Laminopathies: The Nuclear Lamina Alteration

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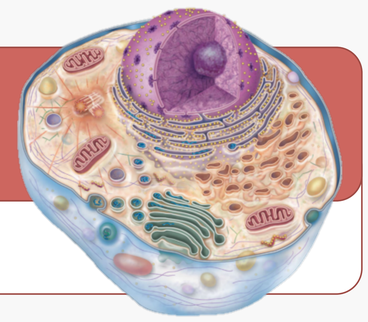

1 Introduction

Mutations in nuclear lamins or other proteins of the nuclear envelope are the cause of a group of genetic disorders known as **Laminopathies** which affect different tissues and organ systems. These diseases brought about by lamins alterations are classified in two types, A and B, depending on the gene that is affected, LMNA and LMNB1 or 2, respectively. The LMNA gene encodes two major isoforms, lamins A and C, and two minor ones, AΔ10 and C2. However, the B-type lamins, B1, B2 and the minor product B3 are encoded by LMNB1 and LMNB2. Taking into account mutations, lamin B alterations tend to result in embryonic lethality in humans. Nonetheless, different mutations in LMNA can be considered to cause four different groups of disorders with overlap between them: Diseases of striated muscle, peripheral neuropathies, lipodystrophy syndromes and accelerated aging disorders. The chosen diseases of each group in the report are: **Emery-Dreifuss Muscular Dystrophy** (EDMD), **Charcot-Marie-Tooth disease type 2B1** (CMT2B1), **Familial Partial Lipodystrophy Dunnigan type** (FPLD) and **Hutchinson-Gilford progeria syndrome** (HGPS) whereas in this review only HGPS will be extensively analyse.

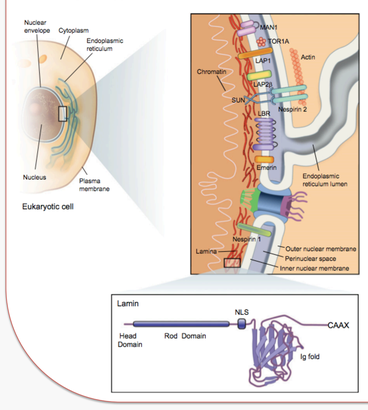

Figure 1. **Nuclear envelope, nuclear lamina and lamin structure.** The nuclear envelope surrounds the nucleus and is made up of the nuclear membranes, nuclear pore complexes and nuclear lamina. Lamins, which are type V intermediate filament proteins, are major structural proteins of the nucleus. Concerning lamin structure, there are three main domains: α-helical rod domain, head domain and tail domain. The α-helical rod domain is critical for the formation of dimers and higher-ordered filaments and within the tail domain, lamins include a nuclear localization signal (NLS), an immunoglobulin-like fold (Ig fold) and a CAAX motif. This sequence at their carboxyl-termini acts as a signal to trigger post-translational modifications such as farnesylation and carboxymethylation. One consequence of farnesylation is an enhanced membrane association, either directly or via protein-protein interactions. *Dauer WT et al. (2009)*

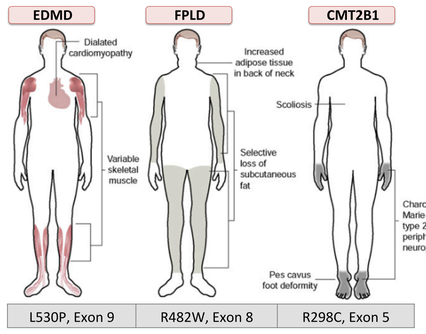

Figure 2. **The most common mutations at lamin A, exon of the LMNA gene affected and symptoms of the Laminopathies that are in the report.** HGPS is not showed. *Dauer WT et al. (2009)*

2 Aims

- To analyse the nuclear lamina and, in particular, lamin A. The objective of this general part focuses on the structure, the posttranslational processing, and main functions of lamin A.
- To evaluate the most common mutations, symptoms and molecular basis of the chosen diseases: Emery-Dreifuss Muscular Dystrophy (EDMD), Charcot-Marie-Tooth disease type 2B1 (CMT2B1), Familial Partial Lipodystrophy Dunnigan type (FPLD) and Hutchinson-Gilford progeria syndrome (HGPS). In this review, the principal aim is to demonstrate, making use of HGPS, the extremely importance of the correct functionality of the nuclear lamina.

