

The major structural framework at the nuclear periphery is the nuclear lamina, whose core structure is formed by type V intermediate filament proteins, the lamins [4]. Lamins assemble into a meshwork of tetragonally organized 10-nm filaments underneath the INM. The attachment of the lamins to the membrane involves several mechanisms, and depends also on the type of lamins. B-type lamins, which are constitutively expressed in all somatic cells, contain a stable C-terminal farnesyl modification, which is important but not sufficient for targeting and anchoring B-type lamins to the membrane [5]. Thus, interactions of B-type lamins with integral membrane proteins must also contribute to the assembly and stable association of lamin B filaments at the membrane [6]. The best-known binding partners for B-type lamins in the INM are the lamin B receptor (LBR) [7] and LAP2β [8] (fig. 1). LBR contains eight transmembrane domains, and interacts with B-type lamins both in vivo and in vitro [9, 10] (however see also [11]).

LAP2β is the best-characterized membrane protein of the LAP2 family, which comprises up to six alternatively spliced mammalian isoforms named LAP2α, β, γ, δ, ε and ζ [12, 13] (also formerly known as thymopoietins) and three *Xenopus* LAP2 isoforms [14, 15]. Except for LAP2α and LAP2ζ, all mammalian LAP2 isoforms have a closely related N-terminal nucleoplasmic domain of variable length, plus a single membrane-spanning region and a short lumenal domain at their C-terminus [16]. LAP2β has the longest nucleoplasmic N-terminal domain (408 residues). Due to alternative messenger RNA (mRNA) splicing, LAP2 ε, δ and γ lack stretches of 40, 72 and 109 amino acids, respectively, but are otherwise identical to LAP2β. LAP2ζ is the smallest isoform of LAP2β, and is missing ~190 residues of the nucleoplasmic domain as well as the transmembrane and lumenal regions. LAP2α is structurally and functionally a unique isoform; it shares only the N-terminal 187 residue 'constant' domain with all other LAP2 isoforms, and then contains a unique C-terminal domain of 506 residues with no transmembrane domain.

LAP2β, but not LAP2α, interacts with lamin B in vitro [17]. The lamin B binding domain maps to 73 residues in the nucleoplasmic region [18], which are also present in the smaller isoforms LAP2ε and δ, and are partly con-

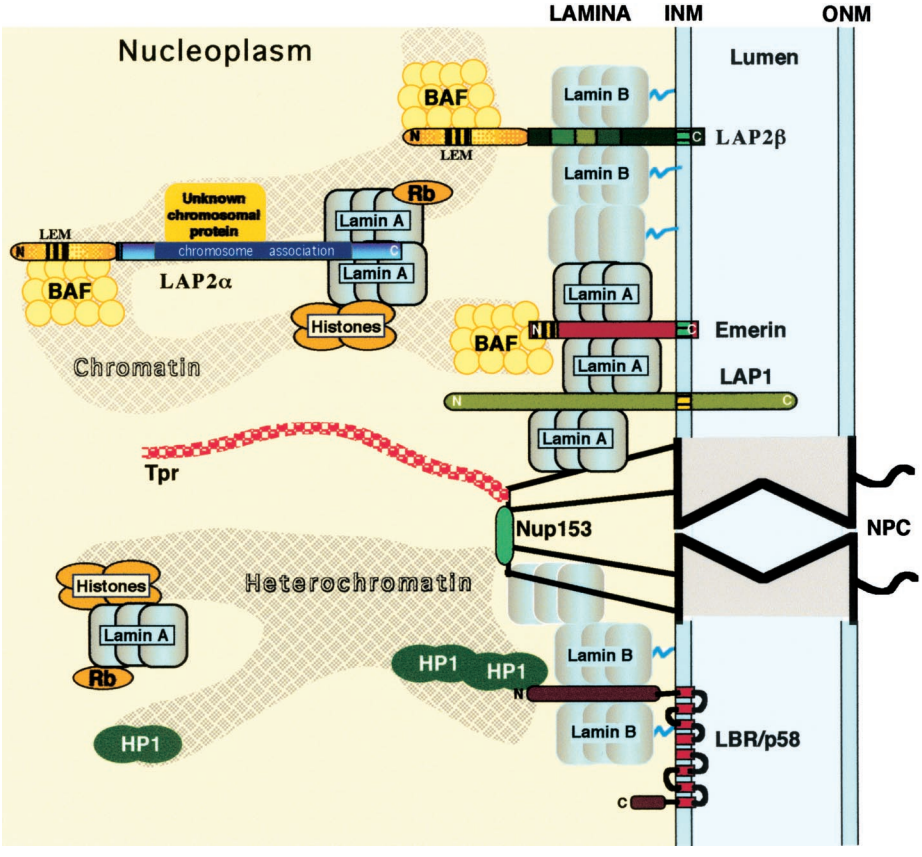

Figure 1. Proposed molecular interactions between components of the peripheral lamina, the nucleoskeleton and chromatin. INM, inner nuclear membrane; ONM, outer nuclear membrane; NPC, nuclear pore complex.

