Nuclear matrix, nuclear envelope and premature aging syndromes in a translational research perspective

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Review

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Pierre Cau[a,b,c,*], Claire Navarro[a,b,1], Karim Harhouri[a,b,1], Patrice Roll[a,b,c,1,2], Sabine Sigaudy[a,b,d,1,3], Elise Kaspi[a,b,c,1,2], Sophie Perrin[a,b,1], Annachiara De Sandre-Giovannoli[a,b,d,1,3], Nicolas Lévy[a,b,d,**]

[a] *Aix-Marseille Université, UMR_S 910, Génétique Médicale et Génomique Fonctionnelle, Faculté de Médecine, 27 Bd Jean Moulin, 13385 Marseille Cedex 5, France*
[b] *INSERM, UMR_S 910, Génétique Médicale et Génomique Fonctionnelle, Faculté de Médecine, 27 Bd Jean Moulin, 13385 Marseille Cedex 5, France*
[c] *AP-HM, Service de Biologie Cellulaire, Hôpital La Timone, 264 Rue Saint Pierre, 13385 Marseille Cedex 5, France*
[d] *AP-HM, Département de Génétique Médicale, Hôpital d'enfants Timone, 264 Rue Saint Pierre, 13385 Marseille Cedex 5, France*

A B S T R A C T

Lamin A-related progeroid syndromes are genetically determined, extremely rare and severe. In the past ten years, our knowledge and perspectives for these diseases has widely progressed, through the progressive dissection of their pathophysiological mechanisms leading to precocious and accelerated aging, from the genes mutations discovery until therapeutic trials in affected children.

A-type lamins are major actors in several structural and functional activities at the nuclear periphery, as they are major components of the nuclear *lamina*. However, while this is usually poorly considered, they also play a key role within the rest of the nucleoplasm, whose defects are related to cell senescence. Although nuclear shape and nuclear envelope deformities are obvious and visible events, nuclear matrix disorganization and abnormal composition certainly represent the most important causes of cell defects with dramatic pathological consequences. Therefore, lamin-associated diseases should be better referred as laminopathies instead of envelopathies, this later being too restrictive, considering neither the key structural and functional roles of soluble lamins in the entire nucleoplasm, nor the nuclear matrix contribution to the pathophysiology of lamin-associated disorders and in particular in defective lamin A processing-associated aging diseases.

Based on both our understanding of pathophysiological mechanisms and the biological and clinical consequences of progeria and related diseases, therapeutic trials have been conducted in patients and were terminated less than 10 years after the gene discovery, a quite fast issue for a genetic disease. Pharmacological drugs have been repurposed and used to decrease the toxicity of the accumulated, unprocessed and truncated prelaminA in progeria. To date, none of them may be considered as a cure for progeria and these clinical strategies were essentially designed toward reducing a subset of the most dramatic and morbid features associated to progeria. New therapeutic strategies under study, in particular targeting the protein expression pathway at the mRNA level, have shown a remarkable efficacy both *in vitro* in cells and *in vivo* in mice models. Strategies intending to clear the toxic accumulated proteins from the nucleus are also under evaluation. However, although exceedingly rare, improving our knowledge of genetic progeroid syndromes and searching for innovative and efficient therapies in these syndromes is of paramount importance as, even before they can be used to save lives, they may significantly (i) expand the affected childrens' lifespan and preserve their quality of life; (ii) improve our understanding

* Corresponding author at: INSERM, UMR_S 910, Aix Marseille Université, Faculté de Médecine, 27 Bd Jean Moulin, 13385 Marseille Cedex 5, France. Tel.: +33 0491 32 43 01/0491 38 82 10; fax: +33 0491 79 72 27/0491 38 46 76.
** Corresponding author at: INSERM, UMR_S 910, Aix Marseille Université, Faculté de Médecine, 27 Bd Jean Moulin, 13385 Marseille Cedex 5, France. Tel.: +33 0491 32 43 01/0491 38 77 87; fax: +33 0491 79 72 27/0491 38 46 76.
E-mail addresses: pierre.cau@univ-amu.fr (P. Cau), nicolas.levy@univ-amu.fr (N. Lévy).
[1] Tel.: +33 0491 32 43 01; fax: +33 0491 79 72 27.
[2] Tel.: +33 0491 38 82 10; fax: +33 0491 38 46 76.
[3] Tel.: +33 0491 38 77 87; fax: +33 0491 38 46 76.

Contents

1. Nuclear envelope, nuclear matrix and lamins

In eukaryotic cells, nuclear genome is packed in the form of the highly organized chromatin within nucleoplasm, delineated by the nuclear envelope (NE). The NE is a specialized cisterna of endoplasmic reticulum (ER), separating nuclear from cytoplasmic compartments and made of two distinct membrane domains only interconnected through nuclear pore complexes (NPC) [1,2]. The outer nuclear membrane (ONM) exhibits several membrane and luminal ER characteristics as well as functions (from ribosome-linked synthesis to post-traductional processing of proteins. . .). The inner nuclear membrane (INM) harbors an unique set of about 80 transmembrane proteins (NPC proteins being excluded), that are synthetized by and inserted into ER or ONM, and reach INM after crossing NPC [3].

Less than 10 of these INM proteins are well characterized because they are yet known to be involved in human genetic diseases [4]. However the great majority of INM transmembrane proteins, most of them discovered through proteomic studies, remain still uncharacterized, even if they could be good candidates for yet unidentified human diseases [5]. Moreover, the expression of some of these INM proteins is cell- or tissue-specific [6–10]. Therefore, these INM proteins could contribute to the phenotype variability exhibited by patients harboring a mutation in the gene encoding an interactor of these INM proteins.

Besides nuclear genome and all the enzymatic and non-enzymatic machinery required for nuclear genome functions, the nucleoplasm also contains a protein network called nuclear matrix (NM) [11], whose peripheral region, known as nuclear *lamina*, interacts with INM proteins, NPC nucleoplasmic domain and peripheral chromatin [12].

Removing in a sequential fashion "soluble" proteins, NE lipids and chromatin components leaves behind about 400 NM proteins being characterized by proteomics methods [13–15]. Besides lamins [16], NM contains other scaffolding proteins such as Nuclear Mitotic Apparatus protein (NuMA) [17], actin and several actin-binding proteins [18–22] and less-known matrins [23] or matrin-domain containing proteins [24,25].

1.1. From farnesylated prelamins to lamins

Lamins are type V intermediate filaments divided into A and B types. In mammals, the two major A-type lamins (lamin A and C), the minor isoforms lamin A Δ10 and the lamin C2, the later expressed in germ cells (as well as in cultured C2C12 differentiating myoblasts [26]) are derived from the same gene (*LMNA*) by alternative splicing [27]. B-type lamins are encoded by two different genes, lamin B1 by *LMNB1*, lamins B2 and germ cell-specific lamin B3 by *LMNB2* [28].

Lamins A, B1 and B2 are first expressed as cytosolic precursors, prelamins, that undergo extensive post-translational processing involving their C-terminal CAAX box. The first three steps are common to A- and B-type prelamins. The C-terminal cysteine is farnesylated by farnesyltransferase. The 15-carbon hydrophobic farnesyl group facilitates the prelamin insertion and anchoring into the cytosolic leaflet of ER membrane (or of the ONM), thus allowing the further processing steps performed by specific ER (or ONM) enzymes, their active site facing cytosol. The AAX motif is then clipped off by one of two proteases, FACE1/ZMPSTE24 or FACE2/Rce1. The third step is the carboxymethylation of the cysteine residue by the isoprenyl-cysteine-carboxy-methyltransferase (ICMT). The processing of B-type lamins terminates at this third step, leading to the permanent farnesylation and carboxymethylation of mature B-type lamins. Prelamin A undergoes a fourth last proteolytic cleavage by FACE1/ZMPSTE24 removing the 15 C-terminal aminoacids, including the farnesylated carboxymethylated cysteine residue, to form mature lamin A [28] (Fig. 1A and B).

Since its mRNA is produced through alternative splicing in *LMNA* exon 10, lamin C is directly synthetized as mature form that lacks the 98 C-terminal aminoacids present in prelamin A and the CAAX box, encoded by *LMNA* exon 12. Lamin C2 lacks the first 112 residues of lamin C. Lamin C2 N-terminus (MGNAEGR) is encoded by exon 1C2 located in *LMNA* intron 1 [29]. Contrasting with lamins A and C, lamin C2 is myristoylated on its N-terminal glycine, this lipid group anchoring the protein into discrete plaques resulting in a discontinuous labeling of germ cell INM [30,31].

1.2. Other post-translational modifications of lamins

Besides acylation, lamins undergo other modifications [32,33], whose analysis has been improved through mass spectrometry (and SILAC) experiments.

In nuclei of *intima* and *media* cells from large elastic arteries, A-type lamins are target for advanced glycation end-products, a phenomenon probably involved in enhanced vascular dysfunction and atherosclerosis exhibited by diabetic patients [34]. O-glycosylation of A-type lamins on at least 4 serine or threonine residues [35–37] could interfere with lamin polymerization as already seen for other intermediate filaments [38] and has been shown to vary during cell cycle [39].

Phosphorylation of lamins and their partners has been shown to be important for NE breakdown at the beginning of mitosis [40,41]. Two serine residues of lamin A and C are substrates for AKT kinase, activated by several signaling pathways [42], the phosphorylation of serine 404 leading to prelamin A autophagic degradation [43]. As several other nuclear proteins such as histones, A- and

