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From the Rarest to the Most Common: Insights from Progeroid Syndromes into Skin Cancer and Aging

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Despite their rarity, diseases of premature aging, or "progeroid" syndromes, have provided important insights into basic mechanisms that may underlie cancer and normal aging. In this review, we highlight these recent developments in Hutchinson—Gilford progeria syndrome (HGPS), Werner syndrome, Bloom syndrome, Cockayne syndrome, trichothiodystrophy, ataxia-telangiectasia, Rothmund–Thomson syndrome, and xeroderma pigmentosum. Though they are caused by different mutations in various genes and often result in quite disparate phenotypes, deciphering the molecular bases of these conditions has served to highlight their underlying basic similarities. Studies of progeroid syndromes, particularly HGPS, the most dramatic form of premature aging, have contributed to our knowledge of fundamental processes of importance to skin biology, including DNA transcription, replication, and repair, genome instability, cellular senescence, and stem-cell differentiation.

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INTRODUCTION

> *''We ought not to set them aside with idle thoughts or idle words about 'curiosities' or 'chances.' Not one of them is without meaning; not one that might not become the beginning of excellent knowledge, if only we could answer the question - why is it rare or being rare, why did it in this instance happen?''*
>
> James Paget (1882)

That much may be gleaned from the study of rare diseases is not a novel concept, as Sir James Paget so aptly pronounced in 1882. With the recent explosion in knowledge arising from the study of rare syndromes associated with premature aging, especially the most dramatic form of human premature aging, Hutchinson–Gilford progeria syndrome (HGPS), this statement has taken on a new relevance. In 1886, a mere 4 years following Paget's statement, Jonathan Hutchinson first described progeria, though it would be another 117 years before the genetic mutation that causes HGPS was identified. This discovery opened the floodgates for progeria research, and within just 4 years, the first-ever clinical trial for HGPS had begun, an unprecedented timeframe for such a rare disease.

Similar advances in our understanding of other progeroid syndromes, including Werner syndrome (WS), Bloom syndrome (BS), Cockayne syndrome (CS), trichothiodystrophy (TTD), ataxia-telangiectasia (AT), Rothmund–Thomson syndrome (RTS), and xeroderma pigmentosum (XP) (Table S1), have been made recently. The knowledge gained from the study of these conditions has provided insights into fundamental basic processes such as DNA transcription, replication, and repair, genome instability, nuclear architecture, chromatin organization, cellular senescence, and stem-cell differentiation. These processes, although distinct, are all interconnected and of critical importance not only for normal skin homeostasis, but also as regulators of skin changes with age and cancerous transformation. Given its easy accessibility, the skin is an ideal model organ in which to study aging and cancer, and many of the fundamental findings in each have been made by studying skin biopsies and fibroblast cultures. Although much has been described regarding the effects of age on the skin and benign and malignant skin growths, many questions remain as to the exact causes and mechanisms behind these changes, as well as how these changes can be controlled, prevented, or even reversed. With Paget's vision in mind, in this review we have attempted to highlight the latest findings relating to these rare conditions, with a particular focus on HGPS, and how these recent advances might have relevance to answering these questions.

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Abbreviations: AT, ataxia-telangiectasia; ATM, AT mutated; BS, Bloom syndrome; CS, Cockayne syndrome; GG-NER, global genome nucleotide excision repair; HGPS, Hutchinson–Gilford progeria syndrome; RTS, Rothmund–Thomson syndrome; TC-NER, transcription-coupled nucleotide excision repair; TTD, trichothiodystrophy; WS, Werner syndrome; XP, xeroderma pigmentosum

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PROVIDING STRUCTURE AND ORGANIZATION: NUCLEAR ARCHITECTURE AND GENOME INTEGRITY

As the command center of the cell, it is not surprising that the nucleus is the focus of global alterations that occur in normal skin aging and cancer. As discussed here, several of the nuclear abnormalities encountered in HGPS are relevant to all individuals. On the phenotypic level, children with HGPS look normal at birth. The first signs of the disease are typically skin changes, including either hyper- or hypopigmented patches or nonspecific scleroderma-tous changes that appear from 6 to 18 months of age (Figure 1). HGPS patients then display progressively numerous other manifestations reminiscent of normal aging such as alopecia, skin wrinkling, osteopenia, and atherosclerosis (Figure 1 and Table S1) (Merideth *et al.*, 2008). Death frequently occurs in early adolescence due to heart attacks or strokes (Capell *et al.*, 2007). On a cellular level, HGPS nuclei take on a progressively blebbed and lobulated appearance with age (Goldman *et al.*, 2004). These alterations portend the changes taking place inside the nucleus, represented by mislocalized nuclear envelope proteins, disrupted heterochromatin organization, and greatly misregulated gene expression (Capell and Collins, 2006).

