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Review

Human progeroid syndromes, aging and cancer: new genetic and epigenetic insights into old questions

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Abstract. Disorders in which individuals exhibit certain features of aging early in life are referred to as segmental progeroid syndromes. With the progress that has been made in understanding the etiologies of these conditions in the past decade, potential therapeutic options have begun to move from the realm of improbability to initial stages of testing. Among these syndromes, relevant advances have recently been made in Werner syndrome, one of several progeroid syndromes characterized by defective DNA helicases, and Hutchinson-Gilford progeria syndrome, which is characterized by aberrant processing of the nuclear envelope protein lamin A. Although best known for their causative roles in these illnesses, Werner protein and lamin A have also recently emerged as key players vulnerable to epigenetic changes that contribute to tumorigenesis and aging. These advances further demonstrate that understanding progeroid syndromes and introducing adequate treatments will not only prove beneficial to patients suffering from these dramatic diseases, but will also provide new mechanistic insights into cancer and normal aging processes.

Keywords. Accelerated aging, progeria, cancer, Bloom's syndrome, nuclear envelope, lamin A, metalloproteinase, Werner syndrome, DNA repair, farnesyl transferase inhibitor, ataxia telangiectasia.

Introduction

Aging is a multifactorial process that manifests itself variously across metazoans and individuals. Molecular events including oxidative stress, telomere attrition and a decline in DNA repair have been implicated in its development [1]. The modern discovery of human illnesses with symptoms resembling – but not fully recapitulating – accelerated aging occurred over a century ago. As they were later known, progeroid syndromes (literally, Greek for 'early old age,' *pro* + *geras*), including 'progeria of the child' (Hutchinson-Gilford progeria syndrome; HGPS) and 'progeria of the adult' (Werner syndrome; WS) were identified between 1886 and 1904 [2–4]. The genetic etiologies of these and related aging syndromes have become less enigmatic only within the past decade. These conditions are said to be segmental, a characteristic that has been defined in two ways. The first one opposes segmental progeroid syndromes, which affect multiple organ systems or tissues, to unimodal progeroid syndromes, which affect mainly one organ system or tissue (e.g. Alzheimer's disease) [5]. More recently, segmental aging syndromes have been redefined with respect to normal aging patterns, describing those pathologies in which only certain phenotypes of human aging manifest themselves precociously while other typical features are absent [5]. Nevertheless, we must emphasize that progeroid syndromes are pathological processes and in many aspects they differ significantly from the physiological process of aging. This fact has generated some debate about the implications of studies on these syndromes – in human or in animal models – for normal aging research [6–10]. However, despite clear caveats and limitations of these studies, a series of recent observations derived from ge-

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Table 1. Classification of human segmental progeroid syndromes.

Mutation class	Syndrome	Affected gene
Defective DNA helicases and DNA repair mechanisms	Werner syndrome (WS)	*WRN*
	Bloom syndrome (BS, BLS)	*BM/ BLM*
	Rothmund-Thomson syndrome (RTS)	*RECQL4*
	Cockayne syndrome (CS)	*CSA, CSB, XPB, XPD, XPG*
Defective lamin A production	Hutchinson-Gilford progeria syndrome (HGPS)	*LMNA*
	atypical Werner syndrome	*LMNA*
	restrictive dermopathy (RD)	*LMNA, ZMPSTE24*
	mandibuloacral dysplasia (MAD)	*LMNA, ZMPSTE24*
Other (e.g. defective kinases)	ataxia telangiectasia (AT)	*ATM*

netic and epigenetic approaches to progeroid syndromes have provided new mechanistic insights that may also be relevant to the normal aging process.

According to work by various groups, two major mechanisms account for the causes of most known progeroid syndromes: alterations in DNA repair systems and defective processing of the nuclear envelope protein lamin A (Table 1). Aberrant DNA repair proteins characterize the first class of segmental progeroid syndromes, which include WS, Bloom Syndrome (BS), Rothmund-Thomson syndrome (RTS) and Cockayne syndrome (CS), as well as xeroderma pigmentosum (XP) and trichothiodystrophy (TTD) [11–13]. The second class of segmental progeroid syndromes encompasses those with mutations in lamin A (*LMNA*; 1q21.2) or the metalloprotease critical to its post-translational processing, FACE-1/ZMPSTE24 (*FACE-1/ZMPSTE24*; 1p34). Defects in lamin A and FACE-1/ZMPSTE24 have been established as primary events leading to HGPS and atypical Werner syndrome, in addition to various laminopathies, including restrictive dermopathy (RD), mandibuloacral dysplasia (MAD), lipodystrophies, neuropathies, muscular dystrophies and dilated cardiomyopathies [14–24].

Although these two mechanisms have been under the most scrutiny in recent years, there may still be other major classes of disruptions common to progeroid syndromes to discover. To offer one important example, ataxia telangiectasia (AT) is a progeroid syndrome induced by defects in ATM kinase, which regulates downstream targets involved in aging mechanisms common to many species, including the insulin-like growth factor-1 receptor [25, 26]. While defective kinases have rarely been implicated as the primary and direct causes of progeroid syndromes, AT may be indicative of a third general mechanism by which segmental accelerated aging originates.

This review discusses the most recent advances in the different classes of progeroid syndromes in addition to the putative treatment strategies conceived for these conditions, including the use of farnesyl transferase inhibitors (FTIs) to ameliorate HGPS. The applicability of several mechanisms involved in pathological aging processes to the understanding of normal aging processes and cancer will also be examined. In particular, the newly evaluated influence of epigenetic changes to *WRN* and *LMNA* will be discussed in the context of its relevance to tumorigenesis in otherwise normal individuals. As our appreciation of the complexity of the genome, the epigenome and the proteome grows, we will hopefully be closer to harnessing technologies for the alleviation of these syndromes as well as some aspects of normal aging [27, 28].

Progeroid syndromes caused by defects in DNA helicases/DNA repair mechanisms

Werner syndrome

WS (OMIM 277700) patients experience normal development until puberty when they typically lack a growth spurt, resulting in short stature as adults. Further features include skin tightness and ulcerations, graying of hair, abnormal distribution of subcutaneous fat, bilateral cataracts, heart disease, calcification of cardiac valves and a high incidence of cancer. Most WS patients do not live past 50 years, and there are currently no treatments directed at the underlying basis of the disease [5].

Elucidated a decade ago, the genetic hallmark of WS is the recessive null mutation of a helicase encoded by *WRN* (*RECQL2*; 8p12-p11.2) [29]. These mutations truncate WRN before its nuclear localization signal (Fig. 1), and so the loss-of-function of Werner protein may be attributed jointly to its inability to localize to the nucleus and the rapid degradation of the aberrant product [29–31]. Loss of WRN significantly affects cells, in part by eliminating the only $3' \rightarrow 5'$ exonuclease domain possessed by a RecQ family member (Fig. 1) [29, 32, 33]. In addition to its unique exonuclease activity, WRN exhibits ATPase, helicase, DNA-binding and annealing activities and associates with several proteins, including Bloom helicase (BLM), another RecQ helicase associated with a progeroid disorder [34].