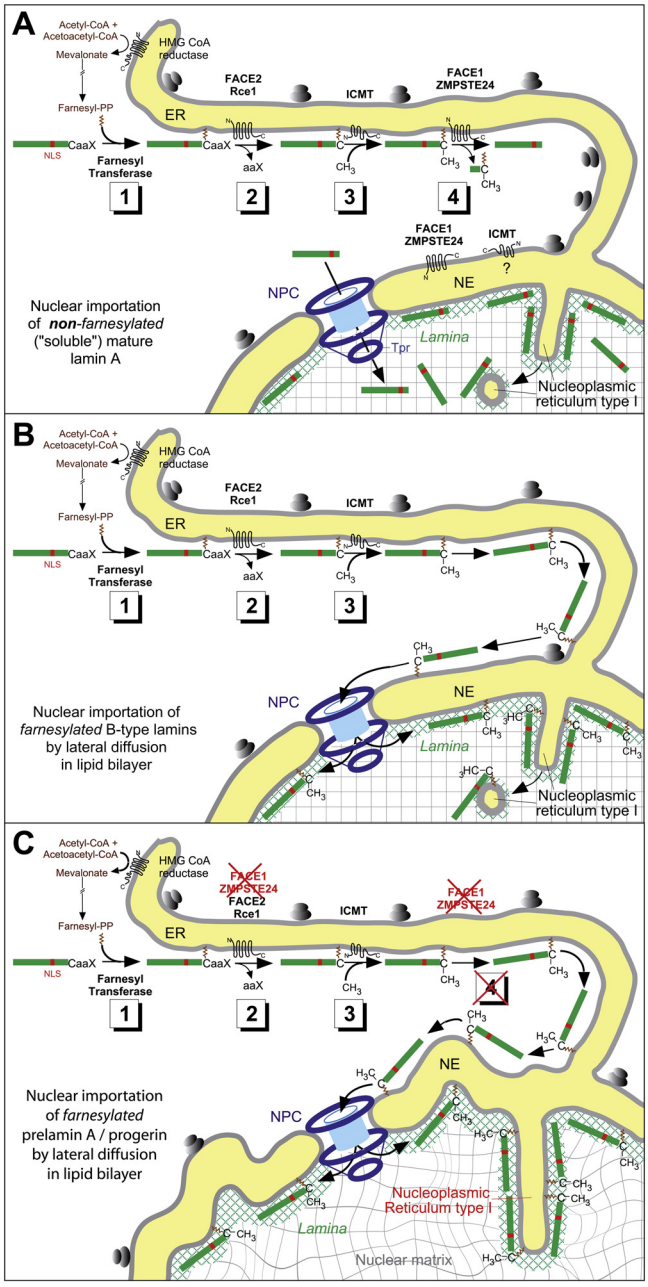


Fig. 1. Post-translational processing of A- and B-type prelamins. (A) Processing of prelamin A in four steps and nuclar import of lamin A. The nuclear importation through nuclear pore complex (NPC) of mature lamin A as a "soluble protein". The interactions of prelamin A with INM protein before their nuclear importation are not described. NLS, nuclear localization signal; Tpr, nucleoporin of the nucleoplasmic basket, (B) processing in three steps of B-type prelamins and nuclar import of B-type lamins. As they keep their farnesyl moiety, B-type lamins remain anchored to membrane bilayers. After their nuclear importation, B-type lamins are anchored to the INM and the IMN extensions toward nucloplasm, called nucleoplasmic reticulum type I, and (C) processing in three steps and nuclar import of progerin (HGPS) or farnesylated prelamin A (RD). While FACE1/ZMPSTE24 cannot cleave progerin (HPGS) or because the protease is absent or inactive (RD), progerin and prelamin A keep their farnesyl moiety, and remain anchored to membrane bilayers. After nuclear importation, progerin and farnesylated prelamin A stay anchored to the INM and to the IMN extensions toward nucloplasm, called nucleoplasmic reticulum type I. The increase in the amount of NE-bound A-type lamins results in the increase of NE surface area leading to nuclear shape deformations and to the expansion of nucleoplasmic reticulum from INM.

B-type lamins have been shown to be acetylated on lysine residues [44], although the role of this modification remains unclear. During C2C12 myoblast fusion, lamin C2 has been shown to be dimethylated on arginin residues [26].

The nucleus contains all the enzymatic machinery involved in regulating the fate of nuclear proteins through their balanced ubiquitylation–deubiquitylation [45–47] and symoylation–desumoylation modifications [48–50]. Lamin A could be ubiquitylated on 25 lysine residues and targeted to proteasomal degradation [51], as shown for wild-type and Δ*K32 Lmna* in mouse cardiomyocytes [52]. Various laminopathies activate several ubiquitin-ligases and increase proteasomal degradation of proteins within nucleus [53]. For example, the proteasomal degradation of ATR kinase within nucleus results in DNA repair defects [54].

Several mass spectrometry experiments evidenced that A- and B-type lamins can undergo sumoylation, another covalent and reversible lysine modification [55–57]. Binding of SUMO1 leads to mono-sumoylation, whereas binding of SUMO2 and SUMO3 results in chains of 4–7 molecules in length, the last one being SUMO1 [58,59]. Lamin A sumoylation is modified by several pathogenic mutations targeting lysines or residues close to sumoylation consensus sequences [60–63].

1.3. Nuclear importation of lamins

Even if A- and B-type lamins bear a nuclear localization signal (NLS) in their tail domain [64], the nuclear importation mechanism could be different between farnesylated B-type lamins, anchored to membranes, and lamins A and C produced as "soluble" proteins lacking this farnesyl anchor. However, several data reported that A and C lamins interact, before lamin nuclear importation, with ER-synthetized membrane proteins and with the same membrane proteins, after their insertion into INM. In human cell lines displaying abnormal expression and/or localization of lamins A and C, the lack of lamins A and C from the nuclear envelope was correlated with emerin mislocalization in the ER [65]. In *Lmna*$^{-/-}$ cells, emerin is not imported into INM and stays mislocalized in ER membrane [66].

INM proteins, synthetized by ribosomes bound to ER or to ONM, interact with the specialized importin-α-16 that recognizes INM sorting signal. Importin-α-16-INM protein complexes slide along ER membrane and ONM, cross NPC to reach their INM final localization [67,68]. The same sliding mechanism probably allows the nuclear importation of lamins bound to membranes through their farnesyl anchor, either B-type lamins or farnesylated prelamin A or progerin produced in Hutchinson–Gilford progeria syndrome (HGPS), restrictive dermopathy (RD) (see below) or experimentally after mutation in the FACE1/ZMPSTE24 cleavage site of prelamin A.

1.4. Nuclear localization of lamins, NE and nucleoplasmic reticulum, nuclear movements

The presence or the lack of the farnesyl group influences the nucleoplasmic localization of lamins. Farnesylated B-type lamins are anchored to INM in the nuclear *lamina* only. Lamins A and C are localized in nuclear *lamina*, where they interact together [16], with B-type lamins [69] and with several INM and NPC proteins [70–72].

Lamins A and C also are components of the NM distributed throughout the nucleoplasm [32,73]. Time lapse imaging confirmed the high mobility of lamins A and C within nucleoplasm, contrasting with the lower mobility, within nuclear *lamina*, of lamins A, C and B, the later being anchored to INM through its farnesyl group [74,75].

However, B-type lamins can also be detected at a distance from nuclear *lamina* in the perinucleolar nucleoplasm [76], and anchored to the membrane of the nucleoplasmic reticulum (NR) membrane (Fig. 1B). This dynamic structure [77,78] fall into two main classes depending on whether the ONM is involved [79]. Type I NR are finger-like expansions into nucleoplasm of the INM only, whereas type II NR involves the invagination of both INM and ONM, including a portion of cytosol and sometimes cell organelles. NR development can be induced by increasing the amount of isoprenylated nuclear proteins [80–84], and was also observed in genetic diseases resulting from prelamin A processing defects [85] (Fig. 1C).

Videomicroscopy evidenced another surprising phenomenon. The entire nucleoplasmic content has been shown to spin in zebrafish embryos [86], and in cultured cells, either migrating fibroblasts [87,88] or developing myotubes [89]. Nucleus rotation affects INM, ONM and their proteins and involves microtubules (MT), dynein and kinesin, whereas centrosome remains stable. MT and their motor microtubule-associated proteins (MAP), that are known to be involved in NE breakdown during mitosis and meiosis [90], also play a role, during interphase, in the folding of NE and in the development of type II NR [91].

The LINC (LInks the Nucleoskeleton and Cytoskeleton) complexes connect the chromatin and the nuclear *lamina* across the NE with the three components of the cytosolic cytoskeleton, actin microfilaments, microtubules, intermediate filaments and their associated proteins [92].

Nuclear movements can be observed in cultured cells linked to interactions between ONM and LINC complex proteins with cytosolic microtubules and motor MAPs [93] or between emerin, located in ONM [94,95] with actin cytoskeleton and myosins [96].

The migration of neurons during development involves saltatory movements of neuronal cell body and nucleus in the direction of migration. Neuronal migration offers another example of the collaboration between, on one hand, actin microfilaments and type II myosin and, on the other hand, of microtubules, dynein [97] and other centrosome-associated proteins such as Lis1 and DCX, all partners involved in various neuronal migration genetic disorders [98]. Lamin B2-deficient mice present severe brain abnormalities resembling lissencephaly, abnormal layering of neurons in the cerebral cortex and cerebellum, demonstrating that lamin B2 plays an essential role in neuronal migration and brain development [99].

B-type lamins could have unexpected extranuclear functions. Lamin B2 mRNAs are present in axons of *Xenopus* retinal ganglion cells and are translated into protein. Axonal lamin B2 associates with mitochondria, while lamin B2-deficient axons exhibit defects in mitochondrial function, shape and mobility, and in axon morphology, thus suggesting that lamin B2 synthetized into axons plays a major role in axon maintenance through promoting mitochondrial function [100].

1.5. NM, lamins, genome architecture and metabolism

Besides providing a structural framework to nucleoplasm, peripheral and nucleoplasmic lamins [28,101] together with their interacting partners [70] and the other NM components [14,102–104] play important roles in epigenetics, chromatin organization, DNA replication and repair, transcription, and their dynamics. DNA replication takes place in a fixed number of sites liked to NM [105]. RNA elongation and processing factories, known to be associated with NM [106] associate RNA polymerases, matrin 3 and A- and B-type lamins [107,108]. A- and B-type lamins are involved in DNA repair [109–111]. Matrin 3 interacts with the nuclear DNA damage response and repair machinery [112]. NuMA is required for the selective induction of p53 target genes [113,114]. A variety of genome-wide mapping techniques result in a picture of interphase chromosome, integrating both their linear segmentation into several domains, exhibiting different protein compositions, and their non-random three-dimensional organization allowing many local and long-range contacts among genes

and other sequence elements [115]. Chromatin dynamics add a fourth dimension to this picture [116]. Within nucleoplasm, dynamic arrangements of the 10 nm chromatin fiber form several loops anchored to NM [117,118], that bring closer intra- and inter-chromosomal domains, called transcription factories, to the same nucleoplasmic location [119], whose organization and regulation are controlled by sequence-specific DNA-binding protein CTCF (CCCTC-binding factor) and the multiprotein cohesin complex [120]. The loops associate co-activated or co-repressed genes and control interactions between regulatory sequences and their target genes [121]. This dynamic genome topology is also observed during DNA replication [122] and play an important role in development, differentiation and aging [123].

Lamins, NM components, INM and NPC proteins also contribute to the definition of chromosome territories [115,124], where nuclear *lamina*-associated domains are different in terms of gene composition and activity from the domains of the same chromosome facing the nucleoplasm center and emitting chromatin loops [125–127]. In metazoan cells, NE, *lamina* and peripheral heterochromatin exhibit complex dynamic relationships, involving the peripheral retention of inactive genes and their release to the more central nucleoplasm [128]. Spatio-temporal changes in *lamina* composition underlie both differentiation- and cell type-specific chromatin organization and genome function [129]. Finally, nuclear dynamic mechanical architecture and functions result from bidirectional interactions between lamins, NM and NE proteins, cytoskeleton, plasma membrane, extracellular matrix components and their plasma membrane receptors [130–132], controlling at least some aspects of nuclear genome metabolism, cell differentiation and development [133,134].

All these cell components and mechanistic aspects should be considered when exploring pathophysiological mechanisms associated to lamin/prelamin associated disorders.

2. Progeria and progeroid syndromes

Progeroid syndromes are heritable human disorders including clinical symptoms that remind aging but appearing prematurely and whose evolution is dramatically accelerated. In these syndromes, premature aging is defined as "segmental" since only some of the aging features are accelerated. Most human syndromes of accelerated aging are caused by one of two major mechanisms: defects in DNA repair systems and alterations in the nuclear *lamina* and matrix proteins. Meanwhile, many nosological entities that include partial or systemic symptoms related to aging still remain of unidentified mechanism.

