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Visions & Reflections

Intermediate filaments: novel assembly models and exciting new functions for nuclear lamins

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Abstract. Intermediate filament (IF) proteins constitute a highly diverse family of fibrous proteins in metazoans, which assemble into 10-nm-thick filaments in the cytoplasm and the nucleus. Novel recent insights into the in vitro assembly mechanism have revealed principal differences in the formation of cytoplasmic and nuclear filaments. Moreover, the past years have seen dramatic developments for the nuclear specific IF proteins, the lamins. While in the past lamins have been assumed to form only a structural scaffold at the nuclear periphery, their discovery in the nuclear interior, the identification of novel lamin-binding proteins and the functional disruption of lamin structures have brought to light essential functions for lamins in fundamental cellular events such as chromatin organization, DNA replication and RNA transcription. Furthermore, mutations in lamins and lamin-binding proteins have been demonstrated to cause various different human diseases, affecting muscle, heart, neuronal, adipose and bone tissue or leading to premature ageing. However, the molecular basis of these diseases is just beginning to emerge.

Key words. Chromatin; coiled coils; filament assembly; lamina; lamina-associated proteins; laminopathy; nuclear membrane; unit-lenght filaments.

Together with microtubules and actin filaments, the intermediate filaments (IFs) form a complex cytoskeletal framework in many higher eukaryotic cells. In addition, a subgroup of IFs is localized in the nucleus and appears to be essential for life in metazoans. IF proteins constitute a large family of proteins encoded by 65 functional genes in the human genome [1], which are expressed in specific patterns during embryogenesis [2]. With respect to sequence homology, vertebrate IF proteins can be grouped into five classes, i.e. sequence homology class (SHC) I to V [3, 4]. Genes encoding IF proteins have not been found in the genomes of plants, yeast or prokaryotic cells, and thus IF proteins appear to be characteristic for metazoans. Yet a relatively simple organism such as the freshwater sponge *Hydra* expresses an IF protein with considerable similarity to human lamin B, suggesting that lamins are, from the evolutionary point of view, the oldest group of IF proteins [5]. Lamins are the nucleus-specific IF proteins and differ from cytoskeletal proteins by the presence of additional 42 residues in coil 1B, a nuclear localization sequence (NLS) in the tail, and in most cases a C-terminal CaaX motif which is the target for isoprenylation and carboxyl methylation [6, 7]. Mammals have three lamin genes encoding at least seven distinct isoforms [8]. Among those, B-type lamins are expressed in all cells, whereas A-type lamins are only expressed following gastrulation in differentiated cells [9].

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Molecular structure of IF proteins

All IF subunits share a common characteristic tripartite domain organization: a central α-helical coiled-coil-forming segment, consisting of coil 1A, 1B, 2A and 2B, is flanked by non-α-helical N-terminal ('head') and C-terminal ('tail') domains of largely varying lengths. In particular, these latter domains may influence the properties of IFs considerably [4]. Unlike the globular subunits of microtubules and microfilaments, IF proteins are remarkably extended, i.e. fibrous, since their coiled coils are forming rodlike structures of more than 40-nm length. While in the past the molecular features of IF proteins have mainly been deduced from their biochemical and biophysical properties, from electron microscopic analyses, and by extensive sequence comparison [2, 4], emerging information on the atomic structure(s) of IF domains will eventually allow to prove or disprove present structural models [10].

Assembly of IFs in vitro

Although it is assumed that all IF proteins form the same type of 10-nm filaments, they can be distinguished into three assembly groups according to their assembly behavior and cellular topogenesis: (i) keratins form obligate heteropolymers of type I and type II keratins (SHC I and SHC II); (ii) vimentin and vimentin-related proteins, (SHC III) and neurofilament proteins (SHC IV) are able to form homopolymers but do often form copolymers with one another in vivo; (iii) the nucleus-specific IF subunits, the lamins (SHC V), assemble into the same scaffold; however, at what stage – and if at all – they integrate into one and the same filament is not completely clear yet [5]. These differences of assembly are evident directly in the first stage of assembly when the soluble subunits are subjected to near physiological ionic conditions. Whereas lamins first exhibit a 'head-to-tail'-type association of dimeric subunits [11], the assembly group 2 members prominently aggregate laterally to form relatively uniform full-width 'minifilaments' that have been designated 'unit-length-filaments or ULFs' [12, 13] (fig. 1 A). The growth of IFs occurs then by direct longitudinal fusion of ULFs. ULFs are generated within the millisecond time range, while elongation is comparatively slow, being in the range of minutes for several hundred nanometer long IFs. Intermediates observed during the elongation phase suggest a subunit-addition-type of filament formation (fig. 1 B). With keratins, the head-to-tail association is much faster so that the ULF formation is hard to dissect from longitudinal growth and is prominently seen only at very low protein concentration and under low ionic strength conditions [14]. As ULF formation has not been

