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Review

Lamina-associated polypeptide (LAP)2α and nucleoplasmic lamins in adult stem cell regulation and disease☆

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ABSTRACT

A-type lamins are components of the lamina network at the nuclear envelope, which mediates nuclear stiffness and anchors chromatin to the nuclear periphery. However, A-type lamins are also found in the nuclear interior. Here we review the roles of the chromatin-associated, nucleoplasmic LEM protein, lamina-associated polypeptide 2α (LAP2α) in the regulation of A-type lamins in the nuclear interior. The lamin A/C–LAP2α complex may be involved in the regulation of the retinoblastoma protein-mediated pathway and other signaling pathways balancing proliferation and differentiation, and in the stabilization of higher-order chromatin organization throughout the nucleus. Loss of LAP2α in mice leads to selective depletion of the nucleoplasmic A-type lamin pool, promotes the proliferative stem cell phenotype of tissue progenitor cells, and delays stem cell differentiation. These findings support the hypothesis that LAP2α and nucleoplasmic lamins are regulators of adult stem cell function and tissue homeostasis. Finally, we discuss potential implications of this concept for defining the molecular disease mechanisms of lamin-linked diseases such as muscular dystrophy and premature aging syndromes.

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Abbreviations: ASC, (somatic) adult stem cell; BAF, barrier-to-autointegration factor; Dam, DNA adenine methyltransferase; DCM, dilated cardiomyopathy; EDMD, Emery Dreifuss muscular dystrophy; ESC, embryonic stem cell; FPLD, familial partial lipodystrophy; INM, inner nuclear membrane; HGPS, Hutchinson–Gilford Progeria Syndrome; iPS, induced pluripotent stem cell; LAD, lamina-associated domain; LAP, lamina-associated polypeptide; LEM, LAP2-Emerin-Man1; LRD, lamin rich domain; MDPSC, muscle-derived stem/progenitor cells; MSC, mesenchymal stem cell; NE, nuclear envelope; pRb, retinoblastoma protein.

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1. Introduction

The nuclear lamina is a proteinaceous network in metazoan cells that underlies the inner nuclear membrane (INM) and provides mechanical stability for the nuclear envelope (NE) (Fig. 1) [1–3]. It also fulfills a plethora of functions in chromatin organization, gene expression and signaling during development and tissue maintenance [4–10]. The lamina network is formed by type V intermediate filaments, the lamins [11–13], and a large number of lamin-binding proteins of the INM [14,15]. Structurally and functionally, lamins are grouped into A- and B-type lamins [16]. The main B-type lamins, lamin B1 and lamin B2 are encoded by *LMNB1* and *LMNB2*, respectively, and at least one B-type lamin is expressed in most cells throughout development. A-type lamins are encoded by the *LMNA* gene, giving rise to two major isoforms, lamin A and C, which are expressed later in development and in a differentiation-dependent manner [17]. Importantly, B-type lamins are processed post-translationally to yield a C-terminally farnesylated mature protein that is tightly associated with the INM through its hydrophobic farnesyl group. In contrast, newly synthesized pre-lamin A is also farnesylated during processing, but in a final maturation step a C-terminal peptide, including the farnesyl group, is proteolytically cleaved, producing a non-farnesylated mature lamin A [18–20]. Therefore, unlike B-type lamins, A-type lamins are less tightly linked to the INM and the lamina and are also found in a more mobile and dynamic pool throughout the nucleoplasm [21–24]. However, the regulation and specific functions of this dynamic, nucleoplasmic pool of A-type lamins are still poorly understood. Recent studies revealed evidence for exciting novel functions of this nucleoplasmic lamin pool in chromatin organization, cell signaling and cell cycle control in adult tissue stem cells (ASCs). In this review we discuss the potential functions of nucleoplasmic A-type lamins in fine-tuning the balance between proliferation and differentiation of ASCs, which is of crucial importance for tissue homeostasis. We also discuss how nucleoplasmic A-type lamins may affect the regulation of stem cell activity and how these functions may be altered in lamin-linked diseases.