Clinical and physiological changes that are observed in the natural course of aging are never totally recapitulated in one or another independant progeroid syndrome. However, after years of studying senescence, aging and progeroid syndromes, it becomes evident that most of the mechanisms identified as the basis of segmental progeroid disorders are also part of mechanisms underlying physiological aging. In this context, Werner syndrome (WS) (OMIM 277700) and Hutchinson–Gilford progeria syndrome (HGPS) (OMIM 176670) have been the most extensively studied, as they are closely reminiscent of natural clinical aging. Pathophysiologically, the known progeroid syndromes are mostly caused, either by mutations in genes encoding DNA repair proteins, such as in WS, Bloom syndrome (BS), Rothmund–Thomson syndrome (RTS), Cockayne syndrome (CS) syndrome, Xeroderma pigmentosum (XP) [135–140]; or by mutations in genes encoding A-type lamins or partners involved in their biological cascade, such as HGPS [141,142], restrictive dermopathy (RD) [143,144] or the more recently identified Nestor–Guillermo syndrome [145]. However, in premature aging animal models, other pathways have shown to be affected such as mitochondrial or TP53 [146,147]. This is of importance, as the cause of premature aging syndromes, namely Hallerman Streiff (OMIM 234100), Wiedeman Rautenstrauch (OMIM 264090), and others still remain to be elucidated (Fig. 2).

A number of cellular and physiological pathways have been linked to aging, including regulation of the insulin/growth hormone axis, pathways involving ROS metabolism, caloric restriction, and DNA repair. Living models, ranging from yeast, to nematodes, mice and rats, have been instrumental in obtaining evidence for these connections [148,149].

2.1. Defective prelamin A processing associated syndromes

In 2003, we and others identified mutations in the *LMNA* gene as causing HGPS, one of the most paradigmatic segmental aging diseases [141,142]. This discovery revealed an unexpected role of lamins and more generally of the nuclear matrix composition and organization, in premature aging disorders. This also allowed entering into a translational era in the context of progeria and related disorders, leading to the characterization of previously unexplored diseases, identification of mechanisms, and the development of proofs of concept toward therapies (Fig. 3). This also raised the crucial question of potential links between nuclear *lamina*, nuclear envelope and matrix-associated proteins with natural aging, while progerin, the resulting product of HGPS-related *LMNA* mutation, is produced by *Ductus arteriosus* cells at birth [150] and in several other cell types during physiological aging [151–153].

2.1.1. HGPS and RD are premature aging related disorders

Since its first clinical description by Hutchinson in 1886, followed by the clinical report by Gilford in 1897, progeria was a fascinating disorder for clinicians and scientists, due to the apparent clinical recapitulation of normal aging, although the similarities are only partial and evolve in the context of a developmental disorder. Following the discovery of the major mutation in *LMNA* causing HGPS in 2003 [141,142], FACE1/ZMPSTE24 mutations have been identified that caused Mandibulo-Acral dysplasia (MAD) [154] another classified progeroid disease, progeria in a very small subset of patients and RD when both alleles exhibit a null mutation [143,144]. These observations provided clues to the search into the pathophysiology of HGPS and other premature aging disorders related to lamins A/C and allowed to identify an abnormal persistence of a farnesylated motif at the C terminal end of misprocessed prelamin A as a major mechanism underlying these disorders (Fig. 1C). This was the basis for designing pre-clinical proofs of therapeutic principles toward including patients in early phases of clinical trials using molecules inhibiting the transfert or the biosynthesis of farnesyl groups (see below Section 4.1).

2.1.1.1. Hutchinson–Gilford progeria syndrome. Progeria is an extremely rare, severe and uniformly fatal developmental disorder characterized by precocious onset of pathologies which are typical of advanced age (Fig. 2). The clinical phenotype is characterized by severe growth retardation, usually associated to skeletal alterations (osteolyses, osteoporosis), marked amyotrophy, lipodystrophy, skin atrophy and alopecia [155–157]. These symptoms usually appear after the first year of life, most of the children being healthy at birth. The mean age at diagnosis is 2.9 years, generally following a fall-off from the growth curves, loss of scalp hair (40%), scleroderma-like focal changes (28%), lipodystrophy (20%), and the appearance of characteristic facial dysmorphic traits, including a characteristic visible vein across the nasal bridge [155]. The mean final height of HGPS children is about 110 cm, the mean final weight 14.5 kg, children linearly gaining a mean of 0.440 kg/year from the second year of age [158].

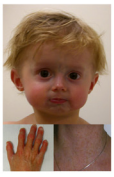
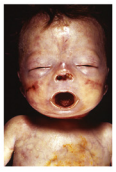
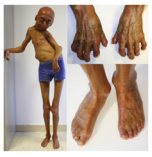
Phenotype	Gene	Mutation [reference]
Deficient prelamin A processing		
Hutchinson-Gilford Progeria syndrome (HGPS) - *progerin*	***LMNA***	
 - growth retardation - pinched nose - micrognathia - alopecia / sparse hair - osteolysis of distal phalanges, clavicles - osteopenia - subcutaneous lipoatrophy - abnormal skin pigmentation - major arteriosclerotic disease	c.1824C>T, p.G608G dominant, *de novo* OMIM 176670 [139] [140]	
Restrictive dermopathy (RD)) - *prelamin A*	***ZMPSTE24***	
 - intrauterine growth retardation - open "O" mouth - micrognathia - thin, tight translucent skin with erosion at flexure sites - sclerodermatous lesions - pulmonary hypoplasia - osteolysis of distal phalanges, clavicles	(two null mutations) OMIM 275210 [141] [142]	
Atypical Progeria syndrome (APS)	***LMNA***	
 - growth retardation - proptosis - pinched nose - micrognatia - dental crowding - alopecia - osteolysis of distal phalanges, clavicles - osteopenia - lipodystrophy	c.1583C>T, p.T528M and c.1619T>C, p.M540T [180]	
Nestor–Guillermo Progeria Syndrome (NGPS)	***BANF1***	
 - growth retardation, - generalized lipoatrophy - dry atrophic skin with pigmentation defects - severe osteoporosis, osteolysis - major skeletal deformations - micrognathia - prominent subcutaneous venous patterning	c.34G>A, p.A12T homozygous OMIM 614008 [143] [181]	
Hallermann-Streiff Syndrome (HSS)	***Unknown gene***	
 - brachycephaly with frontal bossing - hypotrichosis - cataracts and microphtalmia - beaked nose - micrognathia - skin atrophy - dental anomalies - short stature	OMIM 234100 *Hennekam R.C.M, courtesy*	

Fig. 2. Main clinical features and mutations associated to different nosologically classified premature aging syndromes. (A) Hutchinson–Gilford progeria syndrome (3 years old boy) and restrictive dermopathy, linked to prelamin A defective processing, (B) atypical Progeria syndrome, linked to lamin A/C missense mutations, (C) Nestor–Guillermo Progeria syndrome, linked to *BANF1* mutations and (D) Hallermann–Streiff syndrome, one of the nosologically well characterized progeroid syndromes without an identified genetic origin.

Typical facial dysmorphism includes micrognathia, prominent scalp veins, alopecia and a beaked nose. A high pitched voice is common. At the bone level, patients present with clavicular hypoplasia, acro-osteolyses of distal phalanges and generalized osteopenia. Hyperpigmented lesions or hyperplastic scars can be observed [159,160]. Sweat glands and sebaceous glands are reduced in number and subcutaneous adipose tissue is atrophic [161]. Tooth eruption is delayed and dental crowding is often observed. The cardiovascular system is severely affected, with small diameter of the intima and media and major loss of vascular smooth muscle cells with fibrous replacement (reviewed in [162]). These data suggest that the pathophysiology underlying HGPS vascular lesions is somewhat different from that of physiological age-related atherosclerotic lesions since typical plaque formation is usually not observed [163,164]. Strokes are frequent, at a median age of 9 years and myocardial infarction is the most frequent cause of death, at a mean age of 13.5 years. Enlargement of the left ventricle is observed in most patients and valves are often calcified. Cognitive functions are fully preserved in progeria as well as cancer incidence is not increased. These observations must however be taken with caution and be regarded with the early age at death.

Finally, it is of importance to note that, in our experience, progeria is a painful disease, mainly of bone or muscle origin (Sigaudy, Levy et al., unpublished). The incidence of progeria remains unknown while estimated to 1/4 to 8×10^{-6} births, with a balanced sex-ratio.

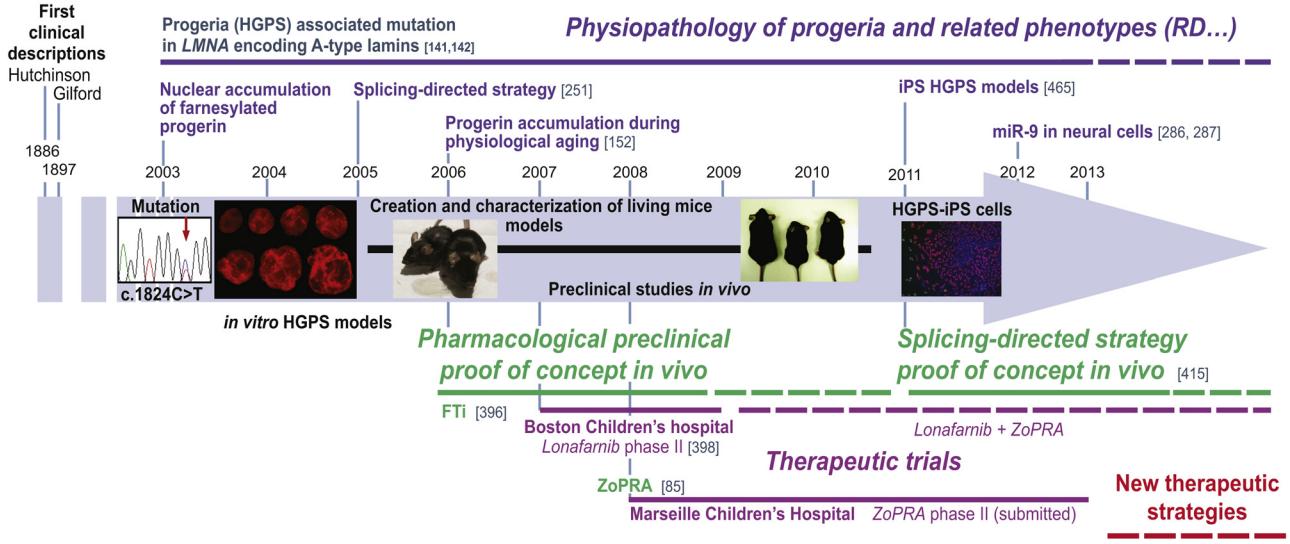


Fig. 3. Ten years of translational research in progeria and related syndromes. Since 2003 and the discovery of the *LMNA* mutation causing Progeria, premature aging studies have entered in a new era. In less than 10 years, the toxic mechanism associated to progerin/prelamin nuclear accumulation has been identified, as well as diverse prelamin A defective syndromes with a similar mechanism as compared to progeria have been deciphered. In the meantime, cell and living models have been developed and used to explore pathophysiological mechanisms, identify defective signalization pathways and develop pre-clinical proofs of principle. It was understood that progerin was progressively produced and accumulated at low levels during physiological senescence. iPS cells have been generated and allowed to understand, in particular, the mechanisms of brain protection in progeria. Finally, two distinct therapeutic trials have been conducted, one using FTI and the other providing patients with a combination of statins and amino-bisphosphonates.