served in LAP2γ. However, the lamin-binding activities of smaller isoforms have not yet been demonstrated.

The most-studied A-type lamins are lamin A and its smaller splice variant, lamin C. A-type lamins are only expressed in later stages of development [5, 19]. Lamin A is transiently farnesylated, and lamin C is never farnesylated. Perhaps due to their lack of fatty acid modification, lamins A and C do not associate stably with membranes during mitosis. A-type lamin structures may also be less stable during interphase, or organized differently, because ectopic expression of headless lamin mutants in mammalian cells selectively mislocalizes A-type lamins into intranuclear aggregates, whereas lamin B remains unchanged [20, 21]. The incorporation of mature, non-farnesylated lamins A and C into the lamina after mitosis might depend on B-type lamins [4] and specific interactions with membrane proteins at the INM (fig. 1). Integral membrane proteins that might link A-type lamins to the INM include three LAP1 proteins (A, B and C), which are alternatively spliced products of a gene unrelated to LAP2 [22], and emerin [23], which shares an ~40 residue domain (LEM domain) with the LAP2 isoforms [16, 24]. LAP1-A, LAP1-B and emerin all bind A-type lamins in vitro [17, 25], and the localization of LAP1-C and emerin at the INM depends on A-type lamins [26, 27]. Thus, multiple interactions between lamins and INM proteins are probably required to form a stable peripheral lamina.

Lamins in the nuclear interior: a component of the nuclear matrix?

Whereas lamins were for a long time believed to localize exclusively at the nuclear periphery, the concept of intranuclear lamins developed more recently. Because the NE can form tubular invaginations that project deep into the nuclear interior [28], care is needed to determine whether internal lamin structures are independent of invaginated nuclear membranes. Nevertheless, a series of studies have shown that A-type lamins are found in intranuclear structures either permanently throughout interphase [29–31], or transiently during G1 phase [32, 33] or transiently during interphase during posttranslational processing [34–36]. Transient localization of intranuclear lamins can be explained in at least three ways. Microinjected lamins A or C accumulate first in intranuclear speckles before being targeted to the lamina [35, 36], and intranuclear lamin foci contain pre-lamin A [34], suggesting that A-type lamins are posttranslationally processed at sites inside the nucleus. Furthermore, the assembly of mature non-farnesylated lamin A into the lamina may be slower than the posttranslational processing steps, leading to the persistence of intranuclear foci of A-type lamins during G1 phase [21, 33]. Alternatively, A-type lamins may be present in the nuclear interior throughout the cell cycle, but often inaccessible to antibody staining due to cell-cycle-specific changes in chromatin structure. The latter hypothesis is strongly supported by the findings that green fluorescent protein (GFP)-lamin A structures are present in the nuclear interior throughout the cell cycle [29], and that lamin A structures in interphase cells can be visualized after extracting DNA [30]. The non-membrane-bound protein LAP2α, which is located in a nucleoskeletal structure rather than the NE [37], binds directly to the C-terminal tail of lamins A and C in vitro. LAP2α is found in stable SDS-resistant complexes with A-type (but not B-type) lamins during interphase and during nuclear assembly [21]. Furthermore the selective disruption of endogenous lamin A structures, caused by ectopic expression of dominant-negative lamin mutants in HeLa cells, caused LAP2α to relocate to intranuclear lamin A/C aggregates, but had no effect on lamin B, LAP2β or NuMA. These results argue for an internal lamin A-LAP2α nucleoskeletal complex that exists throughout interphase. It is still unclear, however, whether lamin A and LAP2α form filaments or other higher-order structures in the nuclear interior. It is possible that the internal 'nucleoskeleton' consists of smaller complexes tailored for specific functions such as DNA replication. It is also not known whether peripheral and internal nuclear lamin A structures are connected. Photobleaching of intranuclear GFP-lamin A argues for the existence of both immobile lamin A structures and free lamin A in the nucleus [29, 32].