The disease, dramatic in phenotype on both the organismal and cellular levels, was discovered to be due to a single base change (1824C>T) in the *LMNA* gene that does not even change the encoded amino acid (G608G) (De Sandre-Giovannoli *et al.*, 2003; Eriksson *et al.*, 2003). Through activation of a cryptic splice site, this mutation produces a mutant version of the lamin A protein, a component of the dynamic scaffolding network of the nucleus, the nuclear lamina, which lies just inside the inner nuclear membrane. This mutant lamin A precursor (prelamin A), termed ''progerin'', contains a 50 amino acid internal deletion that results in its permanent modification by a 15-carbon lipid farnesyl group added post-translationally by the enzyme farnesyltransferase (Eriksson *et al.*, 2003; Dechat *et al.*, 2007). It is believed that this lipid chain serves as a toxic anchor, binding progerin to the nuclear envelope and preventing its insertion into the lamina; thus acting in a dominant-negative manner to lead to all of the downstream nuclear defects (Figure 2) (Scaffidi and Misteli, 2005), and ultimately the HGPS clinical phenotype. Several studies in both HGPS skin fibroblasts (Capell *et al.*, 2005; Glynn and Glover, 2005; Mallampalli *et al.*, 2005; Toth *et al.*, 2005) and mouse models (Fong *et al.*, 2006; Yang *et al.*, 2006; Capell *et al.*, 2008) have shown that inhibiting this farnesylation step pharmacologically by use of a class of anti-cancer drugs known as farnesyltransferase inhibitors can prevent disease phenotypes. Furthermore, that the HGPS phenotype might even be reversible has been suggested by two studies, one where an farnesyltransferase inhibitor reversed the cardiovascular phenotype of a transgenic mouse model (Capell *et al.*, 2008), and another where suppressing the expression of progerin using an inducible transgenic system led to the reversal of a severe skin phenotype that involved