HGPS is caused by a *de novo* point mutation in *LMNA* exon 11 (c.1824 C>T; p.G608G) activating a cryptic donor splice site in *LMNA* exon 11 leading to so-called progerin, that is characterized by the deletion of 50 amino-acids including the cleavage site of the processing FACE1/ZMPSTE24 endoprotease and leading to the abnormal persistence of a farnesylated cystein at the prelamin C-terminal end [141,142].

2.1.1.2. Restrictive dermopathy (RD). In 2003, Agarwal et al. observed for the first time the involvement of FACE1/ZMPSTE24 in severe mandibuloacral dysplasia (MAD-B), a relatively mild progeroid syndrome [154]. This followed the report by Novelli et al. in 2002 of *LMNA* homozygous mutations in MAD-A [165].

Following these reports, RD, a perinatal lethal genodermatosis, was linked to primary or secondary lamin A dysfunction [143,144]. RD is characterized by a severe intrauterine growth delay, generalized arthrogryposis, tight, stiff, translucent skin which is frequently eroded on flexure sites. Clavicules are hypoplasic and bone density is reduced, with fontanel enlargement. Facial dysmorphy includes a small pinched nose, the mouth open in a fixed "O" position, retromicrognathia, and variable loss of scalp hair, eyebrows and eyelashes [166–168] (Fig. 2). Histologically, the skin shows hyperkeratosis, a thin dermis, abnormally dense collagen bundles, with almost completely absent elastic fibers. Patients' death results in most cases from respiratory failure [169,170]. Most patients affected with RD carry homozygous or compound heterozygous null mutations in *ZMPSTE24* [171] while a very small subset of RD cases are associated to splicing mutations in *LMNA* with similar pathophysiological consequences as compared to HGPS [144]. These observations raised the concept of prelamin A-deficient processing associated syndromes, being a clinical continuum of apparently heterogeneous disorders, whose the disease evolution and severity depends the dose of accumulated farnesylated mis-processed prelamin A [144,171,172].

2.1.1.3. Other lamin-linked premature aging syndromes. In addition to these two clinically well characterized syndromes, overlapping HGPS/MAD sometimes or RD/HGPS syndromes were associated with several *LMNA* mutations in exon 11. All mutations reported lead to variable expression levels of progerin or other truncated prelamin A farnesylated isoforms, respecting the rule: low amounts of truncated farnesylated isoformes are associated with milder phenotypes, such as patients carrying *LMNA* c.1968 G>A or c.1968+5 G>A diagnosed as "Werner syndrome like" for whom progerin was detected in lower level compared to classical HGPS [173,174]. A 45 year-old patient was reported carrying an atypical mutation in exon 11, c.1868C>G, that led to another truncated farnesylated isoform named lamin Δ35. The same mutation was observed in a young patient presenting with a progeria-like syndrome and an osteosarcoma [175]. Conversely, higher amounts of truncated isoforms are associated with extremely severe syndromes in which the premature death occurs from the first months to the first year of life [176]. Given their common molecular bases linked to prelamin A-deficient processing, we propose to name this group of diseases "HGPS-like" syndromes. Conversely, a distinct group of premature aging syndromes called "Atypical Progeria Syndromes" (APS) are being delineated [177–179] (Fig. 2). They are characterized by prelamin A-proficient processing and are due to the production of A-type lamins carrying specific missense mutations. They can be transmitted on a dominant or a recessive pattern of inheritance (see [177] for a recent review).

2.2. Nestor–Guillermo progeria syndrome

In 2011, a novel syndrome including several of the clinical signs observed in progeria was reported and named Nestor–Guillermo progeria syndrome (NGPS) [180]. NGPS has been defined as a chronic progeria because of its slow clinical course and relatively long survival, despite its early onset. NGPS clinical findings differ from classical HGPS in several aspects. Remarkably, in NGPS, growth is less retarded than in HGPS and lifespan is longer. A severe osteolysis in all affected bones (mandible, clavicles, ribs, distal phalanges, and long bones) as well as the absence of atherosclerosis, cardiac ischemia, arterial hypertension, or cerebral vascular disease, are marked differences when comparing the two reported patients with NGPS when explored at 24 and 32 years of age, with

typical progeria. Skeletal abnormalities and subsequent pain and disability are at the front of the clinical synopsis (Fig. 2) and affect patients' quality of life, making these bones defects a treatment priority. However, NGPS, like progeria, is a post-natal developmental disorder since diagnosis may not be made before the age of 2 years.

After having performed exome sequencing in one family, Puente et al. identified a homozygous missense mutation in *BANF1* encoding BAF (Barrier to autointegration factor) as the cause of the NGPS [145]. This was confirmed by sequencing *BANF1* in a second family with the same syndrome that retrieved identical mutations and made NGPS an autosomal recessive progeroid syndrome [180]. BAF is a nuclear protein with direct interactions with soluble lamins into the nucleus indicating that HGPS and NGPS share common cellular defective mechanisms and their exploration might lead to the identification of proofs of concept potentially beneficial to patients affected with these two syndromes.

2.3. Progeroid syndromes associated to DNA repair defective processes

These progeroid diseases, involving heritable defects in DNA repair, indicate a central role of genome integrity maintenance [181] in the aging process.

2.3.1. RECQL helicases defective associated syndromes

Werner syndrome (WS), an autosomal-recessive disorder is also known as progeria of the adult and, in most cases, is associated to null mutations in *WRN* encoding RECQL2, a protein belonging to the RECQ helicases family with helicase and exonuclease activities. These proteins are crucial for recombination repair as well as telomere maintenance [182]. WS affected patients are at high risk of cancer [183], the major cause of death and shortened lifespan, as this is the case in Bloom syndrome (BS). BS, an autosomal recessive disorder affecting mainly Ashkenazi Jews [184] is associated to mutations in *BLM* [185] encoding RECQL3, a key player in double strand break repair [186].

Mutations in BS and WS induce a lack of DNA helicase activity. Truncated RECQL proteins do not translocate into the nucleus due to the absence of the NLS located at their C-terminal end [187]. RECQL3 misfolded proteins, also have an abolished function. A lack of exonuclease activity is often associated to RECQL2 deficiency in WS while a lack of ATPase activity may be observed in case of *BLM* mutations [188]. In this context, two other syndromes may be reported: Rothmund–Thomsom syndrome (RTS), caused by mutations in *RECQL4* [189] leading to skin abnormalities as hallmark, and patients susceptibility to cancers, without cognitive impairment [190]; and trichothiodystrophy (TTD), caused by mutations in *XPD*, encoding one of the two transcription factor IIH (TFIIH) helicases [191]. Different *XPD* mutations can induce TTD, Xeroderma pigmentosum or Cockayne syndrome. *XPD* encodes a helicase protein involved in both DNA repair and transcription initiation [192]. As a main clinical difference when compared to the previously reported WS and BS syndromes, TTD affected patients present with neurodegeneration including cerebellar ataxia [193].

2.3.2. Nucleotide excision repair (NER)/base excision repair (BER) associated syndromes

Cockayne syndrome (CS) is mainly caused by mutations in *CSA* or *CSB* [194] with only few patients carrying mutations in *XPD*. CS proteins are involved in both transcription coupled nucleotide excision repair (TCR) and base excision repair (BER). Recently, mitochondrial contribution to aging-associated symptoms of CS has been reported since CS proteins play also a roles in transcription of mitochondrial DNA [195]. CS patients harbor several symptoms in common with TTD such as neurodegeneration, growth retardation, retinal degeneration and are mentally retarded [196]. Surprisingly, patients have no predisposition to cancer as this is the case in XP, due to a defect in one of seven proteins (XPA to XPG) required for nucleotide excision repair [197]. XP patients show dramatically accelerated aging only in areas of skin exposed to the sun and a skin cancer rate more than a thousand times greater than normal [198]. Moreover they frequently develop neurodegenerative processes [199,200]. Genotype–phenotype relationships exist within these three clinically defined but overlapping entities of the NER/BER defective pathways [201]. Finally, nuclear matrix proteins and DNA repair mechanisms exhibit clear relationships, as demonstrated by studying lamin-associated progeroid syndromes [111,202]. As an example, progerin accumulation is induced in cultured fibroblats by UVA-induced oxidative damage resulting in subsequent alternative splicing of the *LMNA* transcript [203].

2.3.3. Ataxia telangiectasia (AT)

AT is caused by a loss-of-function mutation in the *ATM* (ataxia telangiectasia mutated) gene. ATM is involved in cell cycle progression, checkpoint response to DNA damage, and telomere maintenance [204]. Patients have progressive neurodegeneration leading to cerebellar ataxia at early age, and telangiectatic lesions of early onset [205]. AT patients have a high risk of cancer and are sensitive to UV radiations [206].

3. Dissecting the pathways leading to aging in progeria and progeroid syndromes

In a recent very elegant review, Lopez-Otin et al. enumerated nine hallmarks of aging and emphasized that one of the major challenge is to dissect the interrelationships between them [207]: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communication. Progeria and other genetic syndromes characterized by an accelerated aging give the opportunity to dissect some of these hallmarks at the cellular level. Farnesylated progerin/prelamin A and mutated A- and B-type lamins or partners within nucleus lead to several structural as well as functional genomic consequences [208,209] (Fig. 4).

3.1. Abnormal interactions between mutated lamins and protein partners

Lamin mutations induce abnormal interactions within proteins of NM, *lamina*, NE leading to nucleus shape defects and to sequestration of components of the genome functional machinery. The deletion of 50 residues at the lamin A C-terminal increases the stability of progerin Ig fold and tail [210], that could explain the disorganization of A- and B-type lamins into *lamina* of HGPS cells [211]. Nuclear shape and size changes increase in parallel with the amount of farnesylated progerin, giving a crumpled appearance to HGPS nuclei [212], as well as to nuclei, lacking *LMNA* mutation but expressing progerin, of cells from normal aged subjects [152]. The NE shape alterations, protrusions and invaginations, allow the increase in the NE surface area whereas the nuclear volume remains unchanged [213]. Transcription factors regulating gene expression and numerous other proteins are sequestered into *lamina* and/or mislocalized in laminopathic cells, a phenomenon impairing several aspects of nuclear genome activity [21,33,214,215].

