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Review

Lamina-associated polypeptide 1: Protein interactions and tissue-selective functions

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ABSTRACT

Mutations in genes encoding widely expressed nuclear envelope proteins often lead to diseases that manifest in specific tissues. Lamina-associated polypeptide 1 (LAP1) is an integral protein of the inner nuclear membrane that is expressed in most cells and tissues. Within the nuclear envelope, LAP1 interacts physically with lamins, torsinA and emerin, suggesting it may serve as a key node for transducing signals across the inner nuclear membrane. Indeed, recent in vivo studies in genetically modified mice strongly support functional links between LAP1 and both torsinA (in neurons) and emerin (in muscle). These studies suggest that tissue-selective diseases caused by mutations in genes encoding nuclear envelope proteins may result, at least in part, from the selective disruption of discrete nuclear envelope protein complexes.

Contents

1. Introduction

1.1. Nuclear envelope membranes

The nuclear envelope is composed of the nuclear membranes, the nuclear pore complexes and the nuclear lamina (Fig. 1). The nuclear membranes are composed of three continuous but morphologically distinct domains in interphase cells: inner, outer and pore. The outer nuclear membrane is directly continuous with the

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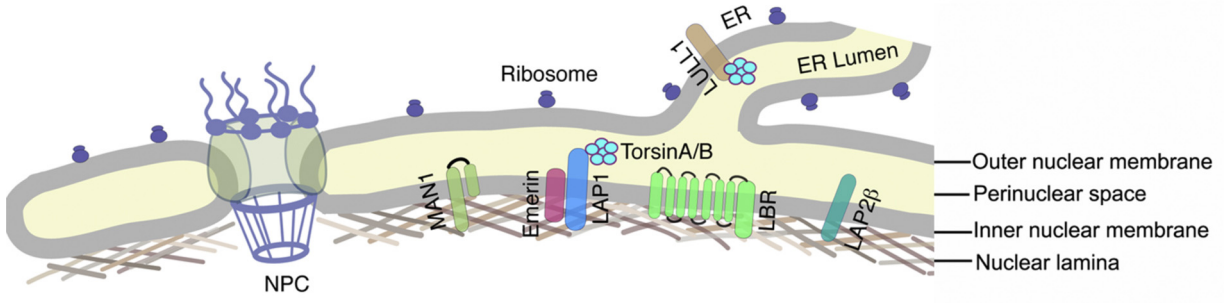

Fig. 1. Schematic diagram of the nuclear envelope showing the nuclear membranes, nuclear lamina and a nuclear pore complex (NPC). The outer nuclear membrane contains ribosomes on its outer surface just like the directly contiguous endoplasmic reticulum (ER). The ER lumen is directly continuous with the perinuclear space. Selected proteins concentrated in the inner nuclear membrane and LULL1 in ER membrane are shown along with torsinA and torsin B (TorsinA/B) in the perinuclear space. LAP1 is shown interacting with lamins, emerin and torsin A/B.

endoplasmic reticulum membrane, with which it shares ribosomes. It is separated from the inner nuclear membrane by the perinuclear space, which is continuous with the lumen of the rough endoplasmic reticulum. The pore membranes connect the inner and outer nuclear membranes at the nuclear pore complexes. The lamina is a meshwork of intermediate filament proteins called lamins, and is localized primarily at the inner aspect of the inner nuclear membrane.

As the nuclear membranes are actually a single interconnected membrane system, one could imagine that integral proteins synthesized on the rough endoplasmic reticulum would be randomly distributed among them. However, certain integral proteins are concentrated in each of these membranes in interphase cells, either as a result of binding to resident structures in specific domains or by active transport mechanisms [1–4]. Approximately 80 transmembrane proteins are concentrated in the inner nuclear membrane [5]. Many of the integral proteins of the inner nuclear membrane bind to nuclear lamins, which likely contributes to their retention within the nuclear envelope.