The premature aging and susceptibility to cancer associated with WS may be derived from the dichotomous roles

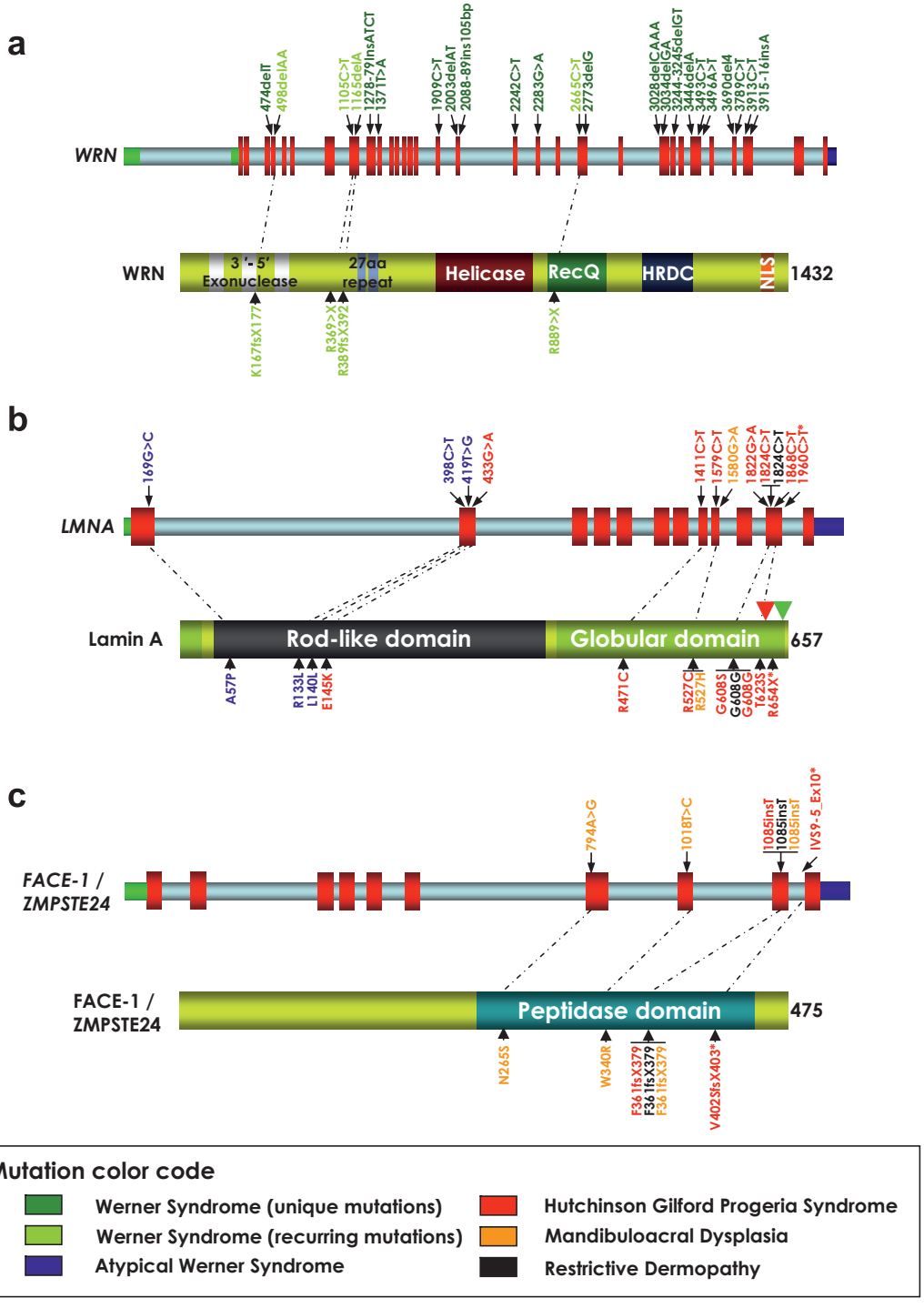

Figure 1. Mutations in *WRN*, *LMNA* and *FACE-1/ZMPSTE24* identified in patients with progeroid syndromes. For each gene/polypeptide duo, the genomic structure is represented above the protein structure. Green and dark-blue boxes indicate 5′ and 3′ untranslated regions, respectively. Light-blue rods represent introns; coding parts of exons are shown as red boxes. Numbers in nucleotide mutations correspond to the coding sequence, considering the A in ATG as nucleotide number 1. Colored segments in proteins depict distinct domains. (*a*) Diverse frameshift and nonsense mutations linked to Werner syndrome are indicated. Recurrent mutations (light green) are also indicated in the protein structure. (*b*) The first and second prelamin A proteolytic cleavage sites are represented by a green and a red triangle, respectively. (*c*) The peptidase domain is compromised by mutations that induce HGPS, RD and MAD. A unique compound mutation involving both *LMNA* and *FACE-1/ZMPSTE24* is indicated by asterisks. A homozygous *FACE-1/ZMPSTE24* splice acceptor mutation (IVS9-5_Ex10) causes a premature termination of the protease (V402SfsX403) which in combination with a heterozygous lamin A premature termination mutation (1960C > T; R654X), causes HGPS [116].

of Werner protein in telomere maintenance and optimization of DNA recombination and repair, respectively [34–37]. In the absence of WRN, cells exhibit chromosomal instability [38] and rapidly acquire stressed, senescent phenotypes characterized by rapid decreases in S phase cell populations [39] and a defective G2 phase decatenation checkpoint [40].

The phenotypic resemblance of WS to precocious aging has often begged the question of how closely WS is related to normal aging processes. Recent microarray studies have indicated that gene expression patterns are similar between WS cells and those from aged individuals after exposure to gamma and UV radiation, suggesting similarities in cellular microenvironments [41]. The diverse roles of WRN and the deleterious effects induced in its absence have prompted several groups to investigate whether allelic variants in WRN are associated with aging-related afflictions in the general population. However, these studies have revealed conflicting results. The inconsistent effects of these polymorphisms in diverse populations may be due, at least in part, to differences in the genetic background of the subjects [42–47].