3 Methodology

- Data come from papers and reviews researched on PubMed and ScienceDirect databases, Disease Associations such as Progeria Research Foundation, and Medical websites.
- The searching was focused on the past 15 years and papers were selected according to their data of publication and the impact factor of the journal, although some of them were chosen for their figures. Taking into account this consideration, a total of 95 references were read but only 73, comprising 53 papers or reviews and 20 websites, were included in the final report. All these data were classified in the file folder in order to display the usefulness of each one.
- **Key words**: Nuclear envelope, Nuclear lamina, Lamin A, LMNA, LMNA gene mutation, Laminopathies, Hutchinson-Gilford progeria syndrome, HGPS, progerin, farnesylation, aging. Another key words used in the report are: LMNB1, LMNB2, Emery-Dreifuss Muscular Dystrophy, EDMD, Charcot-Marie-Tooth disease type 2B1, CMT2B1, Familial partial lipodystrophy Dunnigan type, FPLD, MyoD, SREBP1, etc.

4 Hutchinson-Gilford Progeria Syndrome

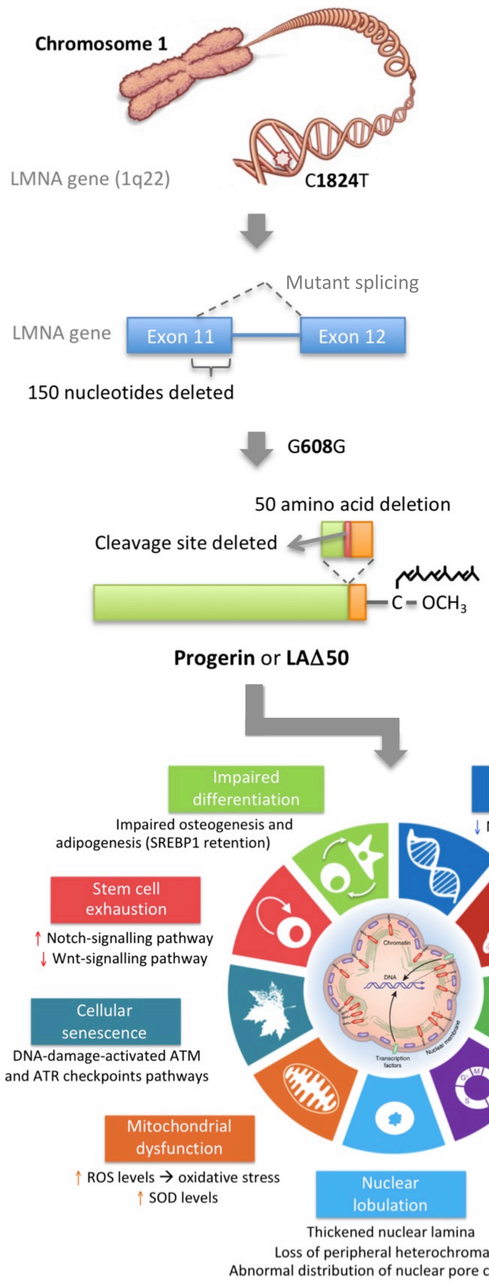

Figure 4. **Molecular and cellular alterations in HGPS.** The single base substitution mutation in LMNA gene activates a cryptic splice site, which implies the deletion of 150 nucleotides and 50 amino acids. The internal deletion of these amino acids include a cleavage site, disrupting the last cleavage step of prelamin A. Therefore, this mutation ultimately results in the generation of a mutant protein termed progerin, which is permanently farnesylated. This protein is toxic to cells and displays altered structural and biochemical properties, leading to disrupted cellular phenotypes and nuclear functions. *Drawn by author, modifying figures of López-Otín C et al. (2013) and Capel BC et al. (2009).*