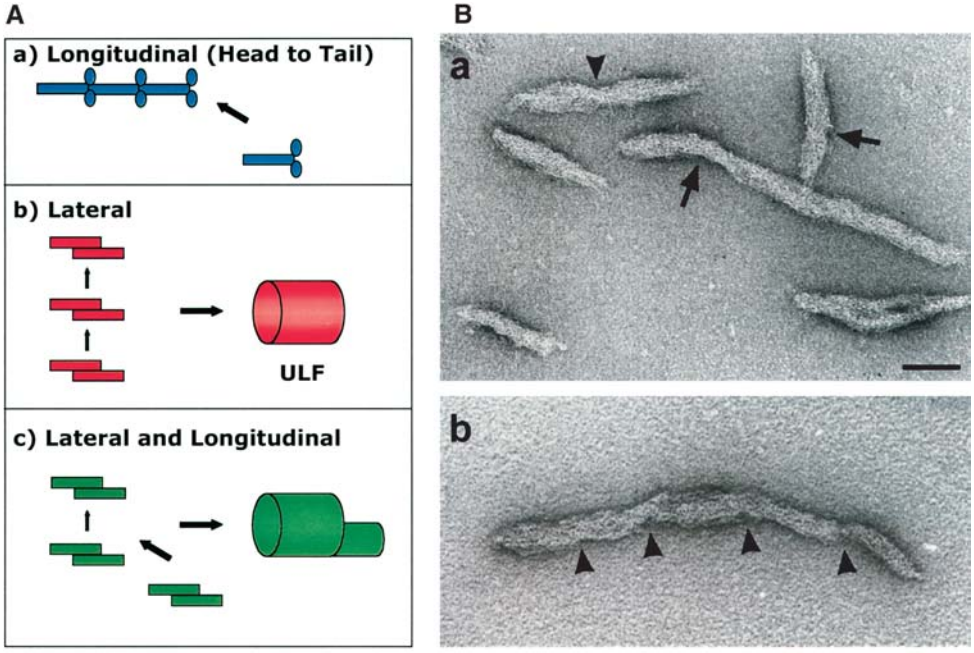

Figure 1. The early phase of IF assembly. (*A*) Schematic view of the prevalent associations of IF proteins from the three assembly groups immediately after initiation of assembly in vitro: (a) lamins, (b) vimentin-like proteins and (c) keratins. (*B*) Longitudinal association of ULFs from a recombinant vimentin: (*a*) shows different assembly forms as encountered a few seconds after initiation of assembly, (*b*) a short immature IF, still clearly segmented. Such structures, detected as dotlike complexes in immunofluorescence microscopy, may be the cargo delivered by microtubule-associated motor complexes. Arrowheads indicate fusion zones; the arrows point to beginning compaction reactions. Bar, 50 nm.

observed with lamins, the assembly of lamin dimers into filaments may proceed in a manner completely different from that of cytoplasmic IF proteins.

Assembly of cytoplasmic IFs in vivo

The factors that help organize IFs within the cytoplasm are largely unknown. However, heat-shock proteins have been demonstrated to be intimately associated with IFs [15]. In addition, vimentin filaments appear to interact with microtubule-based motor proteins [16], which may well be the sites for the generation and stabilization of assembly initiation units, possibly ULFs and short IFs. These may then be transported to places of IF remodeling and activated for end-on-fusion to existing IFs. Such processes are supposed to be further regulated by IF-associated proteins [17, 18] and by distinct phosphorylation reactions [19]. However, the mechanistic details of how plakins and other IF-associated proteins are engaged in a regulated organization of IFs are by no means clear. At present it appears to be rather likely that they may associate with IF proteins after filament assembly, although the possibility remains that they are recruited by cross-bridging proteins, such as plectin, bound to microtubules and/or microfilaments into the cytoskeleton [2, 4]. The seeding of IFs could hence occur along these polymers.

Lamin-type IFs in the nuclear interior?

Lamins have long been known as the major building blocks of the peripheral nuclear lamina underneath the inner nuclear membrane. After many years of debate, the idea that lamins exist also in the nuclear interior is mostly accepted [20, 21]. It remains unclear whether intranuclear lamins form filaments as detected in some electron microscopic preparations [22]. However, free vimentin-type 10-nm filaments within the nucleus, as observed upon ectopic expression of NLS-modified vimentin [23, 24], have not been described for intranuclear lamins. It is also unclear whether lamins in the nucleoplasm represent transient structures during lamina assembly [23] mediating their posttranslational processing, or whether they fulfill specific functions in the nucleus. As lamins are often associated with nuclear bodies [25, 26], they may represent nucleoplasmic functional units involved in DNA replication, transcription, chromatin organization and gene expression [27, 28].