In cancer, however, the role of *WRN* has been more firmly established. Very recently, Agrelo et al. [28] identified *WRN* as a tumor suppressor gene that is epigenetically inactivated in epithelial and mesenchymal tumors by hypermethylation of the CpG island present in its promoter (Fig. 2). *WRN* silencing apparently contributes to genomic instability and induces hypersensitivity to chemotherapy. This study has provided a means of understanding why patients with WS exhibit an increased susceptibility to neoplasms, and has additionally exposed an important tumorigenic factor that may place epigenetic changes affecting *WRN* among clinically relevant parameters of the near future.

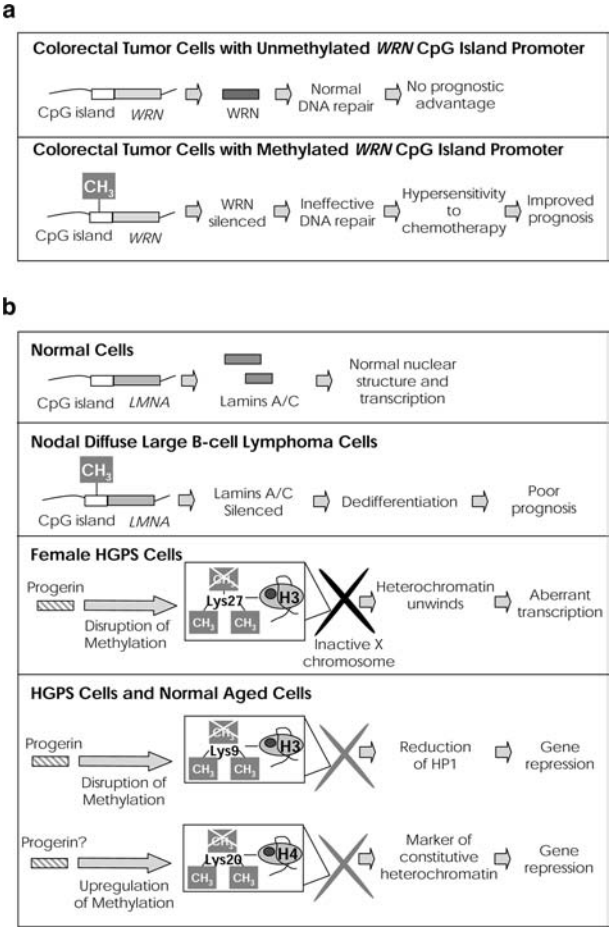

Figure 2. Epigenetic changes associated with *WRN* and *LMNA*. (*a*) When *WRN* is silenced by methylation at its CpG island promoter in colorectal tumors, DNA repair processes are impaired due to the absence of Werner protein. These cancerous cells become particularly susceptible to the effects of chemotherapy, resulting in markedly improved patient prognoses. (*b*) In normal cells, the CpG promoter of *LMNA* is unmethylated. This site is methylated in a significant proportion of leukemias and lymphomas, including nodal diffuse large B cell lymphoma. This epigenetic state is a clinically relevant parameter, as it is associated with poor prognoses. In female HGPS cells, progerin expression reduces trimethylation of Lys27 on histone 3, unraveling condensed heterochromatin on the inactive X chromosome. Besides this, HGPS cells and cells from aged individuals show decreased levels of trimethylated Lys9 on histone 3, reversible upon the inhibition of the aberrant splicing of progerin, as well as increased levels of methylation at Lys20 on histone 4. These altered patterns of histone modification result in the disruption of transcriptional regulation.

Bloom syndrome

In common with WRN, BLM is also a RecQ family helicase with unwinding and annealing capacities whose disruption results in a progeroid syndrome [48, 49]. Mutations in *BLM* (15q26.1) cause BS (BLS; OMIM 210900), a recessive disorder characterized by prenatal growth deficiency, hypo- or hyperpigmented skin, telangiectatic skin lesions, reduced fertility, variable immunodeficiency and predisposition to cancer [50]. The various mutations that have been documented in *BLM* often result either in mislocalization of the DNA helicase due to absence of the nuclear localization signal or alterations that compromise BLM helicase and/or ATPase domains.

In the absence of functional BLM, hyper-recombination cannot be suppressed, inducing about a 12-fold increase in sister chromatid exchanges and recombination between nonsister but homologous chromatids [51]. BLM essentially disrupts the formation of DNA-displacement loops (D-loops) at an early stage, preventing homologous recombination (HR) and sparing cells from the devastating effects of hyper-recombination during the repair of double-strand breaks, DNA synthesis and meiosis. BLM must be modulated *in vivo* to ensure that some degree of HR is present, while impeding indiscriminate recombination [52]. Discovering the identity of these regulat-

ing factors may be a positive step toward understanding mechanisms that ensure genetic stability and prevention of carcinogenesis induced by events such as chromosomal translocations.

Rothmund-Thomson syndrome

RTS (OMIM 268400) is a recessive disorder characterized by growth deficiency, graying of hair, juvenile cataracts, skin and skeletal abnormalities and particular susceptibility to osteosarcomas and skin cancers [53]. Treatments for RTS have typically been directed at alleviating discomfort associated with skin disorders [54, 55]. The lifespan is relatively normal when death linked to neoplasms is not considered. In about two-thirds of RTS patients, the molecular basis of this syndrome has been traced to the truncation of another of the five known human RecQ family members, *RECQL4* (8q24.3) [56, 57]. However, unlike WRN and BLM, purified RECQL4 has curiously been reported to lack detectable DNA helicase activity and to have a novel function in the initiation of DNA replication [58, 59]. In the absence of RECQL4, the ability of cells to recover from oxidative stress and DNA damage is severely impaired, as has recently been observed in fibroblasts from an RTS patient [60]. These fibroblasts exhibited significant difficulty in overcoming damage from 8-oxo-deoxyguanosine formation after treatment with hydrogen peroxide. Growth arrest and a significant decrease in DNA synthesis were indicative of proliferation failure, which may be linked to the dwarfism phenotype associated with this disorder. Oxidative damage is already considered a major contributing factor to aging and cancer, and polymorphisms in RecQL4 may exacerbate these conditions in the general population.

Cockayne syndrome, xeroderma pigmentosum, and trichothiodystrophy

CS, XP and TTD, together with some diseases characterized by combined symptoms of XP/CS and XP/TTD, integrate a family of disorders caused by alterations in genes involved with nucleotide excision repair (NER), a major system for DNA repair encompassing the subpathways of global genome repair (GGR) and transcription-coupled repair (TCR) [13, 61, 62]. GGR operates on damage throughout the genome via a multistep process triggered by the association of complexes (such as XPC and XPE) at the compromised site [63, 64]. TCR is a more specialized pathway, in which stalled RNA polymerase II signals lesions on the transcribed strand of transcriptionally active genes [65]. Most of the genes associated with these processes have been classified as members of the excision repair cross-complementing rodent repair deficiency (ERCC) family (Table 2).

