### Laminopathies: The Nuclear Lamina Alteration

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#### 1. Introduction

Mutations in nuclear lamin 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 lamin alterations are classified into 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, lamin A and C, and two minor ones, A100 and C2. However, the B-type lamin, B2, 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, lamin A 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-Dreisbach Muscular Dystrophy (EDMD), Charcot-Marie-Tooth disease type 2B1 (CMT2B1), Familial Partial Lipodystrophy Dunnigan type (FPLD) and Hutchinson-Gilford progeria syndrome (HGPS).

Eighty percent of patients with a lamin A/C mutations present with a progeria-like phenotype, whereas the remaining 20% present with a muscular dystrophy-like phenotype. This suggests that lamin A/C plays a role in both aging and muscular dystrophy. To date, the mechanism by which lamin A/C is involved in aging is not fully understood. However, lamin A/C might be involved in the regulation of gene expression, DNA repair and cell cycle progression.

#### 2. Aims

- To analyze 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-Dreisbach 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 came 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 10 years, more papers were selected according to their data and 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 holder in order to display the usefulness of each one.

#### 4. Hutchinson-Gilford Progeria Syndrome

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 healthy when they begin to display many aging-associated symptoms at 18-24 months of age. One of these manifestations is a premature atherosclerotic disease that leads to heart attacks and strokes before the ages of 12 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 98% of patients, is de novo autosomal dominant single base substitution in LMNA gene. This mutation produces a truncated lamin A known as progerin. When the lamin proteins in healthy cells move dynamically between the nuclear lamina at the nuclear periphery and the nucleosom, 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 disposition in the arterial walls might render HGPS cells more sensitive to mechanical strain and contribute to the atheroatheroembolization. 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.

Currently there are no effective treatments but discovering that progerin is permanently hyperphosphorylated 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. HGPS is another at options the combination of FTIs with prostate素 and carboxylic acid, that are a stacks and an amino-phosphoketone, respectively. The development of this strategy and others are studied in clinical trials. In particular, this treatment showed has a reduction of the farnesylated form of progerin and a correction of the nuclear dysmorphism in progenitor cells.

#### 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 chromosome organization, DNA replication, transcription, DNA repair and cell cycle progression.
- Mutations in human LMNA gene cause several diseases term 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

- Capell RG, Thauger B, Shao S. From the need to understand insights from progenitor cells into skin cancer and aging. Front Oncol. 2009;2:1–20.