Molecular links between the lamina and chromatin

Transcriptionally silenced, late-replicating heterochromatin is dynamically associated with the NE [19, 38], and lamina thickness along the NE correlates quantitatively with regions most closely associated with chromatin [39], suggesting a molecular link between the lamina and heterochromatin. These links are likely to involve multiple interactions (fig. 1). Lamins can bind directly to DNA, and both A- and B-type lamins bind in vitro to matrix/scaffold attachment regions of DNA [40, 41] and to telomeric and heterochromatic DNA sequences [42, 43]. The physiological implications of lamin binding to DNA in vitro is not clear, but photo-crosslinking supports a close association of interphase lamins with DNA in vivo [44]. Lamin interactions with chromatin might be mediated by the rod domain [45] or C-terminal tail domain, which binds core histones [46, 47], or both. Interactions between lamins and chromatin might also involve lamin-binding proteins, since LBR interacts directly with DNA [10, 48] and also with human Hp1-type chromodomain proteins [49].

LAP2 proteins have several chromatin and/or DNA binding domains, which are either shared, or unique to certain

isoforms. LAP2β, the only membrane-anchored isoform analyzed so far, associates with chromosomes in vitro in a lamin-independent manner [17, 18]. Several subdomains of LAP2β might be involved in this interaction. LAP2β has a nucleoplasmic DNA binding domain [50], which might be present in the smaller isoform (LAP2ε) but is missing in all other isoforms. Residues 1–85, which are common to all LAP2 isoforms, are sufficient to bind chromatin in situ in permeabilized mitotic cells [18]. Finally, an N-terminal region (residues 67–137) common to all LAP2 isoforms was identified by yeast two-hybrid assay to bind a chromosomal protein named Barrier-to-Autointegration Factor (BAF) [51]. The BAF interaction domain overlaps significantly with the LEM domain [52], which is conserved in nuclear membrane proteins emerin and MAN1 [24]. The prediction that all LEM-domain proteins interact with chromatin has not yet been tested.

The chromosome-binding activity of LAP2α has been studied in detail. Although the N-terminal chromatin binding and BAF binding domains are present in LAP2α, these domains were dispensable for LAP2α to interact with chromosomes at early stages of post-mitotic nuclear assembly. Instead, a new LAP2α-specific binding region was identified, which was both essential and sufficient for chromosome binding [53]. Thus, LAP2-mediated links between chromatin and lamina proteins are not restricted to the nuclear periphery.

Tpr- and Nup153-mediated connections between the NE and nuclear interior

Two recently described NPC-associated proteins might also link the peripheral lamina to the internal nucleoskeleton, and mediate chromatin anchorage and organization. Tpr (translocated promoter region) is an ~265 kDa protein whose N-terminal domain has appeared in oncogenic fusions with kinase domains of protooncogenes [54]. Wild-type Tpr is a constitutive component of filaments that attach to the nuclear pore complex (NPC) basket structure and extend at least 100–350 nm into the nucleus [55], and localize to the diffusional spaces between chromatin [56]. The expression of Tpr mutants in mammalian cells suggests a role for Tpr in mRNA export [57]. Based on the characterization of Mlp1 and Mlp2, two homologs of Tpr in yeast, Tpr proteins may also provide tracks to nuclear pore complexes [58]. These proteins also mediate the transcriptional repression of telomeric genes, by tethering the telomere-binding factor yKu70 to the NE [59].

The other candidate for an NPC-associated matrix protein is Nup153, which is a constituent of the nuclear pore basket [60, 61]. Nup153 interacts with both import and export receptors in a Ran GTP-regulated fashion, and is proposed to shuttle between the nuclear and cytoplasmic faces of the NPC [62–65]. However Nup153 might also be involved in NPC formation, and links the NPC to the lamina. Nup153 can bind DNA [66], associates with chromosomes early during nuclear assembly [67, 68] and requires B-type lamins for its assembly in *Xenopus* egg extracts [69].