CS type A is primarily caused by mutations in the gene encoding the group 8 excision-repair cross-complementing protein (ERCC8/CSA), a subunit of an E3 ubiquitin ligase complex [66]. CS type B, which accounts for about 80% of CS cases, is caused by mutations in ERCC6/CSB, a SWI/SNF-like DNA-dependent ATPase [67]. Clinically, CS is a rare autosomal recessive disorder with growth failure, cachectic appearance, severe neurological abnormalities and a mean age of death of 12.5 years. Remarkably, this progeroid syndrome is not associated with an increased risk of cancer [68]. CS shows some overlap with certain forms of XP, another NER disorder characterized by sunlight-induced pigmentation alterations in the skin, photophobia, occasional neurological alterations and multiple skin cancers. XP can be caused by mutations in any of several genes from XPA to XPG, which are involved in GGR, and the XP variant (DNA polymerase η), involved in replication of

Table 2. HUGO Nomenclature for genes associated with Cockayne syndrome, xeroderma pigmentosum and trichothiodystrophy.

Official symbol (HUGO)	Common alias(es)	Location	OMIM
DDB1	*DDBA, UV-DDB1, XAP1, XPCE, XPE, XPE-BF*	11q12-q13	600045
DDB2	none	11p12-p11	600811
ERCC2	*XPD, EM9, MGC102762, MGC126218, MGC126219, TTD*	19q13.3	126340
ERCC3	*XPB, BTF2, GTF2H, RAD25, TFIIH*	2q21	133510
ERCC4	*XPF, RAD1*	16p13.3-p13.11	133520
ERCC5	*XPG, RP11–484I6.5, ERCM2, UVDR, XPGC*	13q33	133530
ERCC6	*CSB, CKN2, COFS, RAD26*	10q11.23	609413
ERCC8	*CSA, CKN1*	5q12.1	609412
GTF2H5	*TTD, C6orf175, TFB5, TGF2H5, TTD-A, TTDA, bA120J8.2*	6q25.3	608780
XPA	*XP1, XPAC*	9q22.3	278700
XPC	*XP3, XPCC*	3p25	278720

damaged DNA [62]. TTD is characterized by sulfur-deficient brittle hair, skin photosensitivity, growth retardation, neurological abnormalities and a strongly reduced life expectancy, but not cancer predisposition. TTD is caused by a subset of mutations in XPB, XPD or TFB5, all of them components of the general transcription factor TFIIH [69].

Interestingly, patients with defects in GGR (XP patients) are vulnerable to extensive genetic insults and have a high risk of skin cancer, while those with alterations in TCR (CS, TTD) have progeroid syndromes without cancer predisposition [62]. Although GGR and TCR involve some overlapping factors, TCR becomes the primary repair pathway in terminally differentiated cells, which require an efficient system to maintain transcriptionally active genes when replication no longer poses the greatest threat to message fidelity [64]. Thus, it appears that the aging phenotype associated with CS results when factors critical to TCR – ERCC6 or ERCC8 – are impaired, which most drastically affect the fates of nondividing cells [70]. Mouse models of these syndromes have been developed which may be helpful in understanding NER pathways and their roles in aging and cancer [71, 72].

Ataxia telangiectasia

AT (OMIM 208900), also known as Louis-Bar syndrome, is an autosomal, recessive disorder with progeroid features, characterized by progressive cerebellar degeneration causing severe ataxia, dilated blood vessels (telangiectasia), immunological defects, increased risk of cancer and extreme sensitivity to ionizing radiation and double-strand break (DSB)-inducing agents [25, 73]. The identification of the ataxia-telangiectasia mutated (ATM) gene provided additional evidence for the role of genome maintenance deficiencies in cancer predisposition and accelerated aging [26]. ATM is a PI3K-like protein kinase which acts as a transducer of the DNA damage signal, placed at the top of the DSB response cascade. DSBs induce ATM autophosphorylation, which leads to activation of its serine/threonine kinase activity. Activated ATM phosphorylates more than a dozen substrates, enhancing or repressing their activities. Among ATM targets, p53 is of paramount importance in the regulation of DNA damage responses. ATM phosphorylates p53 on Ser15, contributing to its transcription factor activity. Moreover, ATM activates CHK2, which in turns phosphorylates p53 on Ser20, increasing its stability. ATM reinforces p53 stability through the direct phosphorylation of MDM2. Other ATM targets involved in the maintenance of genomic integrity include BRCA1, NBS1, FANCD2 and CDC25A. ATM is also linked to the maintenance of telomere integrity, one of the most studied molecular aspects of aging, apparently through phosphorylation of TRF1 [26]. The central role of ATM in orchestrating the cellular response to the deadliest forms of DNA damage and its connections with signaling pathways involved in cancer and aging highlights the usefulness of studying rare syndromes such as AT to obtain information that can lead to a better understanding of these processes.

Progeroid syndromes caused by defects in LMNA processing

Hutchinson-Gilford progeria syndrome

First described by Hutchinson in 1886 [2] and Gilford in 1904 [3], the incidence of this condition is estimated at one in four to eight million live births [74]. HGPS (OMIM 176670) is characterized by alopecia, atherosclerosis, prominent scalp veins, deficiencies in storage of adipose tissue and a high-pitched voice, with death at approximately 13 years from atherosclerosis of the coronary and cerebrovascular arteries [74]. Having been the progeroid syndrome with one of the most perplexing etiologies, HGPS has paradoxically become one of the illnesses in which the greatest progress has been made since the discovery of a recurring lamin A defect by two independent groups in 2003 [75, 76].

LMNA is a gene differentially expressed and spliced to produce the nuclear intermediate filament proteins lamins A and C, with lamin C being the shorter transcript [77]. Lamins share a general structure, which includes a short N-terminal domain, α helical rod domain and a C-terminal globular tail domain (Fig. 1), and serve many direct and indirect roles in the maintenance of nuclear structure, gene expression, chromatin organization, cell cycle regulation and apoptosis [78, 79]. Lamin A belongs to a class of proteins with a conserved C-terminal CaaX (a, aliphatic; X, one among S, M, C, A or Q) motif, which is a potential target for subsequent processing steps. To generate mature lamin A, prelamin A undergoes substantial post-translational modification of its CaaX motif, which includes farnesylation of the cysteine by farnesyltransferase, cleavage of the aaX amino acids most likely by the FACE-1/ZMPSTE24 metalloproteinase, carboxymethylation of the farnesylated cysteine by prenylcysteine carboxymethyltransferase and, finally, a second cleavage of the 15 terminal residues also by FACE-1/ZMPSTE24 (Fig. 3) [80–85]. Mutations in *LMNA* had been previously found in a variety of human syndromes, such as muscular dystrophies, lipodystrophies and neuropathies [24, 86–88].

