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Review

Nuclear envelope-related lipodystrophies

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ABSTRACT

Several alterations in nuclear envelope proteins building up the lamina meshwork beneath the inner nuclear membrane (mutations in lamins A/C, alterations of prelamin-A maturation, lamin B mutations or deregulation) have been shown to be responsible for or associated to human lipodystrophic syndromes. Lipodystrophic syndromes are rare and heterogeneous diseases, either genetic or acquired, characterized by generalized or partial fat atrophy associated with metabolic complications comprising insulin-resistant diabetes, dyslipidemia, and non-alcoholic fatty liver disease. Recent advances in the molecular genetics of different types of lipodystrophies generally pointed to primary adipocyte alterations leading to impaired adipogenesis and/or deregulation of the adipocyte lipid droplet. However, the precise mechanisms linking nuclear envelope abnormalities to lipodystrophies remain largely unknown. The phenotype of nuclear envelope-linked lipodystrophies ranges from the typical familial partial lipodystrophy of the Dunnigan type (FPLD2), due to heterozygous substitutions of the 482nd arginine of lamins A/C, to complex diseases that can combine lipodystrophy, metabolic complications, muscular or cardiac alterations and/or signs of accelerated aging. In this review we present the clinical, tissular and cellular characteristics of the nuclear envelope-linked lipodystrophies, as well as their hypothetical pathophysiological mechanisms.

Contents

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1. Introduction: lamins and the lipodystrophic syndromes

The nuclear lamina is composed of the intermediate filaments A- and B-type lamins, which form a meshwork underlying the nuclear envelope. Lamins have a typical tripartite structure, with a central α-helical rod dimerization domain flanked by a short N-terminal head and a large C-terminal tail containing a globular immunoglobulin-like domain. B-type lamins, ubiquitously expressed, are encoded by the *LMNB1* and *LMNB2* genes, whereas prelamin-A and lamin-C, the main isoforms of A-type lamins, are developmentally regulated splice variants of the *LMNA* gene expressed in most lineage precursors and differentiated cells. Prelamin-A undergoes a complex post-translational maturation process affecting its C-terminal CaaX motif (Fig. 1, left panel). After farnesylation on the cysteine, aaX aminoacyls are removed, farnesyl-cysteine is carboxymethylated, and then 15 C-terminal aminoacyls are cleaved by the metalloprotease ZMPSTE24 to produce mature lamin-A. Lamins are important regulators of assembly, structure, shape and mechanical stability of the nucleus, and also participate to pleiotropic nuclear functions, such as organization of chromatin, gene expression, and DNA replication and repair [1]. Naturally occurring mutations in A-type lamins cause several different diseases called laminopathies, comprising lipodystrophies, skeletal and/or cardiac myopathies, neuropathies, premature aging diseases, and overlapping phenotypes. Lipodystrophic syndromes and/or accelerated aging phenotypes were also linked to acquired or genetically determined alterations of prelamin-A maturation or B-type lamins functions.

Lipodystrophic syndromes constitute a heterogeneous group of genetic or acquired diseases, characterized by generalized or partial fat atrophy (lipoatrophy) and metabolic complications (insulin-resistant diabetes, dyslipidemia, non-alcoholic fatty liver disease). Monogenic causes of lipodystrophies, although diverse, mostly converge on primary alterations affecting adipose tissue (AT), such as impaired adipogenesis or defects in the formation, maintenance and/or regulation of the adipocyte lipid droplet, leading to secondary dysfunctions of the whole body metabolism (Fig. 2) [2]. However, the pathophysiology of lipodystrophic syndromes due to genetic or acquired defects in lamins still remains largely undeciphered. We present here the different forms of laminopathic lipodystrophies, from a genetic, clinical, tissular, and cellular point of view, and discuss the main pathophysiological hypotheses raised by recent studies.

2. Genetic lipodystrophies due to mutations in *LMNA*, encoding A-type lamins

2.1. Clinical characteristics and genotype–phenotype correlations

2.1.1. Familial partial lipodystrophy of the Dunnigan type (FPLD2)

Heterozygous mutations affecting the C-terminal part of A-type-lamins, with a mutational hot-spot substituting the positively charged arginine at codon 482 for a neutral amino-acid (tryptophan, glutamine, leucine), are responsible for the typical form of Dunnigan-type familial partial lipodystrophy (FPLD2) (Fig. 3) [3,4]. Homozygosity for the *LMNA* p.R482Q mutation was observed in a single family, resulting in a combination of lipodystrophic, myopathic and progeroid phenotype [5].

FPLD2 is characterized by the disappearance, around puberty, of AT in the limbs, buttocks and trunk, contrasting with a cushingoid appearance due to fat accumulation in the neck, face and axillary regions. Accumulation of fat also occurs in intra-abdominal areas, and in the perineum in females. Patients show a generalized muscular hypertrophy, with an actual increase in skeletal muscle volume [6] accentuated by lipoatrophy. Metabolic consequences develop progressively, with severe hypertriglyceridemia, insulin resistance (clinically recognized by brownish hyperkeratotic skin lesions of *Acanthosis nigricans* of body folds), diabetes, liver steatosis, premature atherosclerosis [7,8] and frequent ovarian hyperandrogenism in females [9]. Endocrine functions of AT are also affected, with decreased adiponectin and leptin circulating levels. The lipodystrophic and metabolic phenotype is more severe in females than in males [10] suggesting that sex steroids, which are known factors contributing to the physiological sexual dimorphism of body fat distribution, could be involved in the lipodystrophic phenotype resulting from these *LMNA* mutations. Some patients also present muscular and cardiac abnormalities characteristic of other forms of laminopathies [11].

2.1.2. Metabolic laminopathies

Non-codon 482 *LMNA* mutations, diversely affecting the C-terminal, rod, or N-terminal domains of A-type-lamins, can lead to atypical forms of lipodystrophic syndromes. Lipoatrophy can be clinically mild, with android obesity in some cases, but features of the metabolic syndrome including insulin resistance and dyslipidemia are present [12–15]. Metabolic laminopathies can associate with muscular and cardiac abnormalities.

2.1.3. Progeria and progeroid syndromes

The Hutchinson-Gilford progeria syndrome (HGPS) is a rare and severe segmental accelerated aging syndrome. HGPS is mainly due to a *de novo* heterozygous *LMNA* mutation leading to the synthesis of progerin, a mutated prelamin-A lacking its endoprotease cleavage site and remaining constitutively farnesylated [16,17]. The phenotype develops in the first years of life, with growth retardation, bone and cartilage dysplasia, hair loss, scleroderma-like skin alterations, generalized subcutaneous lipoatrophy with insulin resistance and low HDL-cholesterol, and severe and precocious atherosclerosis, leading to early mortality generally at adolescence [18]. Other premature aging syndromes, due to mutations in *LMNA* or *ZMPSTE24*, as mandibulo-acral dysplasia (MAD) [19,20] or atypical progeroid syndromes, present similar signs than HGPS, although less severe, with generalized or partial lipodystrophy, insulin resistance, dyslipidemia and liver steatosis. These observations suggest that lipodystrophies and accelerated aging syndromes share partially common pathophysiological determinants.

2.2. Pathological features of patients' adipose tissue

The different body fat depots have distinct physiological responses, including a depot-specific pattern of A-type-lamins mRNA expression [21]. However, the stereotyped anatomical pattern of lipoatrophy in FPLD2 remains largely unexplained.

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