While the nuclear envelope proteome may vary to some extend among different cell types, integral proteins of the inner nuclear membrane typically exhibit a near-ubiquitous pattern of expression throughout different tissues [5,6]. This pattern implies that such proteins have fundamental roles in maintaining nuclear structure or supporting critical nuclear functions, indicating that alterations in the genes encoding these proteins is likely to be lethal or to cause widespread pathology. Surprisingly, however, the opposite is the case; a range of discoveries link mutations in these genes to human diseases that exhibit striking tissue specificity, typically of muscle, adipose or neural tissue.

1.2. Laminopathies/nuclear envelopathies

In 1994, Toniolo and colleagues reported that mutations in the gene encoding a widely expressed, previously uncharacterized integral membrane protein they named emerin were responsible for X-linked Emery–Dreifuss muscular dystrophy [7]. Subsequent research showed that emerin was localized to the inner nuclear membrane [8,9]. This was the first demonstration that mutations in a gene encoding an integral protein of the inner nuclear membrane widely expressed in many cells and tissues could cause tissue-selective disease. This tissue specificity is even more surprising considering that most pathogenic mutations cause loss of emerin expression, not subtle structural alterations [7–10].

Subsequent discoveries further strengthened the theme of tissue selective disease arising from mutations in genes encoding widely expressed nuclear envelope proteins [11,12]; these diseases are now referred to as “laminopathies” or “nuclear envelopathies” [11,12]. Perhaps the most dramatic example involves mutations in the gene encoding lamins A and C, which encodes extrinsic proteins of the inner nuclear membrane that are building blocks of the nuclear lamina. Distinct mutations in this gene cause over a dozen different diseases, which predominantly affect striated muscle, adipose tissue or peripheral nerve, whereas some mutations disrupt multiple tissues and produce a phenotype of accelerated aging (“progeria”) [11,12]. Among these diseases is autosomal dominant Emery–Dreifuss muscular dystrophy, which phenocopies X-linked Emery–Dreifuss muscular dystrophy caused by mutation in the gene encoding emerin [13]. In addition to emerin and lamins A and C, mutations in genes encoding other widely expressed proteins of the inner nuclear membrane cause tissue-selective diseases. Heterozygous mutations in the gene encoding LBR, an integral protein of the inner nuclear membrane [14], cause Pelger-Huët anomaly, which affects only blood neutrophils [15]. Mutations in the gene encoding MAN1, another integral protein of the inner nuclear membrane [16], cause sclerosing bone dysplasias with or without skin involvement, but without any other major organ pathology [17].

The mechanisms responsible for the apparent tissue-selective functions of nuclear envelope proteins remain for the most part unknown. To obtain insights into this question, we explored the biology of lamina-associated polypeptide 1 (LAP1), an integral protein of the inner nuclear membrane. Our work suggests that the function of protein complexes in the nuclear envelope, rather than of individual proteins per se, may underlie the tissue-selective pathology of the laminopathies/nuclear envelopathies.

2. LAP1

2.1. Discovery

LAP1 was first identified as three polypeptide antigens recognized by a monoclonal antibody generated against rat liver nuclear envelope protein extracts [18]. This antibody recognized antigens with apparent molecular masses of approximately 75 kDa, 68 kDa and 55 kDa in rat liver nuclear envelopes. Biochemical extractions showed the antigens to be integral membrane proteins and immunofluorescence and immuno-electron microscopy localized them to the inner nuclear membrane. Biochemical extraction experiments showed them to be associated with the nuclear lamina and subsequent experiments demonstrated that they bind assembled lamins in vitro [19]. The proteins with apparent molecular masses of approximately 75 kDa, 68 kDa and 55 kDa were named lamina-associated polypeptides 1A-C (LAP1A, LAP1B and LAP1C).

Analysis of the cloned rat LAP1C cDNA demonstrated that it encoded a type II integral membrane protein composed of 506 amino acids [20]. Further sequence analysis showed the human LAP1B cDNA encoded a protein of 584 amino acids with similar topology [21]. Human and mouse LAP1B are 66% identical in amino

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