In approximately 80% of HGPS cases, a *de novo* silent mutation (G608G: GGC$\rightarrow$GGT) in *LMNA* activates a cryptic donor splice site and eliminates 150 bp of exon 11. While the C-terminal CaaX motif required for farnesylation is retained, the signal directing the second cleavage by FACE-1/ZMPSTE24 is not, resulting in a truncated isoform of prelamin A called progerin which can-

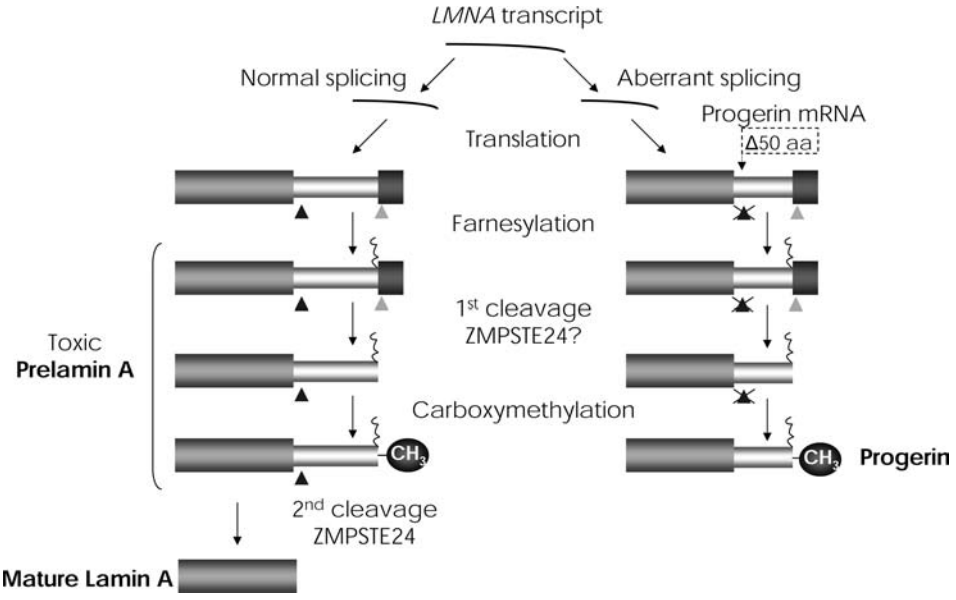

Figure 3. Lamin A and progerin processing. Transcription from a wild-type *LMNA* locus yields normal pre-RNA that is correctly spliced to produce prelamin A mRNA. In HGPS cells, a silent C to T transition at nt1284 introduces a cryptic splicing site, and the deletion of a 150-nt region from exon 11 yields the aberrant progerin mRNA. Prelamin A is a CaaX prenylated protein that undergoes three additional post-translational modifications after farnesylation: proteolytic removal of the C-terminal –aaX tripeptide (grey arrowhead indicates the cleavage site), carboxymethylation of the newly exposed C-terminal cysteine and, finally, a second proteolytic step (black arrowhead indicates the cleavage site), producing mature lamin A. Although FACE-1/ZMPSTE24 protease is necessary for the second proteolytic step, it is also most likely involved in the first step. Therefore, cells lacking FACE-1/ZMPSTE24 cannot complete lamin A maturation and accumulate toxic prelamin A. On the other hand, progerin lacks 50 amino acids including the cleavage site for the second proteolytic event, thus making its correct processing to produce mature lamin A impossible.

not be cleaved by this metalloprotease and consequently remains farnesylated [75, 76]. Remarkably, a mutation affecting the cleavage site by FACE-1/ZMPSTE24 (R644C) has been identified in an atypical form of this syndrome, although the effect of this mutation over the second proteolytic maturation event of prelamin A has not been experimentally explored [89]. Other HGPS mutations that have been described in *LMNA* include E145K, R471C, R527C, G608S, T623S and 1824C > T (Fig. 1) [76, 89–91].

The toxic accumulation of progerin at the nuclear envelope of HGPS patient cells has been regarded as the primary cause of nuclear shape abnormalities and chromatin stress leading to premature cell death [92]. Affected cells frequently exhibit nuclear herniations, or 'blebbing,' which have commonly been quantified to assess the extent of HGPS and HGPS-like phenotypes [93–96]. While the mechanism by which progerin induces nuclear lamina and envelope deformities is not fully understood, it has been suggested that the farnesyl group of progerin interacts preferentially with normally isoprenylated lamin B1, disrupting the normal distribution of lamins that contribute to nuclear structure [97]. An early theory to explain why these deformities result in premature cell death is that nuclei are more susceptible to mechanical stress and damage when lamin A is compromised, as has been observed in lamin A/C-deficient mouse embryo fibroblasts (MEFs) [98, 99]. In light of these data, it is particularly interesting that a mouse model created to express only lamin C is virtually normal, despite the absence of both lamin A and prelamin A [100]. These results underscore the importance of aberrant prelamin A – and not merely the insufficiency of normal protein – to the development of disease phenotypes. Interestingly, HGPS cells have been reported to be as resistant to acute mechanical stress as normal cells, suggesting that the nuclear fragility characteristic of lamin A/C deficient MEFs is not present in HGPS patient cells [101]. The altered arrangement of A- and B-type lamins in the nuclear lamina may contribute to differences in mechanosensitive gene expression and responses to mechanical stress.

However, cells from patients with other progeroid syndromes, including WS, exhibit similarly deformed nuclear phenotypes, perhaps indicating that a structural theory may be incomplete for explaining the source of nuclear fragility and damage [102]. Thus, it has been suggested that generalized DNA damage may be sufficient to induce the altered cellular traits for reasons that are currently not completely understood [103]. In addition to the theory of mechanical stress, aberrantly processed farnesylated prelamin A has been proposed to act in a dominant negative manner, affecting DNA damage response and repair. As mice deficient in *Zmpste24* extensively phenocopy HGPS in humans, this model has been useful in evaluat-

ing the adverse effects of farnesylated prelamin A [84, 85]. Although progerin and farnesylated prelamin A are derived differently (Fig. 3) and are molecularly distinct, they appear to affect cells similarly. *Zmpste24*-null MEFs and fibroblasts from HGPS patients are more sensitive to DNA-damaging agents and exhibit impaired recruitment of p53 binding protein 1 (53BP1), leading to defective repair and a delayed checkpoint response [104].

