

CELL SCIENCE AT A GLANCE

Inner nuclear membrane proteins and the nuclear lamina

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The nuclear lamina is a scaffolding structure at the nuclear periphery and is required for maintenance of nuclear shape, spacing of nuclear pore complexes, organization of heterochromatin, DNA replication, and regulation of transcription factors. The lamina is formed by type V intermediate filament proteins, A- and B-type lamins, which assemble to form a meshwork of 10-nm filaments underneath the inner nuclear membrane (INM). B-type lamins are constitutively expressed in all somatic cells and contain a stable C-terminal farnesyl modification, which mediates tight association with the INM. A-type lamins are expressed only in differentiated cells. They are components of the peripheral lamina and of structures in the nuclear interior. The lamina may be linked to nuclear pore baskets through Nup153.

Various integral membrane proteins of the INM are also components of the lamina. The lamin B receptor (LBR) contains eight transmembrane domains and binds to B-type lamins (B-type-lamin-mediated interactions involving the lamina and INM proteins are shown in green; La B). Nurim has five transmembrane domains, and MAN1 has two predicted membrane-spanning regions. Their interaction with lamins has not been analyzed yet. Three isoforms of lamina-associated polypeptide 1 (LAP1A, LAP1B and LAP1C), emerin, and at least four alternatively spliced isoforms of LAP2 (β , γ , and δ) are type II integral membrane proteins that each have a nuclear N-terminus and a single transmembrane domain. Whereas LAP1 isoforms bind preferentially to A-type lamins (A-type-lamin interactions are indicated in red; La A), and LAP2 β to B-type lamins, emerin associates with both lamin types. LAP2 is the most distantly related alternatively spliced isoform of LAP2, sharing only the N-terminus with the other isoforms. In contrast to LAP2 β , LAP2 is localized in the nuclear interior and forms complexes with A-type lamins. Three proteins (all LAP2 isoforms, emerin and MAN1) are members of a family defined by a 43-residue 'LEM domain' near the N-terminus, which is involved in binding to a chromosomal protein, barrier to autointegration factor (BAF). In addition, LBR binds to heterochromatin protein 1 (HP1), and LBR and LAP2 β interact with HA95, a chromosomal protein that has homology to nuclear A-kinase anchoring protein. Thus, LEM-domain proteins, LBR and lamins, which also bind to chromatin, may be involved in higher-order chromatin organization. Recently an INM protein that has nine membrane-spanning domains, ring finger binding protein (RFBP), an atypical type IV ATPase, was described to interact with RUSH, a member of the SWI/SNF family of transcription factors that remodel chromatin.

A-type-lamin-LAP2 complexes interact with the retinoblastoma protein (pRb), whereas LAP2 β binds to mouse germ cell less (mGCL), which interacts with the transcription factor E2F-associated DP. Thus, these proteins might regulate E2F activity and cell cycle progression. A-kinase-anchoring protein AKAP149 is a protein of the endoplasmic reticulum and outer nuclear membrane (ONM), which associates also with the phosphatase PP1 and is important for post-mitotic lamin assembly.

LBR was identified as part of a huge complex that also contains the integral membrane protein p18, an LBR kinase and p32/34, a low-molecular-weight protein.

Aside from the integral membrane proteins of the lamina, POM121 and gp 210 have been identified as transmembrane components of the nuclear pore complex.