Novel lamin interaction partners – new clues for lamin function?

Numerous lamin-binding proteins in the inner nuclear membrane and in the nucleoplasm may establish func-

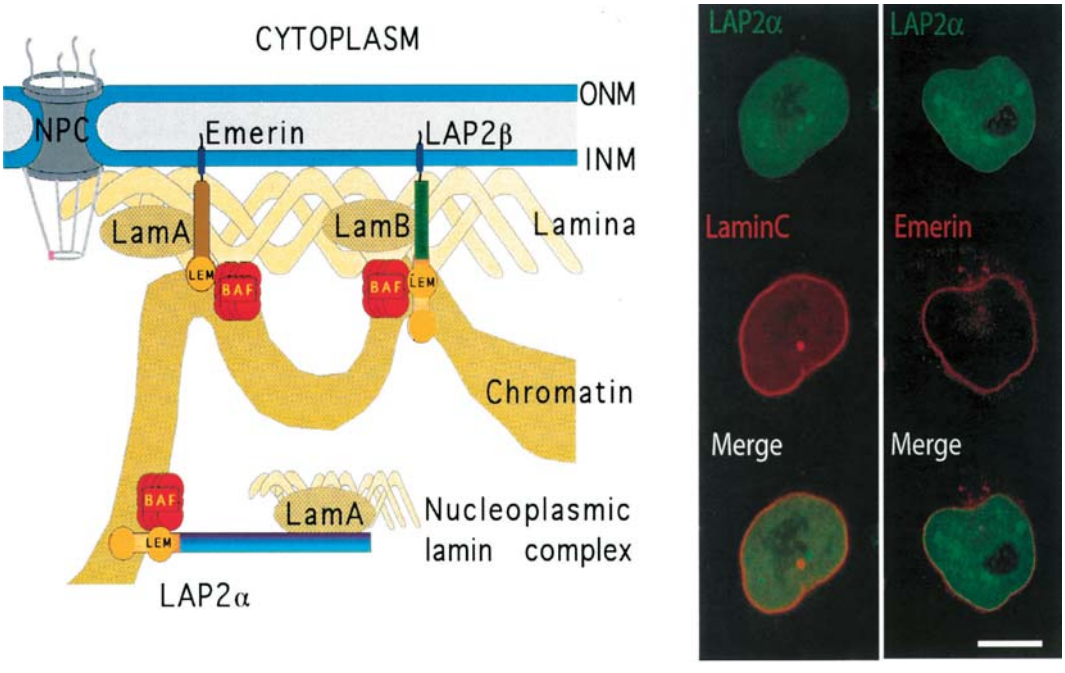

Figure 2. Lamin complexes form functional units at the nuclear periphery and in the nucleoplasm by interaction with specific binding partners. Left image, cartoon depicting lamin A-emerin-BAF, and lamin B-LAP2β-BAF complexes at the nuclear membrane and lamin A-LAP2α-BAF complex in the nucleoplasm, which interact with DNA and may have overlapping and unique functions. LamA, lamins A/C; LamB, lamin B; BAF, barrier-to-autointegration factor; LEM, LAP2-Emerin-MAN1 domain; NPC, nuclear pore complexes; ONM, outer nuclear membrane; INM, inner nuclear membrane. Right panel: Confocal fluorescence microscopy of HeLa cell nuclei expressing YFP-tagged LAP2α (green) and CFP-tagged lamin C or emerin (red). Images at bottom show merge of green and red image. Bar, 5 µm.

tional lamin complexes [29]. We are only at the beginning of realizing these functional lamin units and identifying the role of lamins and their interaction partners in these complexes. The interaction of lamins A/C with the inner nuclear membrane protein emerin may define such a functional unit (fig. 2), where lamins are responsible for proper localization of emerin in the inner membrane. Accordingly, downregulation of lamin A/C expression [30–33] or expression of lamin A mutants [34, 35] in cells can cause emerin mislocalization to the ER or to nuclear aggregates. Proper localization of emerin, in turn, may be critical for its potential function in higher order chromatin organization [36] through its association with the DNA cross-linking protein barrier-to-autointegration factor (BAF) [37]. Thus, mutations in the lamin A gene affecting emerin binding, as well as mutations in emerin, resulting in loss of emerin expression, both disrupt a functional lamin-emerin complex and may cause the same cellular phenotype. This scenario is seen in the two heritable human diseases, X-linked (X-EDMD) and autosomal dominant (AD-EDMD) Emery Dreifuss muscular dystrophy, which are linked to mutations in emerin and lamins A/C, respectively, but show the same clinical phenotypes ([9, 38], see below). This model, however, becomes more complicated, since (i) other lamin-binding proteins, such as the lamin B-interacting LAP2β isoform and MAN1 [39], sharing a 40-amino-acid-long domain with emerin (LEM domain) also bind DNA via BAF [40, 41], and (ii) one of the LAP2 isoforms, LAP2α [42], was found to interact with lamin A in the nucleoplasm [20] (fig. 2). Thus, DNA binding complexes of lamin may have both overlapping and unique functions in the nucleoplasm and the nuclear periphery in specific cell types and differentiation stages.

