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Review

Striated muscle laminopathies

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ABSTRACT

Lamins A and C, encoded by *LMNA*, are constituent of the nuclear lamina, a meshwork of proteins underneath the nuclear envelope first described as scaffolding proteins of the nucleus. Since the discovery of *LMNA* mutations in highly heterogeneous human disorders (including cardiac and muscular dystrophies, lipodystrophies and progeria), the number of functions described for lamin A/C has expanded. Lamin A/C is notably involved in the regulation of chromatin structure and gene transcription, and in the resistance of cells to mechanical stress.

This review focuses on studies performed on knock-out and knock-in *Lmna* mouse models, which have led to decipher some of the lamin A/C functions in striated muscles and to the first preclinical trials of pharmaceutical therapies.

Contents

Abbreviations: ACE, angiotensin-converting enzyme; ANF, atrial natriuretic factor; BNP, brain natriuretic peptide; DCM-CD, dilated cardiomyopathy with conduction defects; EDMD, Emery–Dreifuss muscular dystrophy; EHT, engineered heart tissue; KI, knock-in; KO, knock-out; LAP, lamin-associated protein; LBR, lamin B receptor; LINC, linker of the nucleoskeleton and the cytoskeleton; L-CMD, *LMNA*-related congenital muscular dystrophy; LGMD, limb-girdle muscular dystrophy; mTOR, mammalian target of Rapamycin; MAPK, mitogen-activated protein kinase; MEF, mouse embryonic fibroblasts; MTOC, microtubule organizing center; NE, nuclear envelope; Nup, nuclear pore-associate protein; Rb, Retinoblastoma; UPS, ubiquitin proteasome system; WT, wild-type.

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1. Introduction

LMNA encodes A-type lamins, intermediate filaments of the nucleus, ubiquitously expressed in differentiated cells. Together with B-type lamins and associated nuclear envelope (NE) proteins, they form the nuclear lamina, a meshwork underlying the inner NE. Four A-type lamins are produced by alternative splicing of *LMNA*. Lamins A and C, the major isoforms, are expressed in all committed cells [1]. Lamins A and C (henceforth referred to as lamin A/C) are identical for their first 566 amino acids, but are distinct at their C-terminal domains (Fig. 1). Lamin C has six unique C-terminal amino acids while lamin A is synthesized as a precursor, named prelamin A, which has 98 unique C-terminal amino acids. Prelamin A is farnesylated on the cysteine residue of a C-terminal CaaX box, i.e. CSIM, and is endoproteolytically processed by the ZMPSTE24 (zinc metalloprotease Ste24 homologue) protease to yield mature lamin A, which lacks the last 18 amino acids. Lamin A/C dimerizes and further assembles to form head-to-tail polymers, which associate laterally to form lamin filaments. These filaments, together with B-type lamins, constitute the nuclear lamina. Lamins A and C are also found sparsely in the nucleoplasm and may have multiple functions by association with chromatin, nuclear histones and various transcription factors [2].

Since the first description of a *LMNA* non-sense mutation associated with Emery–Dreifuss muscular dystrophy, EDMD [3], a growing number of publications have reported *LMNA* mutations associated with different clinical entities, commonly named laminopathies [2,4]. These laminopathies can be subdivided in 4 distinct groups, depending on the affected tissue: (1) striated muscles, (2) adipose tissue, (3) nervous system, and (4) accelerated aging syndrome, the later affecting tissues in a systemic manner.

This review focuses on the elucidation of the role of the lamin A/C and the pathophysiological mechanisms in striated muscles through the analysis of knock-out (KO) and knock-in (KI) mouse models, as well as the current and potentially future treatments for these different striated muscle laminopathies.

2. *LMNA*-related striated muscle disorders

In 1999, Bonne and co-workers have identified the first *LMNA* mutation in a large family with EDMD [3]. EDMD is characterized by (1) early development of contractures, mainly affecting Achilles' tendons, the elbows and the spine, (2) slowly progressive muscle atrophy and weakness, first affecting humero-peroneal muscles, and (3) the development of cardiac dilation, with cardiac conduction defects and/or arrhythmias, often leading to cardiac sudden death [5].