At the organismal level, advances have been made in understanding why a predisposition to cancer is not common to HGPS and why HGPS patients often succumb to atherosclerosis. In a *Zmpste24*-null mouse model, we have observed that increased activation of a p53-linked pathway is correlated with severity of the accelerated aging phenotype [105]. In accordance with the theory of antagonistic pleiotropy, the up-regulation of the p53 pathway and related molecular events would lead to cancer resistance at the expense of eliminating damaged cells less selectively, resulting in a significantly shortened lifespan marked by senescent cells and accelerated organismal aging [106]. In addition, HGPS patients are particularly susceptible to vascular disease, and a direct link between progerin expression and atherosclerosis was recently explored [107]. Skin biopsy sections from a subject with HGPS were probed with anti-LMNA G608G antibody, resulting in the observation that progerin accumulates primarily in the nuclei of vascular cells. The complementary work of Varga et al. [108] in a progerin-expressing mouse model of HGPS has demonstrated the loss of vascular smooth muscle cells, accumulation of acellular material and calcification of vessel walls over time. Although human progerin is expressed in a variety of these transgenic mice tissues, vascular smooth muscle cells are the most heavily affected, as these mice do not have the dramatically shortened lifespan of their human counterparts.

Atypical Werner syndrome

In addition to causing several laminopathies including HGPS, mutations in *LMNA* have been described in a subset of atypical cases of WS [109]. These defects include the mutation A57P (within the globular head domain) as well as the R133L and L140R changes (within the alpha-helical coiled-coil domain), which are upstream of the mutations described in HGPS (Fig. 1). These missense mutations are predicted to interfere with key protein-protein interaction domains and contribute to more severe symptoms than those found in WS patients with mutations in the *RECQL2* helicase gene, including earlier onset of disease and more pronounced aging-related phenotypes. Nevertheless, we must emphasize that the clinical designation of 'atypical' Werner syndrome for these patients with mutations in *LMNA* has raised some doubts and is still a matter of discussion [110, 111].

Restrictive dermopathy

Patients with RD (OMIM 275210) have been shown to carry either the same *de novo* G608G *LMNA* mutation responsible for HGPS or, more frequently, loss-of-function mutations in both alleles of *FACE-1/ZMPSTE24* (Fig. 1). These alterations lead to neonatal death from intrauterine growth retardation, facial deformities, tightly adherent skin and congenital contractures [15–17,112]. The reason why the same G608G mutation produces HGPS in some patients and RD in others remains to be addressed, but additional genetic or epigenetic factors are likely to contribute to the resulting clinical picture.

It is worth noting that whereas humans lacking FACE-1/ZMPSTE24 die perinatally, the deficiency of this metalloproteinase in mice does not preclude them from developing postnatally and well into adulthood, producing a milder phenotype which resembles human HGPS. This differential robustness of human and mice when coping with an alteration in the production of normal lamin A protein is not an isolated case, and has also been reported for diverse *LMNA* mutations [113–115], suggesting that although mouse models have proven to be an extremely informative resource in this field, caution should be taken when extrapolating conclusions obtained from them to the human context. Nevertheless, and although the differences between the human and the murine lamin A/FACE-1 system are clear, their similarities may also be extremely suggestive. Thus, very recently, it was reported that a patient with a homozygous *FACE-1/ZMPSTE24*-null mutation in combination with a heterozygous mutation in *LMNA* developed HGPS instead of RD, representing a significant improvement in phenotype [116]. Interestingly, this case reflects a human version of the *Zmpste24*$^{-/-}$ *Lmna*$^{+/-}$ mouse model, which exhibits a virtually normal phenotype, and highlights the beneficial effects of reducing the levels of toxic prelamin A [105, 117].

Mandibuloacral dysplasia

MAD is a rare condition characterized by skeletal abnormalities, features of metabolic syndrome and lipodystrophy. MAD caused by the homozygous R527H *LMNA* mutation is known as MAD with type A lipodystrophy (MADA; OMIM 248370) [18, 20]. In agreement with a disruptive effect of this mutation on the proteolytic processing of the lamin A precursor, cells from patients carrying the R527H *LMNA* mutation have been shown to accumulate prelamin A, developing chromatin disorganization as well as changes in nuclear architecture [118]. MAD with type B lipodystrophy (MADB; OMIM 608612) currently includes two patients with compound heterozygous mutations in *FACE-1/ZMPSTE24*. In both cases, one 1085insT allele, typical for RD patients and reported to cause a complete loss of function of the pro-

tein, is combined with one different hypomorphic allele (1018T > C, p. W340R; and 794A > G, p. N265S) [19, 21]. The partially active W340R or N265S mutant proteins could process a fraction of cellular prelamin A, sparing the patients the more severe RD phenotype.

Connections between lamin A, cancer and normal aging

The nuclear lamina is involved in key cellular functions such as maintenance of nuclear structure, chromatin organization, cell cycle regulation, DNA replication, transcription, differentiation and apoptosis. Consequently, alterations of lamins are of potential relevance to cancer development. Expression of lamins A/C is modified in many types of malignancies, with reduced levels often associated with increased aggressiveness [119]. The proposed link between decreased A-type lamin levels and malignancy is based on the fact that lamins A/C are normally expressed in differentiated cells, being involved in the chromatin reorganization and reprogramming necessary for terminal differentiation and growth arrest. A reduction of A-type lamins would facilitate an undifferentiated phenotype, more favorable for the aggressive progression of a tumor cell. In agreement with this, silencing of lamin A by promoter CpG island methylation has been identified as a major event with prognostic relevance in leukemias and lymphomas [120] (Fig. 2). Interestingly, this methylation could be susceptible to reversion by demethylating agents, such as 5-azacytidine, currently approved by the FDA for the treatment of the myelodysplastic syndrome.

Conversely, it was recently reported that progerin expression specifically affects the epigenetic control of facultative and constitutive heterochromatin. Scaffidi and Misteli [121, 122] have shown how cultured cells from both HGPS patients and normal old individuals display reduced levels of trimethylation of lysine 9 in histone H3 (H3K9me3). In an independent work, low levels of progerin have been shown to be sufficient to disrupt trimethylation of lysine 27 in histone H3 (H3K27me3), a marker of facultative chromatin in the inactive X chromosome, even in the absence of characteristic nuclear deformations [123]. Interestingly, the up-regulation of H4K20me3, a marker for constitutive heterochromatin, in both HGPS cells and old rats [123, 124], indicates that similar mechanisms may be at work between aging individuals and those with HGPS (Fig. 2).

Several additional lines of evidence support the hypothesis that molecular mechanisms responsible for progeroid syndromes are also involved in normal aging. Nuclear-structure alterations similar to those present in cultured cells from progeria patients have been reported in aging multicellular organisms [122, 125]. However, the most remarkable connection between HGPS and normal aging is the presence of progerin in cells from normal people. In the same work mentioned above, Scaffidi and Misteli [121, 122] reported that cell nuclei from old individuals show alterations comparable to those of HGPS patients, including increased DNA damage and morphological abnormalities as well as changes in histone modifications. The sporadic use of the cryptic splice site present in exon 11 of the lamin A gene, which gives rise to the synthesis of progerin, seems to be the cause of these age-related nuclear defects, as the inhibition of this splice site with specific morpholino oligonucleotides prevents their development [122]. Paradoxically, this evidence suggests that a product of *LMNA*, which has been hailed as the 'guardian of the soma' [126], can also reign in its destruction through the leaky expression of progerin.