3.2. NPC dislocation and impaired nucleocytoplasmic exchanges

Lamin mutations dislocate NPC resulting, during interphase, in defects in nucleo-cytoplasmic transports of proteins and RNAs, that are essential for all aspects of nuclear genome metabolism. Most of lamin A partners are *lamina*, NE and NPC proteins, whereas some of

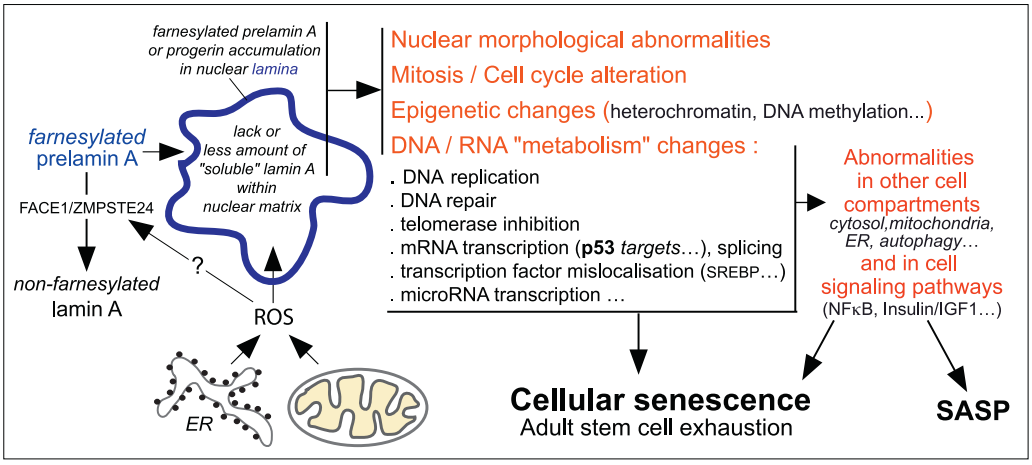


Fig. 4. Cell senescence in laminopathies results from several and combined factors.

them are nucleoplasmic proteins [216]. Both A- and B-type lamins interact with components of NPC [71]. Nuclear protein import is reduced in cells expressing lamin A mutants [217]. The nucleocytoplasmic gradient of monomeric G protein Ran controls the bidirectional transport of proteins and RNAs between the nucleoplasm and cytosol. In HGPS cells, the disruption of this gradient impairs the nuclear import of both the small (19 kDa) SUMO ligase Ubc9, controlling indirectly Ran GTPase activity [218], and of larger proteins such as Tpr (267 kDa), component of the NPC nucleoplasmic basket [219]. ATM and ATR are large proteins whose nuclear import defect and mislocalization impairs DNA repair in HGPS cells [220]. Tpr controls the nuclear level of the SUMO-protease SENP2 and plays a role in the exportin 1-dependant nuclear export of NES-bearing proteins [219], of unspliced [221] and polyA+ mRNAs [222]. NPC components also interact with chromatin and control gene expression during interphase [223,224]. Tpr is required for establishing NPC-associated zones of heterochromatin exclusion [225]. In fibroblast cultures from patients with *LMNA* mutations, live cell imaging evidences intermittent, non-lethal NE disruptions. They allow the nuclear entry of proteins and the nuclear exit to the cytosol of nuclear proteins [226]. This increased NE permeability could be related to the redistribution of phenylalanine-glycine (FG) repeat-containing nucleoporins to the cytosol observed in human muscle cells bearing *LMNA* mutations [227]. Similar NE events have already observed during HIV [228] and adenoviral infection [229].

3.3. *LMNA mutations induce mechanical defects in non-dividing cells*

A mechanical and functional continuum connect the nucleoplasm content, the nuclear genome and NM, to the extracellular matrix (the basal *lamina*), through the NE and nuclear *lamina*, the LINC complexes, each of the three cytoskeletal networks, the plasma membrane and its receptors or cell junctions [230]. Changes in NE, in *lamina* and in NM composition can result in nuclear shape alterations, that are observed during normal development and differentiation [231], during cell aging and genetic diseases [232], as well as during “acquired” pathologies, such as cancer [233,234], nuclear entry or exit of viruses [235]. NE protein [236] and A-type lamin mutations [212] often evidence dramatic changes in nuclear shape, size and mechanical properties [237], impairing nuclear stiffness [238] and nucleocytoskeletal coupling as often observed in laminopathies [239]. In HGPS cells, the INM protein SUN1, member of LINC complexes, is overexpressed and its reduction corrects nuclear defects and cell senescence, thus evidencing the implication of the nucleocytoskeletal coupling in this disease [240]. A-type lamins defects finally impact bidirectional mechanotransduction and signaling pathways [241] controlling cell interactions with extracellular matrix [242] and chromatin organization [243]. As an example, three parameters, the extracellular matrix stiffness, the lamin A amount and phosphorylation status, the lamin A to B ratio, control the genomic program leading to stem cell and tissue differentiation [133].

3.4. *Cell cycle regulation and mitosis defects in laminopathies*

NM and NE proteins play different roles during mitosis and interphase. NuMA [17], the Ran GTPase [244], some nucleoporins [245], associate with mitotic spindle microtubules and/or with kinetochore, together with cytosolic proteins, e.g. clathrin [246]. They control chromosome segregation and migration, involved in the maintenance of genome integrity, chromosomal stability as well as cell cycle progression.

After microtubule-induced tearing of *lamina* and NE breakdown [247], B-type lamins, still bound to membrane vesicles through their farnesyl anchor, are part of a RanGTP-induced vesicular membraneous network, controlling mitotic spindle assembly and orientation [248] through interactions with microtubules and motor (dynein, kinesin) and non-motor MAPs (Nudel) [249,250]. Lamin B1 amount is reduced in HGPS cells [251] and in cells as they enter in replicative senescence [252]. In cultured human dermal fibroblasts and keratinocytes and in aged human skin tissue, senescence results from a decrease in lamin B1 amount, linked to both a reduction in *LMNB1* transcription and to the inhibition by miRNA 22a of lamin B1 mRNA translation [253]. Silencing the expression of lamin B1 slows cell proliferation and is accompanied by a p53-dependent reduction in mitochondrial reactive oxygen species (ROS) production [254].

The expression of progerin [255,256] or of another lamin A/C mutation L52R [257] slows down as well the cell cycle. Besides mechanical defects (see above), *LMNA* mutations could result in abnormalities in the nucleocytoplasmic exchanges and nuclear fate of cell cycle regulatory proteins, pRb, cyclin, PCNA [128]. A-type lamins in complexes with LAP2α promote pRb localization in perinucleolar lamin A/C positive foci, protect pRb from proteasomal degradation, pRb stabilization being associated with cell cycle arrest [257–261]. pRb amount is lower in HGPS cells that exhibit a defective lamin A-pRb signaling network [262]. The loss of pRb is known to compromise centromere function and cohesion, and to cause chromosome segregation errors, leading to the generation of aneuploid cells [263].

3.5. DNA replication, transcription, repair and epigenetic defects in laminopathies

A- and to a lesser extent B-type lamins provide a structural support to chromatin and to the nuclear machinery involved in genome functions [254,264]. Human and experimental animal laminopathies offer the opportunity to dissect out the pathophysiological mechanisms of diseases and to analyze their consequences upon cell development, differentiation, survival and aging [209].

3.5.1. From epigenetics...

Interphase chromosome territory organization, localization of telomeres and of centromeres, differ in HGPS cells and in cells bearing a progeroid lamin A mutation [265,266] and are associated with alterations in chromatin patterns and in active or silencing marks [28,251,267,268]. BAF is a soluble *lamina* protein, whose insufficiency causes a progeroid syndrome [145,180]. BAF interacts with several partners, among them A- and B-type lamins, NuMA, and influences active or silencing marks of histones [269,270]. Aberrant DNA methylation profiles, in particular targeting the NFκB signaling pathway, are among the other epigenetic modifications in cells from HGPS and Werner syndrome patients [271].

3.5.2. ... to DNA repair...

Lamin A/C mutants, progerin and farnesylated prelamin A impair DNA repair, leading to genome instability [85,220,272,273] that represents an important aspect of the aging process [274]. HGPS and RD cells exhibit ROS-induced DNA double-strand breaks [275] that cannot be repaired and are reduced by ROS scavenger treatment [276]. Progerin and prelamin A exhibit elevated binding capacity to SUV39H1, a methyltransferase responsible for H3K9me3, and protect it from proteasomal degradation, leading to increased levels of SUV39H1 and H3K9me3. The abnormal H3K9me3-mediated heterochromatin remodeling results in defective DNA repair that can be improved by the depletion of SUV39H1 [277]. Although senescent-associated heterochromatin foci (SAHF) are common in human senescent cells, they are not found in all such cells. In HGPS cells, hybridization with probes to α-satellite and to satellite II DNA evidences the unfolding of satellite heterochromatin, another epigenetic change called senescence-associated distension of satellites (SADS). This loss of tight packaging of satellite DNA seems to be more obvious in cells expressing low levels of lamin B1 [278]. It has to be noticed that epigenetic abnormalities or defects in DNA repair could result from impaired nucleocytoplasmic exchanges of the involved proteins (see below) but also from their degradation. *LMNA* knock-down or mutation in lamin A/C rod domain activates several E3-ubiquitin ligases, the proteasomal degradation of HP1 proteins and of ATR kinase, that can be reversed by proteasome inhibitors [54,279,280].

3.5.3. ... to microRNAs...

MicroRNAs are new actors in the aging field [281,282]. Several miRNA are deregulated in *Lmnb1*$^{-/-}$ MEF, some of them controlling cell cycle [283]. The decrease in lamin B1 amount during aging is caused by miR-23a [253]. In *Zmpste24*$^{-/-}$ progeroid mice as well as during normal aging in mouse, miRNAs of the miR-29 family are upregulated in response to DNA damage and occurs in a p53-dependent manner [284]. In human mesenchymal stem cells (MSC), miR-143p inhibits the translation of FACE1/ZMPSTE24 mRNAs. The lack of the protease leads to the presence of farnesylated prelamin A within nuclei, responsible for MSC aging [285]. The expression of prelamin A, but not of lamin C, is down-regulated by miR-9 in brain neurons and glial cells as well as in neurons derived from iPSC generated from HGPS fibroblasts [286,287]. In HGPS cells, the transcription of several miRNAs is modified, some of them targeting lamin A/C mRNAs [288]. In addition, dysregulation of miRNAs has been also observed in skeletal muscle cells from patients with *LMNA*-related muscular dystrophy [289].

3.5.4. ...to transcription and splicing...

Lamins and their partners provide a protein scaffold for the organization of transcription factories, interacting with nuclear and nucleolar RNA polymerase machineries and with several transcription factors regulating gene expression, impaired in laminopathies [215]. Within nucleoplasm, mRNA splicing factors and RNA poymerase II are colocalized in specialized foci, called nuclear speckles or interchromatin granules clusters [290] and surrounded by assembly sites for exon junction core complexes [291]. Nuclear speckles are associated with NM proteins [25,292], and regulate/modulate both transcriptional and post-transcriptional events [293]. Nuclear speckles are also involved in the processing and export of transcripts from genes encoding mitochondrial- or ER-targeted proteins and characterized by intron-free 5′ UTR [294]. An age-associated disruption in the balance of alternatively expressed isoforms for selected genes suggests that modification of mRNA processing may be a feature of human aging [295]. This imbalance is related to the decrease in the expression of about 38% of splicing factors and of ATM [296], thus linking pre-mRNA processing and DNA damage response [297]. Downregulation of splicing factor SRSF3 induces an alternatively spliced isoform of p53 that promotes cellular senescence [298]. Senescence-associated stress signals result in the cytoplasmic accumulation of several splicing factors such as SRSF1 in endothelial cells [299], their shuttling being controlled by their phosphorylation status and by RanBP2 (Nup358), constituting the cytoplasmic filaments of NPC [300]. Two splicing factors, SRSF1 and 6, exihibit opposite effect on the progerin production by HGPS fibroblasts [301]. The progeria-specific cryptic splicing site in exon 11, leading to progerin mRNA, is activated during physiological aging, without *LMNA* mutation [152,302]. This splicing machinery defect is reminiscent to another age-related transcription abnormality, where the missreading of GAGAG motifs, within genes involved in Alzheimer disease, lead to the GA dinucleotide deletion in mRNAs and the synthesis of mutated proteins in the absence of mutation within the genes [303]. A similar transcription infidelity is also observed in cancers [304]. In normal human fibroblasts, progressive telomere shortening during cellular senescence induces progerin production through the activation of the cryptic alternative splicing site in *LMNA* exon 11, thus evidencing a synergistic relationship between telomere dysfunction and progerin production [305].