2. Interplay between A-type lamins and LAP2α

Lamina-associated polypeptide 2 α (LAP2α) is one of six splice variants of the mammalian *LAP2* gene (originally termed *TMPO*) [25–28]. All LAP2 isoforms share the first 187 N-terminal residues [29] harboring the LAP2-Emerin-MAN1 (LEM)-domain [30], which mediates interaction with DNA in a sequence-independent manner *via* the adaptor protein barrier-to-autointegration factor (BAF) [31]. The common N-terminal LAP2 domain also contains a LEM-like motif enabling direct interaction with DNA [30,31]. Thus, all LAP2 proteins interact with chromatin by several mechanisms. The C-terminal domain of LAP2α differs considerably from that of the other LAP2 isoforms. Whereas most LAP2 isoforms, such as LAP2β, are stably anchored in the INM *via* a C-terminal transmembrane domain, LAP2α is a non-membrane protein uniformly distributed throughout the nucleoplasm [32]. Furthermore, whereas the LAP2 membrane proteins primarily bind B-type lamins at the nuclear lamina [33], LAP2α's unique C-terminal tail mediates exclusive binding to A-type lamins [22,24] and contains an additional chromosome association domain [34,35], as well as an interaction site for the cell cycle and differentiation regulator, retinoblastoma protein (pRb) [36,37].

The specific interaction of A-type lamins and LAP2α has been extensively studied by several means, including co-immunoprecipitation, cell cycle-dependent co-localization analyses and a proximity based biotin ligase assay in mammalian cells, as well as by *in vitro* solid phase overlay and pull-down experiments [22,32,38,39]. These studies revealed direct interaction of lamins A/C and LAP2α *via* their C-terminal tails [22] and a dynamic association of the proteins during the cell cycle. The nucleoplasmic lamin A/C–LAP2α complexes exist in G1 and early S-phase of proliferating cells but are absent during mitosis [32,40]. Intriguingly, LAP2α appears to be a crucial factor for the regulation and stabilization of the nucleoplasmic pool of lamin A/C and its localization in the nuclear interior (Fig. 1). In cells and epithelial tissues derived from LAP2α-deficient mice, A-type lamins localize exclusively to the nuclear lamina and are absent from the nuclear interior. Re-expression of full length LAP2α, but not of a lamin binding-defective LAP2α mutant, into LAP2α-deficient cells rescues the nucleoplasmic pool of lamin A/C [24]. Furthermore, loss of the nucleoplasmic pool of A-type lamins during myoblast differentiation correlates with the downregulation of LAP2α [41].

Therefore, LAP2α is a master regulator of the nucleoplasmic lamin A/C pool, but the mechanisms by which LAP2α affects nucleoplasmic lamins remain elusive. In G1 phase of the cell cycle, nucleoplasmic A-type lamins may originate from lamin complexes disassembled in the preceding mitosis, or may represent newly synthesized pre-lamin A, which may interact with LAP2α in the nucleoplasm only transiently, before they assemble into the nuclear lamina. The most intriguing scenario, however, is that A-type lamins are dynamically exchanged between the peripheral and the nucleopasmic pool, depending on post-translational modifications and/or the interaction of LAP2α and other factors.

3. Role of A-type lamins in disease

In 1999, Bonne et al. described the first mutation in the *LMNA* gene linked to autosomal dominant Emery Dreifuss muscular dystrophy (EDMD) [42]. Since then about 400 disease-linked mutations were identified in A-type lamins and in several lamin-binding proteins of the nuclear envelope.

These mutations cause a variety of diseases, collectively termed primary laminopathies for lamin A/C-linked diseases and nuclear envelopathies for diseases linked to nuclear envelope proteins They affect different tissues (striated muscle, heart, fat, bone, skin, or neuronal tissues) in isolation or in various combinations, or cause premature aging diseases, *e.g.*, Hutchinson–Gilford Progeria Syndrome (HGPS) [43–47].

Also a mutation in *LAP2α* has been linked to dilated cardiomyopathy (DCM) [39], the pathological features of which resemble those of lamin A-linked DCM. Interestingly, this DCM-causing LAP2α mutation, which leads to a single amino acid exchange in the C-terminal lamin A/C-binding domain of LAP2α was shown to impair LAP2α's interaction with lamin A/C *in vitro* [39].

Most disease-causing mutations in the *LMNA* gene are heterozygous single point mutations in *LMNA* found throughout the gene, leading to the expression of mutant lamin A/C variants with a single amino acid exchange. In contrast, the majority of mutations linked to HGPS introduce a cryptic splice site in exon 11 of *LMNA*, causing incorrect splicing and generation of a slightly smaller pre-lamin A variant (called progerin) that cannot be cleaved in the final step of post-translational processing and therefore remains permanently farnesylated [48]. Given that A-type lamins are expressed in nearly every differentiated cell, the tissue-specific phenotypes of many laminopathies are surprising, and the molecular pathways leading to the different pathological phenotypes are still not understood. Several non-mutually exclusive disease mechanisms have been proposed to explain the tissue-specific aspects and variability of laminopathic phenotypes [49,50].

3.1. The mechanical model

LMNA mutations may disrupt the stability or assembly of lamin networks, rendering the nucleus more fragile and less resistant

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