Since, *LMNA* mutations have been reported in limb-girdle muscular dystrophy (LGMD-1B) [6], dilated cardiomyopathy associated with conduction system disease (DCM-CD) [7,8], congenital form of muscular dystrophy (L-CMD) [9] and numerous syndromes overlapping with other disorders linked to *LMNA* mutations (lipodystrophies or premature aging) [2]. These different disorders differ in term of age at onset, first symptom at onset (contractures, muscle weakness or cardiac involvement), and pattern of affected muscle at onset, but they all share a common denominator, i.e. the cardiac dysfunction.

3. Mouse models for striated muscle laminopathies

Over the years, numerous studies have reported that A-type lamins provide structural support to the nucleus, maintenance of nuclear architecture, nuclear migration, and apoptosis, and also take part in chromatin organization and epigenetics, transcription, cell cycle regulation, cell development and differentiation [10]. To study the role of lamin A/C in skeletal and cardiac muscles, and to understand the pathophysiological processes induced by *LMNA* mutations, several mouse models have been created: A-type lamins KO (*Lmna*$^{-/-}$ also reported as "*Lmna*$^{\Delta 8-11}$", *Lmna*$^{GT-/-}$, *Lmna*$^{\Delta/\Delta}$ and Zp3-*Lmna*) and KI (H222P, ΔK32, and N195K). In addition, mouse models expressing only lamin A (LAO/LAO) or lamin C (LCO/LCO) have been created.

3.1. Knock-out models

3.1.1. *Lmna*$^{-/-}$ (*Lmna*$^{\Delta 8-11}$)

Sullivan and colleagues created the first KO mouse model of A-type lamin (*Lmna*$^{-/-}$) [11]. At birth, homozygous mice are normal but rapidly display a reduction in their growth rate, and by the eighth week, all of the homozygote mice die. *Lmna*$^{-/-}$ mice present with skeletal muscle dystrophy and DCM-CD [12]. Studies performed on *Lmna*$^{-/-}$ mice and derived cell cultures have highlighted the implication of lamin A/C in nuclear protein localization, nuclear integrity, cytoskeletal proteins regulation and mechanotransduction, transcriptional regulation and chromatin remodeling.

3.1.1.1. Role of lamin A/C in NE protein localization and cytoskeleton organization. Lamin A/C has a critical role in maintaining the structural integrity of the nuclear lamina and the spatial

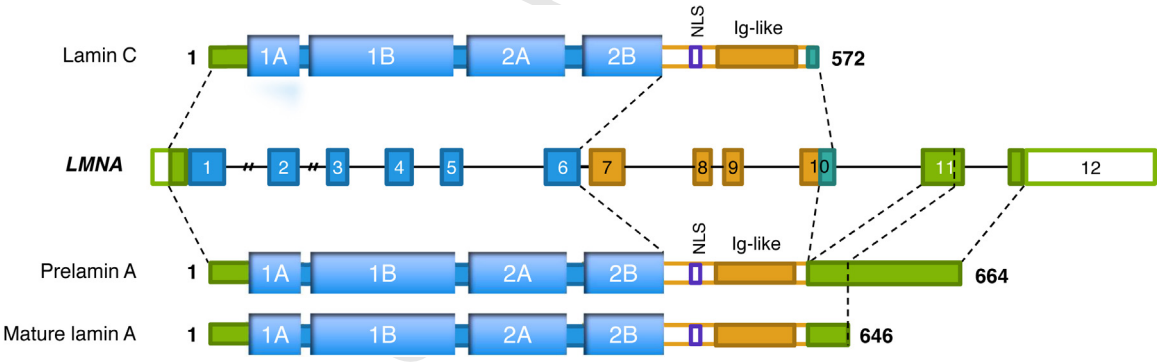

Fig. 1. Schematic representation of the *LMNA* gene and the two main protein isoforms: lamin A and lamin C. Lamins A and C are identical in their first 566 amino acids, but have distinct C-terminal domains. Lamin C has six unique C-terminal amino acids, encoded by the end of exon 10. Lamin A is synthesized as a precursor, prelamin A, which has 98 unique C-terminal amino acids, encoded by exon 11 and 12. Post-transcriptional modifications of prelamin A lead to the truncation of the last 18 amino acid to produce mature lamin A. Lamin A and C proteins are structurally composed of an unfolded N-terminus domain, a long coiled-coil rod domain (blue boxes) implicated in lamin dimerization, and a tail domain comprising the nuclear location sequence (NLS), and an immunoglobulin-like domain (Ig-like) involved in the interaction with other proteins.

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