Therapeutic strategies for progeroid syndromes

The nature of the molecular alterations causing the above discussed premature aging syndromes makes the development of effective therapies against these diseases very challenging. Consequently, patients with progeroid syndromes have access to severely limited treatments, most of which are aimed at palliating particular symptoms of the disease rather than combating its underlying basis. In the case of WS, for example, it is currently impractical to design a therapeutic strategy based on the restoration of the missing helicase activity. Since insulin resistance is a common manifestation of WS, many therapeutic efforts have been directed at re-establishing the glucose homeostasis in these patients. One such intervention concluded that pioglitazone was effective in ameliorating insulin resistance, improving ratios of fat distribution, and potentially retarding the progression of WS [127]. As a drug prescribed for the management of type 2 diabetes, the method of action of pioglitazone involves activation of peroxisome proliferator-activated receptor γ, increasing the triglyceride content of white adipose tissue and lowering the triglyceride content in liver and muscle [128].

Through a more recent alternative strategy, inhibition of mitogen-activated protein kinase (MAPK) p38 by treatment with SB203580 significantly increased the replicative lifespan and growth rate of WS cells [129]. Among the MAPK pathways critical to signal transduction in a wide range of biological contexts from development to apoptosis, MAPK p38 has been implicated in senescence induced by oxidative stress, Ras activation and telomere shortening [130]. Currently in phase 2 clinical trials for the management of rheumatoid arthritis, p38 inhibitors may become candidate therapeutic agents for WS in the same serendipitous manner that FTIs have come under scrutiny for HGPS.

Despite some hope in these strategies, the most life-threatening aspects of the majority of these progeroid syndromes is cancer. Unfortunately, specific anti-cancer

approaches for these patients are not available and standard clinical care is still the only option. In individuals with progeroid syndromes caused by mutations in DNA helicases and DNA repair mechanisms, prevention of potential DNA-damaging behaviors seems to be the most effective approach for delaying the onset of the symptoms (i.e. reducing direct exposure to sunlight in XP patients) [62].

As with the progeroid syndromes described previously, there has been no treatment available for HGPS patients. As in WS, limited attempts have been made to ameliorate symptoms of the disorder. One group proposed nutritional therapy and growth hormone treatments for a small group of patients. Although their growth velocity seemed to improve at first, response to therapy quickly ceased and progression of atherosclerotic disease could not be prevented [131]. However, in those progeroid syndromes caused by defects in *LMNA* processing, development of a series of specific therapeutic opportunities has begun and some of them have already been tested in mouse models [81].

Interestingly, reduction of H3K9me3 levels has been associated with both HGPS and normal aging [122]. This modification of histone 3, associated with active transcription and previously thought to be permanent, has recently been shown to be reversible by the action of JHDM3A, a histone demethylase [132]. If JHDM3A is shown to be involved in the reduction of H3K9me3 levels in HPGS and aged cells, a therapeutic approach based on inhibiting its demethylase activity could be explored. In connection with this, trichostatin A, an inhibitor of histone deacetylase has been shown to act synergistically with mevinoline, an inhibitor of the synthesis of precursors of the farnesyl group, to re-establish the correct chromatin organization in cells from HGPS patients [133].

As discussed above, the primary cause of the symptoms developed by HGPS patients seems to be the accumulation of farnesylated progerin. Accordingly, the therapeutic strategy which has attracted the greatest interest of the scientific community involved in progeria research is based on blocking protein farnesylation, taking advantage of the availability of FTIs. FTIs were developed as potential anti-cancer drugs aimed at preventing post-translational prenylation of Ras and thus interfering with the Ras-associated signaling cascades typical of these malignancies [134]. Despite some early disappointments and paradoxical behavior, FTIs are showing promise in preliminary studies to evaluate their effects against diverse malignancies and, in most cases, these drugs have been reasonably well tolerated with few adverse effects reported [135].

In the context of progeroid syndromes, FTIs have proven effective in reducing the incidence of nuclear deformities associated with HGPS. Several groups have demonstrated that FTIs reduce the accumulation of progerin and ameliorate some aberrant cellular phenotypes of HGPS, including nuclear deformities [93, 94, 96, 133]. However, the effects of FTIs on other phenotypic features characteristic of HGPS cells, such as altered histone modification patterns, compromised response to DNA damage or reduced cell growth remain to be analyzed. FTIs might also be effective against laminopathies with other mutations in *LMNA* by misdirecting mutant lamin A, or at least blocking its association with lamin B1, thus preventing dramatic changes in nuclear architecture [95].

Very recently, Fong et al. [136] reported that treatment of *Zmpste24*-null mice with a potent FTI (ABT-100) relieved some symptoms of premature aging and extended the lifespan. This preliminary evidence demonstrates that FTIs might be capable of alleviating symptoms of HGPS in human patients by reducing intracellular levels of toxic farnesylated prelamin A. However, as mice tend to be more robust than humans in tolerating the genetic insults that induce HGPS-like phenotypes (e.g. *Zmpste24*-null mice phenocopy HGPS, while humans with deleterious defects in *FACE-1/ZMPSTE24* often die from RD during gestation), caution must be exercised before placing expectations for the effectiveness of FTIs too high. These caveats aside, the initial data from this biological system demonstrate that the administration of FTIs to alleviate symptoms of pathological aging is more than a theory.

The farnesylation of aberrant lamin A variants can also be targeted by drugs acting on the synthetic pathway of farnesyl pyrophosphate (FPP), the molecule used as substrate by farnesyl transferase. Among the drugs able to block this pathway, the best known and most widely used are statins and bisphosphonates. Statins were developed as lipid-lowering agents, because they exhibit potent inhibition of 3-hydroxy-3-methylglutharyl-coenzyme A (HMG-CoA) reductase, therefore inhibiting the synthesis of cholesterol. Since HMG-CoA is also the precursor of isoprenoids, statins affect protein prenylation as well [137]. Nitrogen-containing bisphosphonates, which are widely used for the treatment of osteoporosis, act on the last step of the same synthetic pathway inhibiting FPP synthase [138]. Moreover, bisphosphonates could provide an additional benefit, ameliorating the bone alterations present in these patients. The main drawback of both statins and bisphosphonates as blockers of protein farnesylation is that the reduction of FPP levels inhibits sterol synthesis and geranylgeranylation of proteins before affecting protein farnesylation, because farnesyl transferase has a much higher affinity for FPP than the enzymes that use this compound in the other two pathways [139]. However, since there is extensive clinical experience with both statins and bisphosphonates, and these drugs show diverse clinical benefits without major negative effects after prolonged treatments, it is worth exploring their potential as anti-progeria treatments.