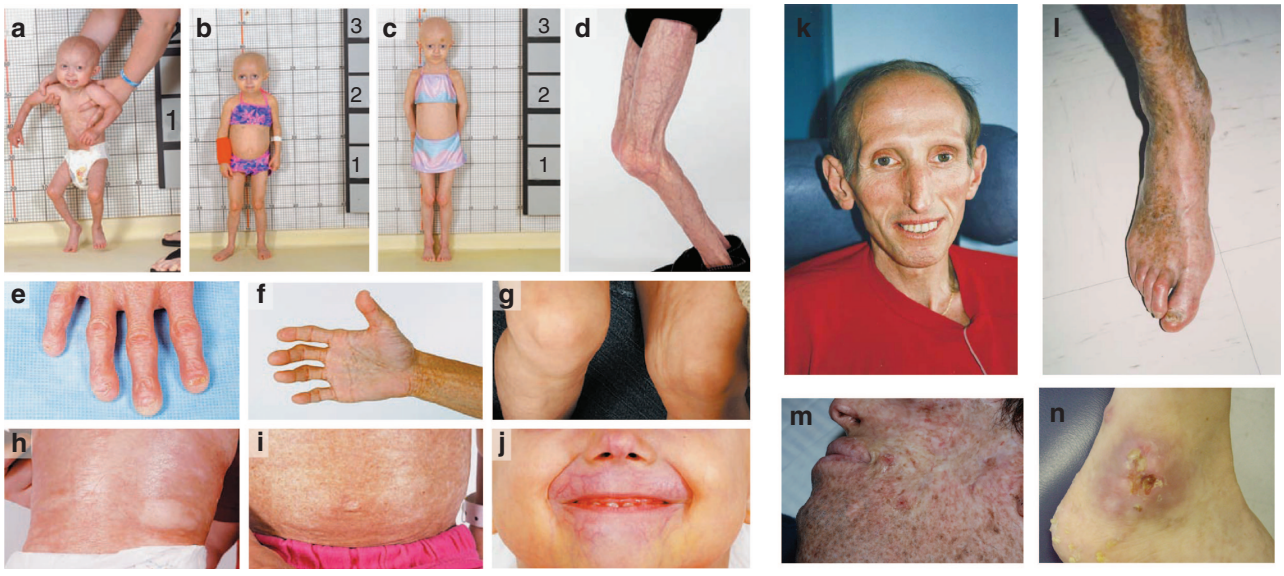

Figure 1. Clinical features of progeroid syndromes. (**a–j**) Hutchinson—Gilford progeria syndrome (Merideth *et al.*, 2008) (Copyright *2008 Massachusetts Medical Society. All rights reserved.*). (**a**) Shows short stature at 21 months of age. (**b**) Shows alopecia at 4 years of age and an even further progression of premature aging in Panel **c** at age 7. (**d**) Shows prominent veins, knee joints, and contractures under maximal passive extension. (**e**) Shows tufting of fingers. (**f**) Shows phalangeal joint contractures. (**g**) Shows dimpling in the left leg. (**h**) Shows areas of hypopigmented skin. (**i**) Shows abdominal outpouching and reticulated hyperpigmented skin interspersed with hypopigmented skin. (**j**) Shows circumoral cyanosis. (**k**, **l**) Werner syndrome (Adoue, 1997) (Copyright *1997 Massachusetts Medical Society. All rights reserved.*). (**k**) Shows a 37-year-old man the characteristic beak-like appearance of Werner's syndrome. Further examination of this patient demonstrated scleroderma-like skin changes and sensory neuropathy of the lower limbs (Panel **l**). (**m**) Shows the face of a teenager with XP due to a mutated *XPC*. Mottled pigmentation and scars from multiple surgeries to remove skin cancers are evident. (**n**) Shows a longstanding leg ulcer on the ankle of an 8-year-old boy with Rothmund—Thomson syndrome. Patients gave written consent for the publication of clinical photographs.