Similarly, recently identified nuclear envelope proteins, such as nurim, Unc-84, LUMA, ring finger binding protein (RFBP), Nesprin-1 (Myne1, Syne1) and Nesprin-2 [9, 43], which may directly or indirectly interact with the lamins, will most likely help to define lamin units with novel functions. Also, the previously identified association of lamins with major nuclear components, such as histones and DNA (for review see [7, 8]), and with regulatory proteins (e.g. retinoblastoma protein, Rb [44]) provide hints for lamin functions, which will have to be analyzed in detail in the future.

Lamina proteins in heritable diseases: new aspects for studies on lamin functions?

Probably the most intriguing discovery in recent years was that mutations in three different lamina proteins (lamin A/C, emerin [6, 8, 9, 38, 45, 46], LBR [47]) can cause seven distinct heritable human diseases (laminopathies) that affect a diverse set of tissues, including skeletal muscle, heart, adipose tissue, bones, nerve and blood cells. The latest, exciting addition to lamin-linked human diseases is Hutchinson-Gilford grogeria [62, 63], a premature ageing syndrome. These findings brought lamins back into the spotlight of cell biological and clinical research and also emphasized the need for further functional studies, since the molecular mechanisms underlying these diseases remain unclear. The major challenges in the future will be to understand how mutations in lamina proteins cause the highly heterogeneous types of diseases and why only a subset of tissues are affected despite the nearly ubiquitous expression of these proteins. There are three, not mutually exclusive models that try to explain laminopathic diseases. The structural model suggests that mutations in lamina proteins cause defects in lamin assembly and lamina structure leading to nuclear fragility or loss of nuclear organization. The gene expression model suggests that lamin complexes are important control elements of gene expression such that their absence is fatal. Finally, the cell fate model suggests that their mutation is linked to early apoptosis or premature aging.

Lamin functions not related to structural organization?

The formation of small deformed nuclei upon depletion of some or all lamins [32, 48, 49] clearly suggests a structural role for lamins. However, there may be much more to lamins than just a scaffolding function. B-type lamins are essential in *Drosophila* [50], *Chaenorabditis elegans* [49] and mammalian cells [31]. A-type lamins are not essential for embryonic development in mice but serve more specialized functions in cell differentiation and tissue homeostasis such that lamin A –/– animals die shortly after birth [32]. It is not at all clear whether the reported functions of lamins all depend directly or indirectly on their scaffolding role, or whether lamins may also serve direct regulatory functions.

Nuclei assembled in vitro in *Xenopus* egg extracts lacking a functional lamina fail to replicate DNA [28, 48, 51] and to transcribe RNA polymerase II-dependent genes [27]. There are at least two possible interpretations for these results. (i) Since most studies used dominant-negative lamin mutants able to destroy the endogenous lamina, one may conclude that lamina-mediated nuclear organization is essential for DNA replication and transcription, probably by anchoring replication and transcriptional complexes. (ii) Alternatively, lamins may more directly regulate the activities of the replication and transcription machinery, respectively. A-type lamins, for instance, interact with the adipocyte transcription factor SREBP-1 (sterol response element binding protein) [52], and A-type lamins [53, 54] and LAP2α [44] both bind Rb, sug-

gesting that lamin complexes may regulate adipocyte differentiation and Rb-mediated control of E2F activity during cell proliferation [55, 56], respectively. It will be very important to analyze the direct effect of lamin binding on the activity of these proteins in the future. With other lamin binding proteins these types of studies have already yielded more information on direct regulatory functions. LAP2β interacts with the E2F-DP complex associated repressor protein [57], germ cell less (GCL) [58], and overexpression of LAP2β can directly repress E2F transcriptional activity.

Finally, there is strong evidence now that lamina proteins are also involved in apoptosis, since inhibition of lamin cleavage delays apoptosis [59, 60], and conversely, inhibition or downregulation of lamin B triggers apoptosis [31, 61]. Hence, IF proteins and, in particular, lamins appear to be true multifunctional proteins which are integrated into a multitude of not necessarily overlapping cellular processes in metazoans.

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