Reducing the levels of abnormally processed lamin A by reducing the total levels of the protein results in a dra-

matic reversal of the disease, at least in animal models [105, 117], suggesting potential therapeutic strategies for progerias caused by *LMNA* or *FACE-1/ZMPSTE24* mutations. Small interfering RNAs (siRNAs) designed to target lamin A mRNA have already been shown to effectively down-regulate lamin A production. However, to date no widespread delivery mechanism has been developed to allow siRNAs to reach the several tissues affected in these progeroid syndromes [140]. Finally, specific targeting of progerin pre-mRNA could lead to therapies aimed at attacking the primary cause of the disease. Modified oligonucleotides designed to specifically inhibit the truncated pre-mRNA encoding progerin have already been used *in vitro*. As this pre-mRNA form is only a small percentage of total *LMNA* mRNA in HGPS patients, smaller amounts of interfering oligonucleotides in the target cell could be enough to produce results [121].

Conclusions

More than 100 years ago, a group of dedicated physicians including J. Hutchinson, H. Gilford and C. Werner first described different human diseases of unknown etiology but devastating consequences. These diseases, collectively known as progeroid syndromes, have now attracted considerable interest because they recapitulate some aspects of normal aging. Over the last few years, our understanding of these diseases has considerably improved due to the application of powerful and innovative

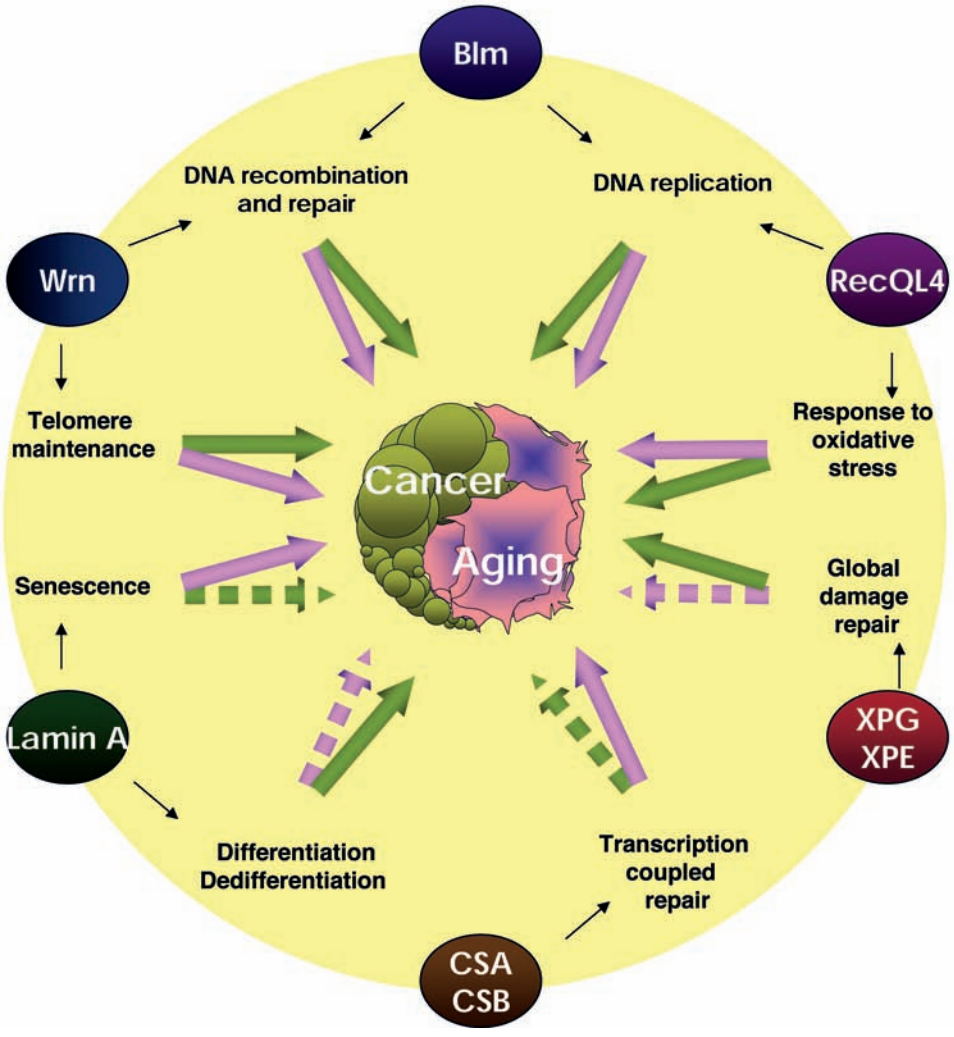

Figure 4. Connections of proteins mutated in progeroid syndromes with cancer and aging processes. Cancer and aging, represented by round, green tumor cells and enlarged flat senescent cells, respectively, are closely related processes. Epidemiologically, aging is the main risk factor for cancer development. However, cellular senescence may be the price we, as complex multicellular organisms, must pay to reduce malignant transformation. Ovals in the periphery represent proteins mutated in different progeroid syndromes. These proteins are connected by black arrows to the processes in which they are involved. Alterations in these proteins lead to disruption of such processes, which may contribute to the onset of tumoral and/or aging phenotypes indicated as green and pink arrows, respectively. A broken arrow indicates a relatively reduced contribution.

genetic and epigenetic approaches. These studies have allowed for the identification of the molecular basis of most of these syndromes and the generation of animal models which phenocopy the corresponding human diseases, thus opening new avenues for their exploration. As a direct consequence of these studies, the characterization of defects in lamin A processing, DNA helicases and ATM kinase causative of progeroid syndromes is already beginning to shed light on the mechanisms underlying these resonant conditions. Likewise, the observation of human progeroid syndromes under a molecular and mechanistic prism has shed light on new aspects of the connections between these disorders and diseases of much wider incidence, such as cancer (Fig. 4). Furthermore, very recent findings linking lamin-A-processing defects and nuclear architecture abnormalities to physiological aging have emphasized the idea that studies on segmental progeroid syndromes may be very helpful in formulating novel mechanistic hypotheses for the analysis of the normal human aging process.

Hopefully, this new knowledge derived from the intense study of progeroid syndromes over the past decade will lead to the introduction of molecularly targeted therapies for patients suffering from these dramatic diseases. As recent and stimulating examples, the rapid transition of Hutchinson-Gilford progeria from a condition of unknown cause to one with several conceivable treatment options and the discovery of the Werner protein as a key player in some cancers highlight the critical role of these syndromes in understanding both perplexing pathologies and fundamental biological processes.

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