3.6. Telomerase complex defects in laminopathic cells

Accelerated telomere shortening and replicative senescence is observed in *LMNA* null cells [202] and in cells (over)expressing mutant and wild-type lamin A [306–308]. This phenomenon can be corrected by telomerase overexpression or p53 inactivation [309]. Telomerase complex defect could be related to epigenetic changes in telomeric heterochromatin [268,310]. In human senescent mesenchymal stem cells or in cells expressing mutant lamin A or B, telomeres (and centromeres) aggregate with nuclear *lamina* and are colocalized with phosphoH2AX, but not with telomerase catalytic subunit TERT, suggesting that telomere aggregates are sites of DNA damage [311]. The telomere mobility is increased in cells lacking A-type lamins, is reduced in HGPS cells [312]. An oxidative stress including ROS overproduction and a reduced level of antioxidant defenses is encountered in the two types of progeroid syndromes, laminopathies and DNA damage response defects [313–316] (see below Section 3.8). Upon oxidative stress, TERT can shuttle from the nucleus to the mitochondria, where it protects mitochondrial function, decreases mitochondrial ROS levels and prevents nuclear DNA damage, but does not correct telomere shortening [317,318].

Reciprocal relationships have been observed between TERT and the Wnt/β-catenin signaling pathway involved in cell differentiation (see below Section 3.10) [319,320]. In hematopoietic stem cells, in heart and liver from *Tert*$^{-/-}$ mice, telomere dysfunction activates p53 which in turn binds and represses two master regulators of mitochondrial metabolism (PGC-1α and PGC-1β), thereby impairing mitochondrial biogenesis and function, increasing reactive oxygen species production and forging a direct link between telomere and mitochondrial biology [321].

3.7. Abnormal p53 signaling

p53 functions is a transcription factor involved in cell-cycle control, DNA repair, apoptosis and cellular stress responses. However, p53 also modulates cell senescence and organismal aging, as p53 stands at the crossroad of several mechanisms: mitochondrial function, ROS generation and scavenging, mTOR signaling and autophagy [322] and telomerase activity. The activation of p53 (and of pRb) signaling pathways is observed in cells bearing mutations in A-type lamins [308,323] or in FACE1/ZMPSTE24, the phenotype of *Zmpste24*$^{-/-}$ mice being improved by breeding with *p53*$^{-/-}$ mice [324]. Citrullination of lamin C (and of histone H4), that could be a pro-apoptotic signal, is triggered by DNA damage-induced p53 activation [325]. The activation of p53 reduces lamin B1 level [252,253]. A p53 binding site on the *LMNA* promoter controls the p53-induced increase in lamin A/C. p53 also increases lamin B2 level but lacks a binding site in *LMNB2* promoter [326]. Cell cycle, p53 and pRb expression are also controlled by emerin, LAP2 and other less characterized NE transmembrane proteins [327]. The NM protein NuMA also modulates the expression of p53 target genes [113,114]. During the replicative senescence of human normal fibroblasts, the downregulation of SRSF3 induces the upregulation an alternatively spliced isoform of p53 that promotes senescence [298]. Besides protein coding genes, p53 also controls the expression of several microRNAs [328]. For example, miR-34a, whose maturation requires the splicing of a 30 kb intron [329], up- or down-regulates more than two hundred of genes [330,331], among them *LMNB1* and *LMNB2*. Furthermore p53 also regulates several actors of the miRNA processing complex [332]: miR-9, known to inhibit the expression of lamin A within neuron and glial cells, regulates DGCR8, a dsRNA binding protein involved with Drosha in the first cleavage of pre-miR; miR-29 inhibits both the mRNAs of DICER and of FACE1/ZMPSTE24 [284,333]; miR-143 and miR-34 control the expression of exportin 5, responsible for pre-miR nuclear export, that is activated during the ATM-induced the DNA damage response [334].

3.8. Mitochondria, endoplasmic reticulum, oxidative stress and nuclear-mitochondria signaling

A- and B-type laminopathies are accompanied by altered levels of ROS and by a higher susceptibility to oxidative stress [315,316]. Mitochondria are the major source of ROS [335], mainly produced by complexes I and III of the respiratory chain [336]. ROS, besides their toxic effects, also elicit various physiological events from differentiation to aging [337]. Mitochondrial DNA only encodes 13 proteins inserted into inner membrane, whereas the other ∼1100 proteins are encoded by nuclear genome, synthetized into cytosol and imported into mitochondria [338]. Normal human aging is associated with a progressive decline in muscle mitochondrial DNA abundance and protein synthesis that plays a major role in regulation of life span [339]. The specific loss of mitochondrial, but not nuclear, encoded respiratory chain subunits results from a non-classical nuclear to mitochondrial communication pathway triggered by a decrease in nuclear NAD+ content. The phenomenon can be reversed by raising NAD+ levels [340]. Transcription of genes encoding mitochondrial proteins is impaired during laminopathies leading to an imbalance between mitochondrial and nuclear proteins especially those constituting complexes I, III and IV of the respiratory chain and the ATPsynthase [341–343]. This imbalance triggers the mitochondrial unfolded protein response (UPRmt) [344], whereby mitochondria send a signal to the nucleus to induce the production of stress-related proteins, which restore the mitochondrial balance. The increased UPRmt is correlated with longer lifespan in mice and in *Caenorhabditis elegans* [345]. One of the genes activated by the UPRmt is CHOP, also involved in the ER unfolding protein response [346], and activated in cells bearing R482W mutant lamin A [347]. Mitochondria and ER domains interact in MAM (Mitochondria-associated membranes), that represent highly specialized platforms involved in several functions [348] among them NFκB activation and autophagy [349]. The imbalance between nuclear and mitochondrial proteins could also result from the overexpression of miRNAs in brain and liver of aged mice, that target selectively mRNAs encoding subunits of complexes I, IV and of ATPsynthase [350]. Mitochondria elicit dynamic relationships with cytosolic P bodies involved in mRNA decay through miRNAs. The inactivation of mitochondria by CCCP leads to a strong decrease of miRNA efficiency [351].

3.9. NFκB, "inflammaging" and senescence-associated secretory phenotype (SASP)

Known as a family of ubiquitously expressed transcription factors activated in response to cell stress and mediating innate and adaptive immunity, NFκB is involved in the induction of cell senescence [352]. NFκB signaling pathway is activated in three different mouse progeroid models bearing defect in DNA repair [353] or in prelamin A processing [354]. Mice aging is slowed down and lifespan is rescued by pharmacological inhibitors of NFκB signaling pathway or by crossing the progeroid mice with mice defective in one (RelA/p65) of the NFκB protein complex, thus leading to the inactivation of the pathway. Senescent cells secrete a growing collection of factors that alter their microenvironment and the neighboring cells in a paracrine way, a phenomenon called the senescence-associated secretory phenotype (SASP), whose NFκB is a major regulator [355–357]. Vascular smooth muscle cells (VSMC) from aged subjects or aging *in vitro* express farnesylated prelamin A, due to a decreased amount in FACE1/ZMPSTE24 mRNA and protein [358]. Prelamin A expression by these cells induce a SASP and promote VSMC calcification [359]. Besides signaling proteins and other aging-inducing factors, several miRNA appear to be secreted by aged cells and to participate to SASP [360]. miRNAs are secreted in exosomes or microparticles, are exchanged by cells and modulate gene expression in target cells [361–363].

3.10. Adult stem cell exhaustion related to defects in signaling pathways

Naive adult mesenchymal stem cells from HGPS patients express low levels of progerin *in vivo* but accumulate nuclear progerin with increasing passages *in vitro* [364]. The presence of farnesylated prelamin A or of progerin in nuclei of epidermal [365] or mesenchymal [366] adult stem cells lead to their progressive exhaustion, another pro-aging phenomenon, linked to defects in Wnt or Notch signaling pathways respectively. In another progeroid mouse model (*Lmna*$^{\Delta 9/\Delta 9}$), the deletion of exon 9 causes the proliferative arrest and death of postnatal, but not embryonic, fibroblasts. The defects are associated with inhibition of the Wnt/β-catenin signaling pathway, resulting in the inability of cells to synthetize a functional extracellular matrix (ECM) [241]. The synthesis of β-catenin is controlled by two splicing factors, SRSF1

and 9, exhibiting an aging-related decrease [296] that could explain the Wnt/β-catenin signaling defect. The same two SRSF are overexpressed in cancer cells and promote Wnt-signaling tumorigenesis through the production of β-catenin mRNA [367].

Two other studies evidence the anti-aging role of diffusible factors secreted by wild-type adult stem cells. Adult skeletal muscle stem cells from two progeroid XP (*Ercc1*$^{-/-}$) or RD (*Zmpste24*$^{-/-}$) mouse models, show impaired muscle regeneration, reduced proliferation and myogenic differentiation *in vitro*. Progeroid symptoms are corrected in *Ercc1*$^{-/-}$ mice by the intraperitoneal transplantation of adult skeletal muscle stem cells from wild type mice [368]. Proliferation and myogenic differentiation *in vitro* of *Zmpste24*$^{-/-}$ adult skeletal muscle stem cells are rescued by yet unknown factors secreted in the conditioned medium by adult skeletal muscle stem cells from wild-type mice [369].

3.11. Autophagy is altered in laminopathies

Eukaryotic cells have two major systems for the regulated degradation of proteins. The membrane-dependent autophagic-lysosomal pathway interests both membrane organelles and cytosolic proteins. The ubiquitin-proteasome system (UPS) is restricted to nuclear and cytosolic proteins [370], some of them being retrotranslocated into the cytosol from the ER, through the ERAD mechanism [371]. Proteasome function is impaired during aging, suggesting that this decrease in proteasomal activity might be involved in the aging process and in the occurrence of age-associated diseases [372,373]. Mammalian cells exhibit three types of autophagy mechanisms: chaperone-mediated autophagy, microautophagy and macroautophagy [374]. Several observations changed recently the view that UPS and macroautophagy are independent degradative pathways. For example, ubiquitylation target substrates for degradation *via* both pathways; perturbations in the flux through either pathway affect the activity of the other system [375]; ubiquitylation of mitochondrial outer membrane proteins triggers mitochondrial autophagy (mitophagy) [376,377].

Furthermore, several cross-talk have been reported between aging, UPS and autophagy degradative pathways [378] and their triggers, activators or regulators, DNA damage [379,380], mitochondria dysfunction and oxidative stress [375,381], ER stress [382,383], p62/SQSTM1 [384,385], p53, NF-κB and partners [356,386–389]. Macroautophagy regulation becomes recently more complex through the involvement of a transcriptional network, microRNAs and epigenetic histone marks [390]. Chaperone-mediated autophagy (CMA) activity declines with age, due to a decrease in the stability and in the net content of LAMP-2A in the lysosomal membrane. Genetic manipulations aimed at preventing the decrease of LAMP-2A with age, through the expression an exogenous Lamp-2A in mouse liver, restore CMA activity and extend mouse life-span [391]. Macroautophagy also declines with age, its inhibition leading to premature aging, while its activation delays aging and extend longevity, through cell and organismal effects (innate immunity, inflammatory responses, neuroendocrine regulation) [392]. These observations lead to pharmacological approaches to fight against aging in laminopathies (see Section 4.3 below). However, a paradoxal up-regulation of basal macroautophagy is observed in progeroid *Zmpste24*$^{-/-}$ mice, that is linked to mTOR inhibition, AMPK activation and severe metabolic alterations in glucose and lipid metabolism [393].