Cell cycle dynamics of nuclear lamina and matrix proteins

Multicellular eukaryotes reversibly disassemble the nuclear lamina, NPCs and the nucleoskeleton during mitosis [19]. Disassembly is driven by the phosphorylation of lamins, LBR, LAP1, LAP2 and nucleoporin proteins, by mitotic cyclin-dependent kinases and perhaps other kinases (reviewed in [5, 16, 70]). Mitotic A-type lamins are distributed in the cytoplasm probably as dimers or tetramers, whereas B-type lamins remain associated with membranes due to their C-terminal farnesyl modification, and possibly also by binding to LBR and other NE proteins that bind lamin B [71]. Phosphorylation of LAP2β [17] and LAP2α [37] at mitosis-specific sites causes their dissociation from lamins and chromosomes. There are reported discrepancies depending on the cell systems used as to whether nuclear membrane proteins (LAP2β, LBR and emerin) and ER proteins segregate into distinct membrane structures during mitosis or whether both disperse throughout the ER (see [72]).

Nuclear reassembly is phosphatase dependent and, at least for lamins, involves phosphatase PP1 [73]. Lamins and LAP2 proteins are targeted to chromosomes in a temporally and spatially regulated manner, suggesting that they fulfill different functions during assembly. LAP2α appears to be the first among these proteins to associate with chromosomes during anaphase, accumulating before LAP2β-containing membranes enclose the decondensing chromosomes [53] (fig. 2). Although a subfraction of lamins might associate with LAP2 proteins early during NE formation, the majority of at least A-type lamins clearly assemble into stable nuclear structures at later stages of nuclear reformation [17, 32].

We propose that the sequential association of LAP2α and -β with chromosomes during nuclear assembly might be explained by differential use of specific binding domains within each protein. The early association of LAP2α with chromosomes requires the α-specific C-terminal domain, which is absent in LAP2β [53]. The N-terminal BAF binding domain, present in both LAP2α and -β, does not interact with BAF at this stage of nuclear assembly, perhaps due to posttranslational modification of LAP2 and/or BAF. The binding of LAP2α and -β to BAF may be activated later, for example by local phosphorylation or dephosphorylation. Alternatively, the formation of

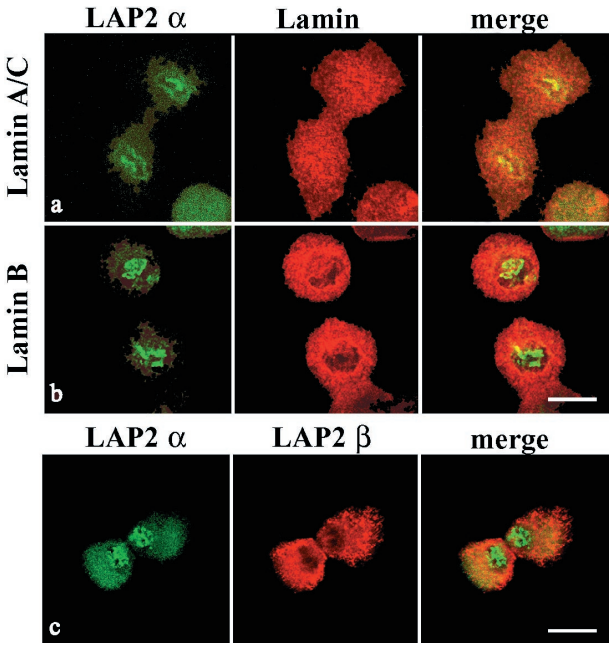

Figure 2. Confocal immunofluorescence images showing the localization of LAP2α and various lamina proteins in HeLa cells at early stages of nuclear assembly. For details, see text. Bar, 10 µm.

BAF-DNA oligomeric structures might subsequently promote binding (see [74]).

The early accumulation of LAP2α around decondensing chromosomes suggests that it might provide a scaffold for chromatin organization. Considering that LAP2α has at least two chromatin interaction domains, it is ideally suited to crosslink chromosomal regions and might structurally organize chromatin in postmitotic nuclei [16].

LAP2β was originally proposed to target membranes to chromosomes [17], but this activity has not yet been demonstrated directly. Microinjection of the chromatin and lamin binding domain of LAP2β into mitotic cells did not inhibit nuclear membrane targeting or assembly, but did subsequently block NE growth [75]. The same fragment had similar effects when added to *Xenopus* nuclear assembly reactions [15]. A smaller N-terminal LAP2β fragment that included only the chromatin and BAF binding regions also failed to inhibit nuclear membrane binding to chromatin in *Xenopus* extracts [15], but unfortunately this fragment was not tested in the mammalian system. Thus, we do not yet know whether the BAF binding region is important for membrane recruitment to chromosomes. LBR, which accumulates on chromosomes at the same time as LAP2β [67, 76, 77], appears to mediate membrane-chromosome interactions as shown by in vitro binding studies using LBR-immunodepleted membrane fractions [78].