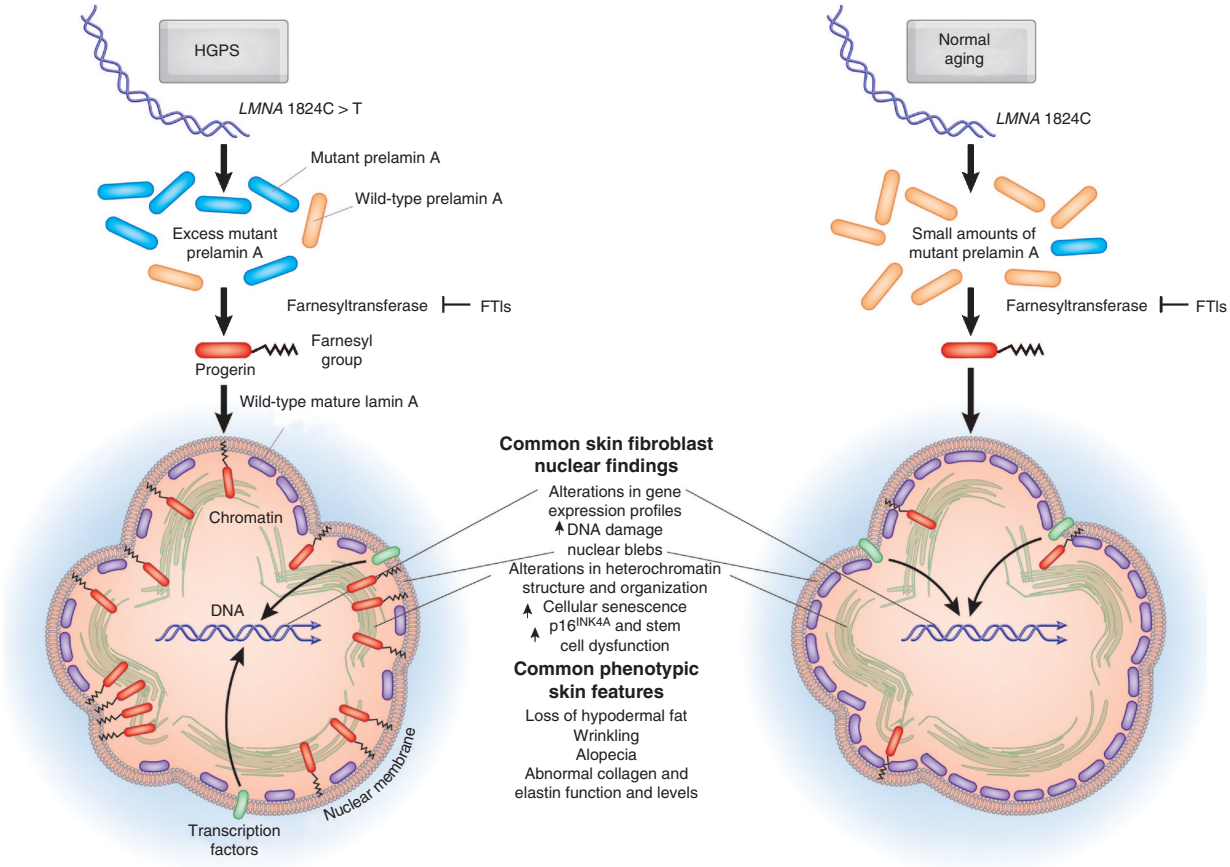

Figure 2. Progeria and normal aging: common nuclear and phenotypic skin findings. Though normal cells do not possess the typical HGPS *LMNA* 1824C>T mutation, leaky activation of a cryptic splice donor site results in the production of small amounts of the mutant prelamin A isoform (represented in blue) that is missing a final processing cleavage site and is thus permanently modified by a 15-carbon lipid farnesyl group, producing increasing levels of progerin (red) with age. This mutant version of prelamin A, which is made in abundance in HGPS, leads to the nuclear abnormalities that are characteristic of HGPS (left side) and that are also seen in nuclei from aged individuals (right side). It should be noted that due to space constraints, the relative amounts of mutant prelamin A, or progerin, is not precisely represented by this schematic representation. Current data suggests that expression levels in HGPS are greater than 160-fold higher than those seen in unaffected individuals (Rodriguez *et al.*, 2009). These nuclear defects include alterations in normal gene expression, nuclear blebbing, disorganization of the underlying heterochromatin, stem cell dysfunction, and increased DNA damage, cellular senescence, and $p16^{INK4A}$ levels. At the organismal level, these nuclear alterations may play a role in the skin findings that are common to both HGPS and normal aging such as wrinkling, alopecia, loss of hypodermal fat, and alterations in the levels and function of collagen and elastin.

fibrosis, loss of subdermal adipocytes, and structural defects in the hair follicles and sebaceous glands (Sagelius *et al.*, 2008). These results have served as the impetus for an ongoing clinical trial of the efficacy of the farnesyltransferase inhibitor lonafarnib for HGPS (Kieran *et al.*, 2007).

Is this potentially important beyond HGPS? Despite carrying a normal *LMNA* sequence, it has now been shown that all individuals make small amounts of the mutant progerin protein due to leaky activation of the aforementioned cryptic splice site (Figure 2) (Scaffidi and Misteli, 2006; Cao *et al.*, 2007; Rodriguez *et al.*, 2009). Strikingly, progerin builds up in human skin with age, localizing mainly in fibroblasts of the papillary dermis in young adults and then proceeding to spread to the deep reticular dermis and to a few terminally differentiated keratinocytes in the elderly (McClintock *et al.*, 2007). Progerin has no predilection for sun-exposed areas, even appearing in newborn foreskin. Furthermore, beyond just the presence of progerin, skin samples from aged individuals also display nuclear defects similar to those of HGPS patients. The presence of progerin in aged skin led to similar changes in nuclear morphology, histone modifications, upregulation of p53 target genes, as well as increased levels of unrepaired DNA damage (Figure 2). Remarkably, silencing the production of progerin by using an antisense oligonucleotide reversed all of these nuclear defects associated with aging, thus implicating this mutant lamin A in physiological and skin aging (Scaffidi and Misteli, 2006).