4. Therapeutic approaches in progeria and lamin A-related progeria-like syndromes

Three main strategies have been designed to correct the defects in progeroid syndromes linked to prelamin A processing (Fig. 5): to decrease the toxicity of farnesylated prelamin; to block the cryptic splicing site leading to mature progerin mRNA production; to degrade progerin or farnesylated prelamin A within cells. Only the first strategy led to therapeutic trials in human patients up to date. In addition, targeting the insulin-IGF1 signaling pathway has also been investigated in a progeroid mouse model.

4.1. Decreasing progerin/prelamin A toxicity by reducing their isoprenylation

Three human genetic diseases leading to accelerated aging, mandibuloacral dysplasia, progeria and restrictive dermopathy, elicit the same pathophysiological mechanism: mutation in either *LMNA* or in the *ZMPSTE24* results in the persistence within cells of farnesylated proteins, progerin or prelamin A. Among several studies, the improvement of life span in *Zmpste24*$^{-/-}$ × *Lmna*$^{+/-}$ mice for example evidences that the cell toxicity is linked to the farnesyl moeity bound to progerin or to prelamin A [394]. Two strategies have been designed targeting the isoprenoid biosynthesis pathway (Fig. 5D).

Farnesyl-transferase inhibitors (FTI), designed to block the activation of Ras in several cancers [395], were used to block or minimize progerin/prelamin A farnesylation. FTI gave better results in cultured cells from human patients than in mouse models of progeroid syndromes or expressing various isoforms of progerin or of (pre)lamin A, either prenylated or not. Indeed only a small percentage of progerin/prelamin A seems to be unprenylated in FTI-treated animals [396,397]. FTI improve some parameters (e.g. nuclear shape) in cultured cells but not other parameters such as the DNA damage response [220].

From 2007 to 2009, an FTI (lonafarnib) was given to 25 patients enrolled in the first therapeutic trial for progeria that took place in Boston Children's Hospital (Clinicaltrials.gov identifier NCT00916747). The published results [398] do not evidenced a clear improvement for the main endpoints. Body weight gain under FTI, was presented as increased by 50% in 6 children, as compared to the expected weight gain when untreated. However, a previous natural history study, in a cohort of untreated progeria children, indicated that the mean weight gain was very similar [156]. In all other patients, the rates of weight gain were either stable or decreased [399]. HGPS patients under FTI treatment developed many side effects, most of them known as being related to the molecule. This was not surprising since it was demonstrated that an alternative prenylation pathway, geranylgeranylation, toxic as well, was activated in the presence of FTI. The published results [414] did not indicate a clear improvement for the main endpoints. Body weight gain under FTI, was presented as increased by 50% in 6 children, as compared to the expected weight gain when untreated. However, a previous natural history study, in a cohort of untreated progeria children, indicated that the mean weight gain was very similar [156]. In all other patients, the rates of weight gain were either stable or decreased [415]. HGPS patients under FTI treatment developed many side effects, most of them known as being related to the molecule. This was not surprising since it was demonstrated that an alternative prenylation pathway, geranyl-geranylation, toxic as well, was activated in the presence of FTI [85]. However, potentially interesting results on the cardiovascular system protection were reported [399].

The benefit of FTI for progeria is controversial since donut-shaped nuclei appear in cultured cells and in tissues from wild type mice or from human progerin expressing model after FTI treatment, a phenomenon linked to an increase of the proteasomal degradation of pericentrin, a centrosomal protein [400]. Stop mutations in pericentrin lead to dwarfism [401] and to

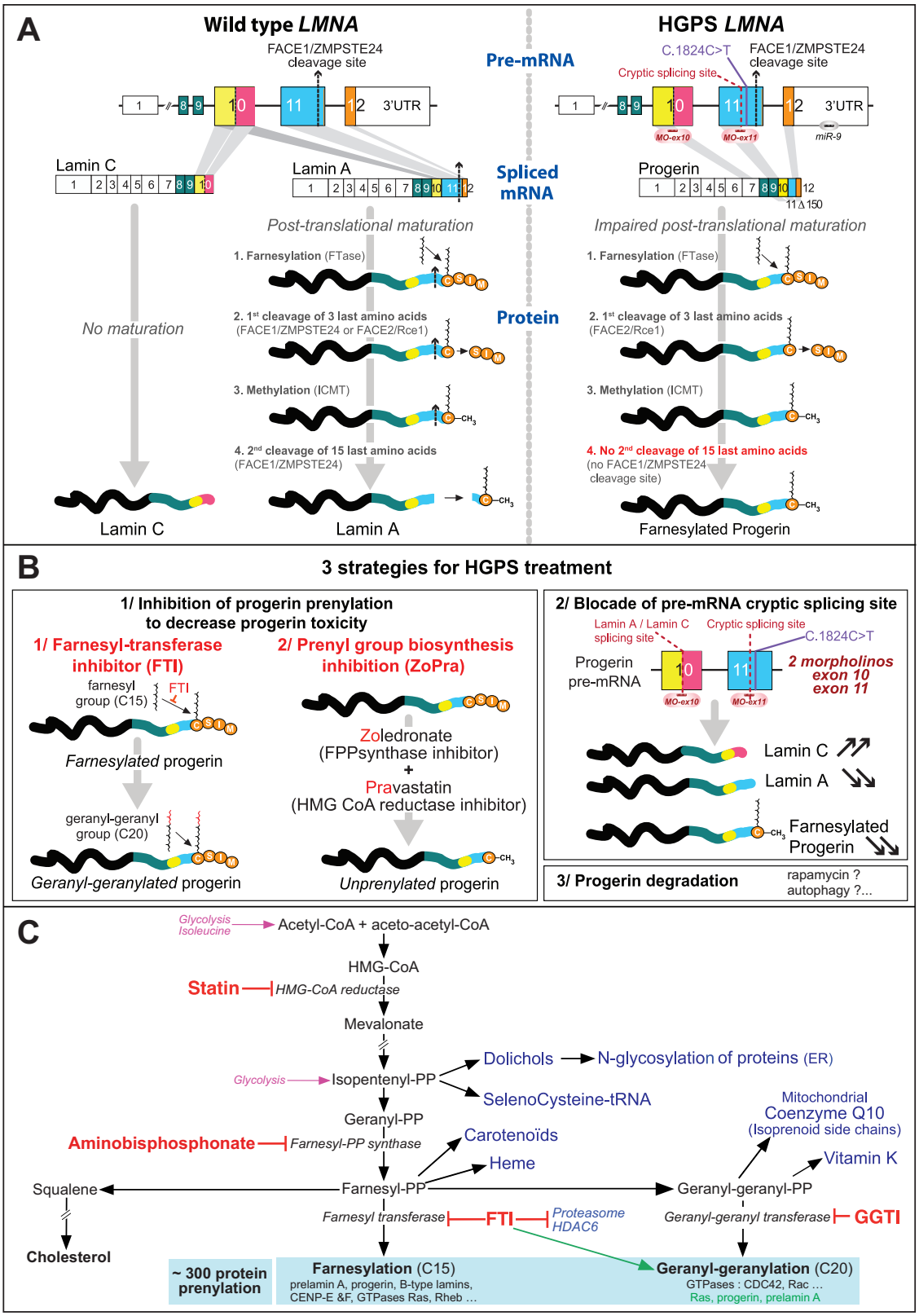


Fig. 5. Biosynthesis of A-type lamins, from pre-mRNA to proteins, in normal conditions and in HGPS. (A) Biosynthesis and maturation of lamin A, C and of progerin, (B) strategies designed for HGPS treatment. MO-ex10 and 11: morpholino oligonucleotides blocking pre-mRNA splicing site in exon 10 or 11. FTase, farnesyltransferase; FTI, farnesyltransferase inhibitor; FPP, farnesylpyrophosphate; HMG-CoA, hydroxy-methyl-glutaryl coenzyme A and (C) isoprenoid biosynthesis pathway. Three inhibitors, statin, aminobisphosphonate, farnesyltransferase inhibitor are approved for human therapeutic use. GGTI, inhibitor of type I geranyl-geranyl-transferase.

abnormalities in ATR-dependant DNA damage response [402]. FTI are known inhibitors of the histone deacetylase HDAC6 [403,404], whose main cytosolic targets are α-tubulin [405], tau [406] and several other MAP [407]. Therefore, FTI-induced nuclear shape abormalities could result from defects in both mitotic spindle microtubules and in centrosome organization and functions [408].

Another pharmacological strategy targeting progerin/prelamin A isoprenylation was designed and tested in HGPS cultured cells and in *Zmpste24*$^{-/-}$ mice model, that combines the inhibitors of two enzymes of the isoprenoid biosynthesis pathway: an aminobisphosphonate (zoledronate, Zo) for farnesyl-pyrophosphate synthase and a statin (pravastatin, Pra) for HMG-CoA reductase [85]. This synergistic ZoPra combination offers the advantage to block both farnesylation and geranyl-geranylation of progerin/prelamin A, avoiding the alternative isoprenylation by geranyl-geranyl transferase I induced by FTI, already reported for Ras [409,410]. The alternative geranyl-geranylation of prelamin A and of progerin, as well as its similar toxic effect as compared to prelamin A farnesylation, was demonstrated in mass spectrometry experiments, after FTI but not after ZoPra treatment [85]. It is also of note that Zoledronate activates macroautophagy in human PC3 prostate cancer cells [411].

Twelve patients received the ZoPra combination from 2008 to 2013 in the European clinical trial for progeria that was organized in Marseille's La Timone Children's Hospital (Clinicaltrials.gov identifier NCT00731016) [412]. Interestingly, it was demonstrated that a similar combination associating another statin (lovastatin) and another farnesylpyrophosphate synthase inhibitor (N6-isopentenyladenosine) blocks progerin and prelamin A isoprenylation in cultured cells [413].

An additional therapeutic trial is currently in progress in Boston associating the FTI lonafarnib, a statin (pravastatin) and an aminobisphosphonate (zoledronate) (Clinicaltrials.gov identifier NCT00916747). One has to notice that this triple-drug regimen induces more donut-shaped nuclei than the treatment by FTI alone [400]. Furthermore, no *in vivo* pre-clinical studies were performed to evaluate the efficacy and eventual toxicity of this triple drug combination, and their additive toxicities remain questionable.

