An emerging interplay between altered human lipid metabolism, lipodystrophy and aging

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LMNA-Lipodystrophies are a group of heterogeneous syndromes, with either genetic or acquired origin, characterized by the accumulation of prelamin A, an immature form of the protein lamin A, one of the major components of the nuclear lamina. Several molecular studies suggest lamin A is involved in adipocyte development, the disruption of which leads to compromised regulation of adipogenesis, adipocyte lipid droplet formation and maintenance, and subsequent secondary dysfunctions in fat metabolism. Moreover, these diseases clinically present with generalized or partial fat atrophy connected with metabolic complications, such as insulin-resistant diabetes and dyslipidemia, in addition to age associated manifestations. There is a real need to increase our understanding regarding these syndromes because of their import in human health and the lack of knowledge of their etiopathology. To gain deeper insights into these metabolic diseases, we have taken advantage of a previously generated “disease in a dish” model of human LMNA-lipodystrophy based on the pathological accumulation of the precursor prelamin A in stem cell derived adipocytes. This experimental model recapitulates phenotypes observed in lipodystrophic patient’s samples and animal models, and it has been critical in elucidating new insights into the molecular mechanisms governing this set of disorders. Recently, we have identified alterations in fundamental processes of lipid homeostasis such as lipolysis, as well as mitochondrial and endoplasmic reticulum functions, similar to what can be observed in some metabolic and aging phenotypes. Additionally, the lipidomic profile of this lipodystrophic experimental model displayed a lipid metabolic signature similar to aging systems, providing new information concerning metabolic pathways affected during the aging process. By clarifying the fundamental mechanisms governing these aging associated diseases, future novel interventions could be developed that will at least delay the appearance of aging phenotypes and thereby increase the health span or disease-free time of an individual.

**Keywords:** LMNA-lipodystrophy; prelamin A; aging, lipid metabolism; “human disease in a dish”

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The biological human disorders associated with the process of aging have been, and are being, extensively studied in animals such as nematodes, flies and mice. However, interspecies differences prevent extrapolation of much of the achieved knowledge from the non-human to the human situation. Hence, insights concerning many of the human age-related processes and diseases remain elusive and largely unknown. A “human disease in a dish” system might offer potential to discover important information regarding the pathophysiology of human conditions.

One human disease which has been a focus of interest due to the importance of adipose tissue in whole-body energy homeostasis, (wherein processes as diverse as energy balance, blood pressure, immune function and angiogenesis are regulated), is lipodystrophy.
Lipodystrophic syndromes characterized by generalized or partial fat atrophy in addition to metabolic complications [1] are founded on primary alterations disturbing adipose tissue (impaired adipogenesis, formation and maintenance of lipid droplet etc.) with secondary negative repercussions in whole body metabolism [2]. Some of these syndromes are caused by alterations in nuclear envelope proteins which are the principal components of the nuclear lamina meshwork underlying the inner nuclear membrane, such as lamin proteins. These lipodystrophy disorders can be either genetic (due to mutations in the LMNA gene or genes involved in the processing of lamin A protein) or acquired (as a consequence of antiretroviral therapy utilizing HIV protease inhibitors).

Lamin A protein, encoded by the LMNA gene, is one of the major regulators of structure and stability of the nucleus. This protein is crucial for significant functions such as gene transcription, chromatin organization and DNA replication and repair [3]. Intriguingly, mutations in the LMNA gene cause a varied number of diseases besides lipodystrophies, such as neuropathies, skeletal and/or cardiac myopathies and premature aging disease. In some cases these diseases show overlapping phenotypes, and they are therefore globally referred to as laminopathies. In fact, some LMNA associated lipodystrophy (LMNA-lipodystrophies) patients show a high prevalence of severe cardiovascular disorders at early ages [4], among other age related manifestations [5]. Aging is an area of heightened interest and concern due to its broad social and economic impact as numerous chronic diseases associated with aging rapidly prevail with increased populations of the aged. This, at least for now, inevitable process is characterized by molecular alterations leading to a deterioration of cellular homeostasis as a consequence of an inability to defeat the damage, stress, and disease accumulated throughout the life of an individual [6]. One of the most exciting areas of aging research is based on the “hallmark of aging,” stem cell exhaustion. Stem cells persist throughout the life of the organism, and are thus quite vulnerable to the accumulation of cellular damage which eventually can cause senescence, functional failure and cell death. Consequently, the aged organism suffers limited efficacy of cell replacement and tissue regeneration. One of the most relevant specialized types of repairing cells is mesenchymal stem cell (MSC) [7].