The Hutchinson-Gilford progeria syndrome is a premature aging disorder that affects children. Given the current world population and according to Progeria Research Foundation, there are between 350 and 400 children living with Progeria worldwide. Most patients are born looking healthy though they begin to display many aging-associated symptoms at 18-24 months of age. One of these manifestations is a premature arteriosclerotic disease that leads to hearts attacks and strokes between the ages of 13 and 20, causing their death at an early age. But in contrast with other features, age-related conditions such as Alzheimer disease, dementia, osteoarthritis and cancer are absent.

The most frequent mutation, affecting approximately 90% of patients, is *de novo* autosomal dominant single base substitution in LMNA gene. This mutation produces a truncated lamin A known as **progerin**. Whereas the lamin proteins in healthy cells move dynamically between the nuclear lamina at the nuclear periphery and the nucleoplasm, they become immobilized in HGPS patient cells, leading to thickening of the lamina. Furthermore, in spite of increased expression of progerin in physiological conditions, its deposition in the arterial walls might render HGPS cells more sensitive to mechanical strain and contribute to the aberrant mechanotransduction. These alterations might affect the response of cells in tissues that are particularly exposed to mechanical stress such as the vasculature, bone and joints. Another consequence is that tissues characterized by a high degree of cell turnover such as skin or tissues that undergo continuous growth, exhaust their progenitor cells resulting in an early depletion of stem cell pools. Therefore, these observations demonstrate that the nuclear envelope dysfunction is associated with altered nuclear activity, impaired structural dynamics and aberrant cell signaling.

Therapeutic Approaches

Currently there are no effective treatments but discovering that progerin is permanently farnesylated suggests therapeutic strategies. The use of farnesyltransferase inhibitors (FTIs) such as lonafarnib, is a potential approach but progerin was also modified by geranylgeranylation as an alternate modification. It hints at another option based on the combination of FTI with pravastatin and zoledronic acid, that are a statin and an aminobisphosphonate, respectively. The development of this strategy and others are studied in clinical trials. In particular, this treatment has showed a reduction of the farnesylated form of progerin and a correction of the nuclear dysmorphology in progeroid cells.

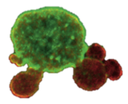

Figure 3. **Nuclear morphology of HGPS cells.** Double labeling with lamin A/C (red) and lamin B (green). *Adapted from Butin-Israeli V et al. (2012)*

Future Approaches

The expression of lamin A/C can serve as a **risk biomarker**. For example, in colon cancer there is a correlation between low expression levels of A-type lamins and increased recurrence in advanced stage of tumour.