4.2. Blocking progerin mRNA cryptic splicing site in vitro and in vivo

An elegant experiment demonstrated that a short (25-mer) antisense morpholino oligonucleotide can sterically blocks the cryptic splicing site of progerin pre-mRNA in exon 11, induces the concentration-dependant decrease in progerin mRNA and protein and reverses the phenotype of cultured cells from progeria patients [251]. A similar strategy was tested on *Zmpste24*$^{-/-}$ mice and on a progeria mouse model (*Lmna*$^{G609G/G609G}$) designed by our team in close collaboration with Carlos Lopez-Otin team in Oviedo (Spain). Phosphorodiamidate morpholinos, modified by covalent binding of octaguanidin dendrimere, in order to increase the uptake of oligos by tissues [414], were administered by IV injection and showed a clear correction of progeria phenotype as well as a significant lifespan extension extended life span in this progeria mouse model. Two oligonucleotides were associated, the first one blocking the exon 11 cryptic site and the other one targeting the exon 10 splicing site, directing the production of mRNAs encoding lamin C or lamin A, in order to favor splicing toward lamin C mRNA [415]. Together with the increasing evidence that the use of oligonucleotides for splicing redirection has growing therapeutic applications in animal models and in human diseases [416], this prompted our team, in close collaboration with Carlos López-Otín, to set up a clinical trial under design.

4.3. Progerin degradation through macroautophagy in cultured cells

The mammalian targets of rapamycin (mTOR) complexes are two key modulators of cell growth, aging and age-related diseases, integrating nutrient and hormonal signals, and are inhibited by rapamycin [417,418]. This macrolide antibiotic is approved by the U.S. Food and Drug Administration for several clinical applications, including immunosuppression [419,420]. Among a broad range of biological pathways, rapamycin extends life span from yeast to mammals [421], activates macroautophagy [422,423], a mechanism that could benefit to aging and the treatment of degenerative diseases [386].

In cultured HGPS fibroblasts, rapamycin reduces progeria phenotype cell symptoms and increases the clearance of progerin by inducing macroautophagy [424]. Rapamycin also improves the health status of skeletal and cardiac in *Lmna*$^{-/-}$ mice [425], whereas another mTOR inhibitor corrects the cardiomyopathy exhibited by *Lmna*$^{H222P/H222P}$ mice through the same mechanism [426]. Besides reducing progerin level, rapamycin restores BAF and LAP2α normal levels and distribution in HGPS cells [427]. In fibroblasts from centenarian subjects, FACE1/ZMPSTE24 downregulation results in the accumulation of farnesylated prelamin A, inducing the nuclear import of 53BP1, one of the DNA damage response actors. In these cells, rapamycin activates macroautophagy that probably degrades selectively farnesylated and carboxymethylated prelamin A but not full-length prelamin A [428]. In Werner syndrome cells, rapamycin restores also some of the consequences of DNA damage [429,430]. These data prompted to plan to increase the autophagic clearance of progerin through the use of mTOR complexes inhibitors, in the treatment of human progeria patients. The "4-drug trial", associating an FDA-approved mTOR inhibitor, an FTI, zoledronate and pravastatin has been announced [431].

Despite these encouraging data from *in vitro* experiments, caution should remain a topical issue when thinking to treatment of human patient with rapamycin. This drug shortens the life span of progeria *Lmna*^{G609G} mice, and reduces their body weight (Navarro et al., publication in preparation). FTI is also known to be an inhibitor of mTOR complexes in melanoma cells [432]. The first upstream activator of mTOR, the small GTPase Rheb, is the farnesylated protein [433]. The inhibition of Rheb farnesylation by FTI blocks mTOR activation [434] and its downstream activities among them autophagy [435]. Besides, HDAC6, another regulator of macroautophagy [436,437], is inhibited by FTI. Therefore, the macroautophagy activation by rapamycin could be strengthened by protein prenylation inhibitors.

4.4. Correction of endocrine, metabolic and inflammatory signaling pathways

The insulin and IGF1 signaling pathway, its several targets and their regulators, among them the transcription factors of FOXO family, the sirtuins [438], the Klotho hormone [439], the mTOR complexes (see above), represents the most conserved network controlling aging from nematodes to humans [440–442]. The insulin and IGF1 signaling pathway exhibits several cross-relationships with other aging-controlling pathways, such as proteostatis [443], oxidative stress and mitochondria [444,445], innate immunity and inflammatory responses through NFκB network [446], recently shown to control hypothalamic neuroendocrine activity [447]. The inhibition of NFκB signaling pathway slows down aging and recues lifespan in different progeroid mice models [353,354]. The administration of recombinant IGF1 to *Zmpste24*$^{-/-}$ mice, that present extremely high levels of growth hormone (GH) and a drastic reduction in plasma IGF1, restores the normal balance between IGF-1 and GH, delays the onset of many

progeroid features, and extends the lifespan of these progeroid animals [448]. Resveratrol, a natural activator of Sirtuin 1 [449], extends the lifespan of the same mice model [450]. Two INM transmembrane proteins could be involved in the modulation of the mTOR-IGF2-AKT signaling pathway, one master regulator of skeletal myogenesis [451]. NET39 blocks IGF2 transcription by inhibiting mTOR activity at the NE [452], whereas NET37, through its glycosidase activity, contributes to the maturation of pre-IGF2 in the secretory pathway and therefore to the activation of the pathway promoting myogenesis [453].

5. Recent and promising issues: iPSC, mouse models

5.1. Induced pluripotent stem cells (iPSC)

Derived from adult cell types, iPSC have enabled the creation of patient-specific stem cells, giving the opportunity to identify aberrant disease-associated pathways allowing disease modeling [454–456]. iPSC are used for *in vitro* development and testing of new therapeutic agents and regimens [457], for high-throughput drug screening [458,459] and imaging in industrial platforms [460]. iPSC have been derived from HGPS [461] and Werner syndrome cells [462]. Adenoviral vectors can be used to provide large genomic regions that correct *LMNA* mutations in HGPS iPSC and their derived mesenchymal stem cells [463]. Lamin A level influences the induction of iPSC, the higher lamin A level, the lower reprogramming efficiency of somatic cells into iPSC. Reduced levels of lamin A are associated with increased expression of pluripotent genes *Oct4* and *Nanog*, and of telomerase genes *Tert* and *Terc* [464]. As progeroid syndromes affected mainly cells from mesenchymal lineage, HGPS iPSC have been differentiated into several derivates from mesenchymal stem cells [465], cardiomyocytes [466] and adipocytes, whose differentiation is impaired through the inhibition by progerin of two transcription factors, PPARγ2 and C/EBPα active at late stage [467]. HGPS iPSC were also differentiated into neural cells [465], where miR-9 negatively controls lamin A and progerin expression [287]. An original strategy offers an unique opportunity to model late-onset human pathologies, such as neurodegenerative diseases. The expression of progerin has been induced in iPSC-derived fibroblasts sampled from Parkinson disease patients, after transfection with modified progerin RNAs produced by *in vitro* transcription. This strategy allows to analyze the progerin-related aging by dopaminergic neural cells [468].

5.2. Mouse models

Besides FACE1/ZMPSTE24, two other ER enzymes are involved in A- and B-type prelamin post-translational processing. *FACE2/Rce1*$^{-/-}$ mice died during late gestation or soon after birth [469], whereas ICMT-deficient mice exhibit a more severe phenotype [470].

Breding *Zmpste24*$^{-/-}$ mice with *Icmt*$^{hm/hm}$ mice, expressing hypomorphic alleles of ICMT, corrects the progeroid phenotype of *Zmpste24*$^{-/-}$ mice. The decrease in the amount of methylated prelamin A is associated with increased AKT-mTOR signaling pathway, but does not improve the nuclear shape. The last result adds to the evidence that nuclear shape correction alone has only little relevance in exploring progeria, and that its correction should not be an endpoint during clinical trials. However, decreasing ICMT activity might be a new way for treating prelamin A-associated progeroid disorders [471].

Finally, an elegant mice model highlights the hypothesis that supplementation by systemic factors or cell-based therapies (see Section 3.9) are of great promise for the treatment of progeroid syndromes, while opening new fields in aging-related cancer or degenerative diseases.

By the use of crossing strategies coupled to recombination, *Zmpste24* mosaic female mice were obtained. While they are null for the autosomal *Zmpste24* locus, they contain an extra copy of *Zmpste24* gene introduced in their X chromosome. Because of random X inactivation, contains, these mice contain in a similar proportion, two cells types: *Zmpste24*-deficient ones, accumulating farnesylated prelamin A; and *Zmpste24*-expressing cells in which prelamin A maturation is normal.

Mosaic mice develop normally and do not express progeria markers, thus evidencing that the development of progeroid phenotype is under the control of cell-extrinsic mechanisms. Furthermore, as farnesylated prelamin A accumulation prevents the initiation and the invasion of tumors triggered by known chemical carcinogens, this mice model strongly suggests that the prelamin A processing FACE1/ZMPSTE24 metalloprotease could be a new target for cancer therapy [472].

6. Conclusion

None of the known progeroid syndromes recapitulates global aging. All of them are characterized by segmental premature and accelerated aging, many of those involving defective DNA repair mechanisms and genomic integrity are associated to high predisposition to malignancies, while others such as HGPS, MAD, NGPS and CS, do not correlate with an increased risk of cancer.

Premature and accelerated aging diseases constitute a heterogeneous group of rare diseases, among which several entities have been nosologically defined. Most of them are genetically determined as being genetically inherited with at least one major gene being in cause. However, while progeria and other related defective prelamin A associated syndromes, as well as numerous defective DNA repair associated syndromes have been deeply characterized at the clinical and pathophysiological levels, other aging syndromes remain to be elucidated. Exploring and characterizing these disorders is of major interest for at least three main reasons. First in terms of human rights, considering that any individual must equally benefit from research programs in health, and have an equal access to care. Even patients affected with rare or exceedingly rare diseases, like progeria with probably no more than 200 living children worldwide, should be able to get scientists' attention in order to better characterize their disease at the clinical, genetic, and cellular levels and develop therapeutic approaches. Second, many examples have demonstrated that rare diseases may be essential for understanding more common diseases or physiological mechanisms. In this instance, progeria and related disorders represent a perfect paradigm. Mis-processed progerin, first identified in progeria, was demonstrated to be physiologically produced and progressively accumulated through the entire life, and further studies have shown its involvement as one of the mechanisms of natural aging. Third, translational research aiming at filling the gap between the identification of proofs of concept molecules and patient's inclusion in early phases of clinical trials may be considerably accelerated, taking advantage of specific access conditions for the use of therapeutic molecules. Repurposed and innovative molecules identified through research programs in rare diseases may benefit from orphan drug designations and accelerated procedures designed by regulation agencies. In that, it is remarkable to note that in a matter of five years after the 1st identification of the main mutation affecting progeria, two independent Phase II therapeutic trials have been designed and started, one in the US and the other in France, this latter using a combination of molecules having obtained the orphan drug designation and being developed toward obtaining EMA and FDA approval.

Each premature aging disease only partially recapitulates physiological aging. However, each of these clinically and pathophysiologically elucidated distinct entities is associated to a specific mechanism involved in normal aging. Many studies have demonstrated aging pathways' interactions. This is the case for DNA repair machinery whose defects directly induce premature aging diseases, but also play a key role in defective prelamin A associated syndromes, themselves involving p53 and its targets' activation. Development of molecules for rare aging diseases will help treat disorders usually associated to physiological aging as well as it could help patients affected with deficient p53 associated cancers.

In all, different research approaches have been used to study aging, but studying monogenic segmental progeroid syndromes is certainly one of the most promising. This will not only provide major insights and accelerate our understanding of senescence and aging, but should, in the end, change patients' life and, hopefully, be beneficial for children affected with these dramatic and devastating diseases that continue to kill at early age.

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