The precise mechanisms of LMNA-lipodystrophy physiopathogeny remain largely unknown, making it difficult to develop appropriate and effective treatments. Our goal in studying the LMNA-lipodystrophy disease is to provide new insights that could help to understand the etiopathology of the disease and ultimately to design an effective and enduring therapy.

Because adipocytes and their progenitors come solely from cells of mesenchymal origin [8], we previously generated an in vitro human LMNA-lipodystrophy model based on mesenchymal stem cell derived adipocytes which accumulate the precursor of lamin A, prelamin A. This in vitro model recapitulates the phenotypes observed in LMNA-lipodystrophy patients [9,10].

The LMNA-lipodystrophic model displayed a clear attenuation in lipid droplet size, strongly suggesting that prelamin A accumulation is responsible for the altered lipid homeostasis. This phenotype has also been exhibited by a cellular model of a premature aging laminopathy, Hutchinson-Gilford progeria, which show lipodystrophic features too [11]. In addition, the in vitro prelamin A accumulation model has been critical for the elucidation of an aspect of the molecular mechanisms causing LMNA-lipodystrophy; namely, the accumulated prelamin A is responsible for the altered function of Sp1 transcription factor, through a direct physical interaction with it [9]. The theory that accumulated prelamin A can modify the nuclear lamina meshwork and therefore the function of transcription factors associated with the lamins, either directly or indirectly, has also been supported by prelamin A factors associated with the lamins.

Thus, human mesenchymal stem cells which have been induced to accumulate prelamin A by a pharmacological approach displayed features matching the hallmarks of aging described in the notable review by Lopez-Otin et al [6] and collaborators, supporting the system as a compelling experimental model of human aging [14]. Thus, our “human disease in a dish” reveals the aging consequences that the non-physiological accumulation of prelamin A produces in human mesenchymal stem cells [12].

The current study delves into the functional abilities of lipodystrophic cells, revealing an increase in basal lipolysis which could account for the lipid droplet size reduction shown by these syndromic cells [9]. Furthermore, defects in mitochondrial structure and function, as well as apparent endoplasmic reticulum stress, illustrate effects on major players in lipid degradation and lipid biosynthesis, respectively [15].

These alterations in lipid processes with evident detrimental consequences in lipid homeostasis have been associated to greater or lesser extents with aging processes observed in human and animal models [16, 17], as well as in lipodystrophic patients [18].
Such similarities with aging might not be surprising since lipids comprise a wide group of biomolecules that take part in essential biological roles, including energy storage, cell signaling, homeostasis and cellular membrane structure.

In order to characterize the lipid content of the LMNA-lipodystrophic cells, a global analysis of lipid components was performed using lipidomics, wherein 333 lipid species were evaluated\(^1\). Lipidomics is an emergent technology with great potential for the study of human diseases and drug screening\(^2\).

The LMNA-lipodystrophic cells showed enrichment in some of the main lipid components of mammalian membranes and in the products resulting from their hydrolysis. In addition compared to control samples, a categorical decrease of monounsaturated over polyunsaturated fatty acids rate was observed, consistent with several aging animal studies\(^3\). Interestingly, the opposite trend has been associated with human longevity\(^4\).

The laminopathy experimental model furthermore exhibited altered activity of enzymes which play fundamental roles in lipid metabolism, and whose dysregulation has been related to aging processes. With the present study we show that the accumulation of prelamin A in a lipodystrophic experimental model altered several metabolic pathways resulting in an age-linked lipid metabolic signature.

Although undoubtedly there is much still to be elucidated regarding aging, lipid metabolism and related diseases, such as lipodystrophies, what we describe here clearly demonstrates a close relationship among these fields, encouraging further studies.

Understanding the molecular processes controlling the homeostasis and functional potential of prelamin A accumulating stem cell derived adipocytes and their relationship with aging is essential to establish the drivers and effectors associated with LMNA-lipodystrophies, as well as other associated metabolic diseases accompanying aging phenotypes. Furthermore, such knowledge will be critical to develop a therapeutic intervention designed to avoid, minimize, or at least delay the appearance of the phenotypes associated with lipid associated diseases and/or the aging process, and therefore increase the health span of the individual.

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**Conflict of interest**

No conflict of interest could be disclosed for any author.

**References**