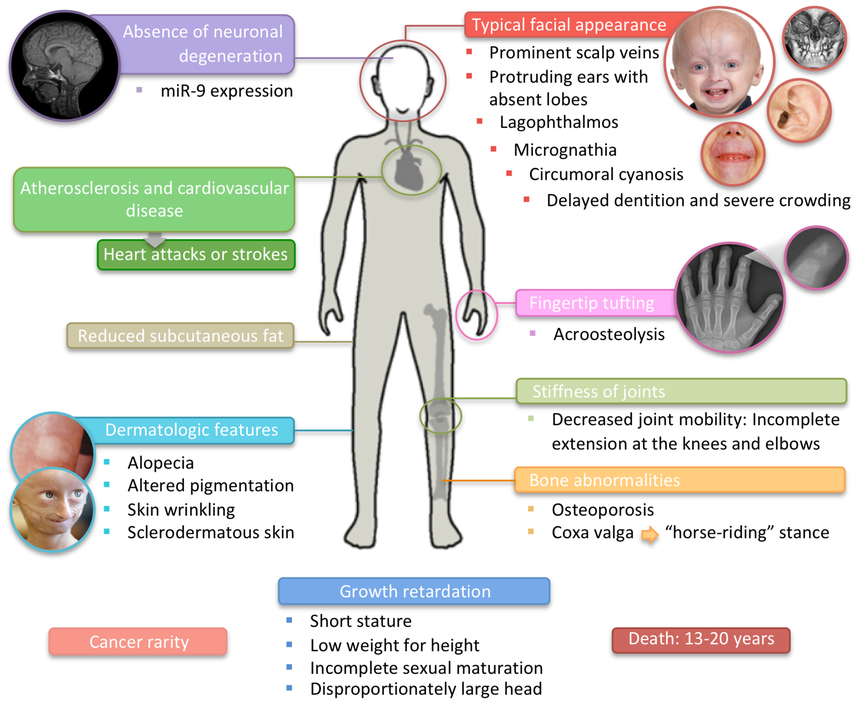

Figure 5. **Clinical manifestations of HGPS patients.** Children mainly present accelerated degenerative changes of the skin, musculoskeletal and cardiovascular systems. The absence of primary central nervous system has been connected with the expression of a brain-specific miRNA, which might down-regulate lamin A and progerin. In these patients, mortality is primarily due to accelerated atherosclerosis and cardiovascular disease at the age range of 13-20 years old. *Lagophthalmos: inability to close the eyelids completely. Micrognathia: small jaw. Circumoral cyanosis: bluish appearance around the mouth. Acroosteolysis: resorption of bone at distal phalanges.* *Drawn by author, using figures of Dauer WT et al. (2009), Capell BC et al. (2009) and Progeria Research Foundation (2010).*

Abbreviations of figures

- L530P: Substitution of leucine for proline at amino acid 530 of lamin A.
- R482W: Substitution of arginine for tryptophan at amino acid 482 of lamin A.
- R298C: Substitution of arginine for cysteine at amino acid 298 of lamin A.
- C1824T: Substitution of cytosine for thymine at nucleotide 1824 of the gene LMNA.
- G608G: Substitution of glycine for glycine at amino acid 608.
- NuRD proteins: Nucleosome Remodeling Deacetylase proteins.
- DDR: DNA damage response.
- H4K16ac: Acetylation of histone H4 at lysine 16.
- H4K20me3: Trimethylation of histone H4 at lysine 20.
- H3K4me3: Trimethylation of histone H3 at lysine 4.
- H3K9me3: Trimethylation of histone H3 at lysine 9.
- H3K27me3: Trimethylation of histone H3 at lysine 27.
- p53: Tumor supressor protein p53.
- pRB: Retinoblastoma protein.
- ROS: Reactive Oxygen Species.
- SOD: Mitochondrial Superoxide Dismutase.
- ATM: Ataxia Telangiectasia Mutated.
- ATR: ATM- and Rad3-related.
- SREBP1: Sterol Regulatory Element-Binding Protein 1.
- miR-9: micro RNA 9, which is brain-specific.

5 Conclusions

- **In addition to their structural roles, providing mechanical stability, lamins are implicated in the correct spatial and temporal progression of nuclear processes such as chromatin organization, DNA replication, transcription, DNA repair and cell-cycle progression.**
- Mutations in human LMNA gene cause several diseases termed Laminopathies. One of the laminopathic diseases is Hutchinson-Gilford progeria syndrome (HGPS), which is caused by a spontaneous mutation and characterized by premature aging.
- In HGPS patients, progerin affects mostly tissues of mesenchymal origin, including bone, skin, fat, teeth, hair and blood vessels.
- Noteworthy, the cryptic splice site activated in HGPS to produce progerin is also used at low frequency in healthy individuals.

6 Bibliography

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