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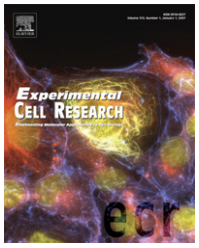

Review Article

Proteins that associate with lamins: Many faces, many functions

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ABSTRACT

Lamin-associated polypeptides (LAPs) comprise inner nuclear membrane proteins tightly associated with the peripheral lamin scaffold as well as proteins forming stable complexes with lamins in the nucleoplasm. The involvement of LAPs in a wide range of human diseases may be linked to an equally bewildering range of their functions, including sterol reduction, histone modification, transcriptional repression, and Smad- and β-catenin signaling. Many LAPs are likely to be at the center of large multi-protein complexes, components of which may dictate their functions, and a few LAPs have defined enzymatic activities. Here we discuss the definition of LAPs, review their many binding partners, elaborate their functions in nuclear architecture, chromatin organization, gene expression and signaling, and describe what is currently known about their links to human disease.

Contents

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Abbreviations: Crx, cone-rod homeobox; gcl, germ cell-less; LAP, lamin-associated polypeptide; NE, nuclear envelope; ER, endoplasmic reticulum; INM, inner nuclear membrane; ONM, outer nuclear membrane; NPC, nuclear pore complex; LEM domain, LAP2-Emerin-MAN1 domain; Lmo7, Lim-domain only 7; NET, nuclear envelope transmembrane protein; LBR, lamin B receptor; SUN, Sad1-UNC homology domain; Nesprin, nuclear envelope spectrin repeat containing protein; HP1, heterochromatin protein 1; BAF, barrier to autointegration factor; HDAC3, histone deacetylase 3; Rb, retinoblastoma protein; TGFβ, transforming growth factor beta; BMP, bone morphogenic protein; FRAP, fluorescence recovery after photobleaching; FRB, FKBP-rapamycin binding; NLS, nuclear localization signal; EDMD, Emery–Dreifuss muscular dystrophy; PHA, Pelger–Huet anomaly

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Introduction

The eukaryotic nucleus is a complex organelle with essential functions in genome stability, DNA replication, and gene expression. It is structurally and functionally organized into distinct sub-compartments, most prominently the nuclear envelope (NE), which separates nuclear and cytoplasmic activities. The NE is comprised of three major structures (Fig. 1) [1,2]: (i) two concentric membrane layers, the outer (ONM) and the inner (INM) nuclear membrane facing the cytoplasm and nucleoplasm, respectively, and separated by the perinuclear lumen; (ii) nuclear pore complexes (NPCs) inserted into the double membrane, which mediate nucleo-cytoplasmic exchange of components; and (iii) the nuclear lamina protein meshwork that is tightly associated with the INM and provides mechanical stability. The ONM is directly linked to and functionally related to the endoplasmic reticulum (ER) and thus contains ribosomes and other ER proteins. Yet a subset of ONM proteins is unique and not shared with the ER. The INM (although joined with the ONM at NPCs) contains its own unique group of integral membrane proteins that selectively and efficiently target to the INM [3,4]. Many of these INM proteins are components of the nuclear lamina, the core of which is formed by the nuclear-specific, type V intermediate filament lamin proteins. Details of lamins are covered elsewhere in this issue; however, critical to this review is that there are different lamin subtypes: B-type lamins expressed throughout development, and A-type lamins found predominantly in differentiated cells [5,6]. Lamins are post-translationally modified by farnesylation [7]. B-type lamins are permanently farnesylated and thus tightly associated with the INM, in contrast with A-type lamins that either are not farnesylated at all or have the farnesyl group removed by an additional post-translational proteolytic cleavage of the C-terminal 15 residues. The transient farnesylation of lamin A may facilitate its incorporation into the lamina, but after cleavage it should be less tightly associated with the membrane and accordingly, a subfraction of lamin A (estimated at ~5 to 10%) can also be found in the nuclear interior [8]. Multiple stable interactions of lamins with INM proteins within the nuclear lamina are fundamental for the mechanical integrity of the NE. This review focuses on mammalian lamin-associated proteins, most of which are components of the NE and the lamina. We attempt to resolve confusion between the terms lamin-versus lamina-associated polypeptides, which have been synonymously used in literature, and describe interactions, dynamics, and potential functions of the best studied lamin-associated polypeptides in mammals, as well as their potential involvement in human diseases.

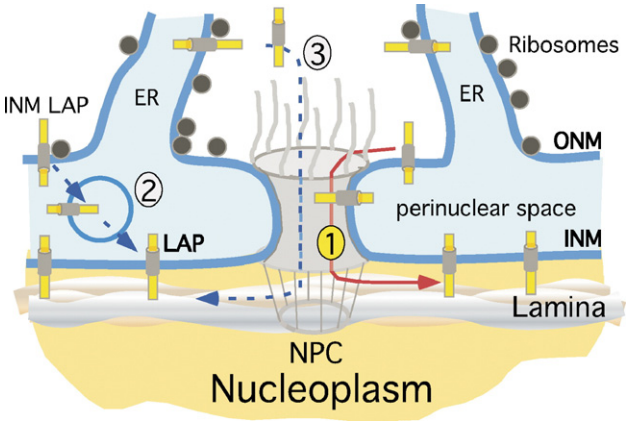

Fig. 1 – Schematic representation of the nuclear envelope and potential transport mechanisms of membrane proteins to the inner nuclear membrane: the nuclear envelope (NE) is comprised of a double membrane system of outer (ONM) and inner (INM) nuclear membranes. The ONM is continuous with the endoplasmic reticulum (ER). Several integral membrane proteins are embedded in both ONM and INM. Many of those in the INM physically interact with the lamin polymer that underlies the INM (LAP, Lamin-associated polypeptides). Nuclear pore complexes (NPC) perforate the nuclear membrane where ONM and INM join and appear to be involved both in transport of soluble factors between the nucleus and cytoplasm through their inner channel and in transport of INM LAPs on their outer face. INM proteins may diffuse laterally along the membrane from the ER to the INM in an energy-dependent manner and are retained by interaction with the lamina (pathway 1). In theory, alternative pathways for INM protein transport into the nucleus include budding off of vesicles with the protein from the ONM and fusion with the INM (pathway 2); or release of the INM from ER membranes, transport through NPC by classical transport pathways and insertion into the INM (pathway 3). Pathways 2 and 3, however, are energetically unfavorable and have little or no support in the literature.

Definition of LAPs as lamin-associated polypeptides

The term LAP was originally used to designate "lamina-associated polypeptides", INM proteins stably associated with the lamina at the nuclear periphery. These proteins bound lamins and cofractionated with lamins upon extraction with buffers containing high concentrations of monovalent salts and non-ionic detergents [9,10]. As the lamina is restricted to the nuclear periphery, LAPs by this definition are located at the NE. However, thereafter the term LAP has also been used for lamin-associated polypeptides, including proteins associated with the ~5% of lamins not located at the nuclear periphery. As the intranuclear lamins are presumably not assembled into a filamentous structure like in the lamina, epitopes may be accessible in nucleoplasmic lamins that are