The dynamics of Nup153 and Tpr during mitosis have been tested. Nup 153, but not Tpr, is recruited to chromosomes at the same time as LAP2β and LBR [67, 68]. The reported interaction of Nup153 with lamin B, and the dependence of Nup153 on the lamina for its recruitment and maintenance at the NE [69], suggests that the assembly of structures on the nucleoplasmic side of the NPC depends on the lamina. Consistent with the assembly of an internal nuclear structure, Tpr is assembled after the nuclear envelope.

Potential interphase functions of the lamina and nucleoskeleton

As an intermediate filament-type structure, the nuclear lamina is predicted to confer mechanical stability. Consistent with this function, nuclei assembled in vitro under lamin-depleted conditions are rather fragile, and nuclei devoid of A-type lamins have irregular shapes (reviewed in [38]). The lamina might also help organize chromatin and thereby regulate gene expression. For example, the highly silenced human chromosome 18 occupies a more peripheral territory in the nucleus than the highly active chromosome 19 [79], consistent with a gene silencing function of the lamina. This effect may be mediated by lamina interactions with heterochromatin protein Hp1, and BAF (see above).

Alternatively, lamina proteins might be involved in gene expression by direct binding to transcriptional regulators. Lamins A and C bind in vitro to Rb (retinoblastoma protein) [80, 81], which represses the activity of E2F transcription factors by recruiting histone deacetylase [82]. Interestingly, LAP2β was found in a yeast two-hybrid screen to interact with Germ Cell-less, a transcriptional repressor that binds the DP component of the E2F heterodimer [19]. Thus, LAP2β might also be involved in gene repression.

Lamins and LAPs are also required for DNA replication. Nuclei assembled in the absence of lamin B3 in *Xenopus* nuclear assembly extracts failed to replicate their DNA [83, 84], but the addition of lamin B3 partially restored the phenotype [85]. Similarly, the addition of mutant lamin proteins to *Xenopus* nuclear assembly reactions, or microinjection of these mutants into mammalian cells, inhibit lamina assembly or disrupt the existing lamina and prevent DNA replication [86, 87]. Based on slightly different results seen with different lamin mutants, it was concluded that the lamina either promotes the assembly of replication foci [87], or is required for the elongation phase of DNA replication [87, 88], probably by forming a structural scaffold upon which replication factors are organized. Interestingly, addition of the chromatin and lamin binding fragment of LAP2β to *Xenopus* nuclear assembly extracts either inhibited replication completely, or enhanced DNA replication 2.5-fold, depending on concentration [15]. Microinjection of the same fragment into

G1-phase HeLa cell nuclei prevented nuclear growth and DNA replication [75]. Thus, LAP2β might also be involved in DNA replication either directly or indirectly by affecting lamina assembly.

These diverse functions of lamina/matrix proteins may explain how mutations in lamina proteins cause different heritable diseases. For example, the X-linked form of Emery-Dreifuss muscular dystrophy (EDMD) is caused by mutations in the emerin gene [23], and autosomal dominant EDMD is caused by mutations in the gene encoding A-type lamins, *LMNA* [89]. Other mutations in *LMNA* cause cardiomyopathy [90] or lipodystrophy [91, 92]. It was proposed that missense mutations in different molecular regions of lamins [93] may disrupt lamina structure or may interfere with specific interactions of lamins [38]. Because LAP2α interacts with the C-terminal region of A-type lamins, where many lipodystrophy and EDMD mutations map, we speculate that some of these mutations may impair LAP2α-lamin A interactions and thereby cause the specific phenotype. The disruption of lamin/emerin interactions would mostly affect the peripheral lamina, whereas mutations that affect LAP2α binding to lamins might disrupt internal nuclear structures, and thus cause different disease phenotypes. It is not known if mutations in LAP2 cause human disease.

Conclusions and future prospects

The discovery of novel binding partners for lamins and lamina-associated proteins has expanded their potential functions from purely structural roles, to potentially regulatory roles in DNA synthesis, positional gene silencing of heterochromatic DNA and transcriptional regulation of the Rb-E2F complex. Thus, many diverse nuclear functions seem to be directly or indirectly linked to the nuclear lamina. We believe that the identification of more binding partners, particularly those expressed specifically during differentiation, will provide a clearer picture of the mechanisms of lamina function. The detailed molecular analysis of the dynamics, structure and interactions of nucleoskeletal proteins is a prerequisite for understanding the molecular mechanisms of human diseases linked to lamina proteins.

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