These data are all the more compelling considering the growing body of evidence in both model organisms and humans suggesting the conserved role of nuclear architecture, particularly nuclear lamins (Shimi *et al.*, 2008), in organizing and regulating chromatin and the effects that this organization has on gene expression and cellular senescence (Oberdoerffer and Sinclair, 2007; Shimi *et al.*, 2008), as well as in

DNA repair (Dimitrova *et al.*, 2008) and skin cancers like melanoma (Richards and Medrano, 2009). For instance, the same changes in nuclear shape and loss of peripheral heterochromatin organization that are seen in HGPS are also observed in the normal aging of *Caenorhabditis elegans* (Haithcock *et al.*, 2005). Furthermore, other diseases due to mutations in *LMNA* and presenting with premature aging phenotypes, mandibuloacral dysplasia, and restrictive dermopathy (Table S1), also display dysmorphic nuclear shape and chromatin alterations due to an accumulation of the lamin A precursor, prelamin A (Novelli *et al.*, 2002; Agarwal *et al.*, 2003; Navarro *et al.*, 2004, 2005; Filesi *et al.*, 2005; Moulson *et al.*, 2005). Similarly, WS, due to mutations in *WRN* (encoding WRN) and ataxia-telangiectasia (AT), caused by mutations in the AT-mutated (*ATM*) gene, both of which display features of premature aging, are also characterized by defective nuclear architecture, chromatin changes, and genomic instability (Adelfalk *et al.*, 2005; Grattarola *et al.*, 2006) (Table S1). Underscoring the importance of these relationships, there have been numerous cases of an atypical (and more severe form) of Werner syndrome associated with mutations in *LMNA* as well (Chen *et al.*, 2003). As discussed further below, both ATM and WRN appear to play a role in telomere maintenance and the relationship of telomeres with the nuclear matrix (Smilenov *et al.*, 1997; Machwe *et al.*, 2004), and given the association between telomere attrition and cellular senescence (Allsopp *et al.*, 1992) and aging (Tomas-Loba *et al.*, 2008), the implications for the roles of these various genes and their resulting proteins with regard to aging and cancer is clear.

DNA DAMAGE AND REPAIR GONE AWRY

It is estimated that each cell undergoes thousands of strand breaks and various DNA lesions each day (Lindahl, 1993; Garinis *et al.*, 2008). Even though sophisticated mechanisms of genome maintenance and repair have evolved, aging is associated with significant increases in DNA mutations (Vijg, 2000), chromosome losses (Rehen *et al.*, 2005), and DNA oxidation (Hamilton *et al.*, 2001) over time. In addition to intrinsic age-related skin changes, Ultraviolet-A generates reactive oxygen species that affect lipid peroxidation and generate DNA double-strand breaks. Likewise, within minutes of exposure, ultraviolet-B causes thymidine dimer formation that leads to further DNA damage and mutations. This oxidative stress may have many consequences for dermatological conditions (Bickers and Athar, 2006), and repair of this damage is essential to avoid aging and cancerous transformation. The progeroid syndromes, though displaying a variety of phenotypic manifestations and differing propensities towards precocious aging or malignant disease, all exhibit some evidence of increased DNA damage or defective repair, changes clearly seen in the human skin with age (Moriwaki *et al.*, 1996). The study of each condition has highlighted various aspects of the DNA damage and repair process.

The first evidence of DNA damage in HGPS occurred when it was shown that HGPS dermal fibroblasts showed an age-dependent reduced growth and lifespan in culture as well as a delayed and hypersensitive response to heat stress (Liu *et al.*, 2005; Paradisi *et al.*, 2005). It was later demonstrated that HGPS fibroblasts, as well as fibroblasts from mice lacking the lamin A processing enzyme, Zmpste24, and thus only producing unprocessed and permanently farnesylated lamin A, show increased DNA damage and chromosomal aberrations and the mice are more sensitive to DNA-damaging agents. Further, the recruitment of 53BP1 and Rad51, both involved in DNA double-strand break repair, to sites of DNA damage was defective in both the HGPS patient and mouse model fibroblasts, resulting in a delayed checkpoint response and impaired DNA repair (Liu *et al.*, 2005). As both mandibuloacral dysplasia and restrictive dermopathy also show an accumulation of prelamin A and can arise due to mutations in *ZMPSTE24*, future research should consider the role DNA damage might play in their phenotypic manifestations.

Relative to HGPS, in WS, AT, xeroderma pigmentosum (XP), Bloom syndrome (BS), TTD, RTS, and Cockayne syndrome (CS), the genotype–phenotype correlations between defective DNA repair and premature aging and cancer susceptibility are more clearly established. WS is characterized by numerous age-related symptoms such as atherosclerosis, osteoporosis, type II diabetes mellitus, and an increased susceptibility to cancer, especially those of mesenchymal origin (Figure 1 and Table S1) (Muftuoglu *et al.*, 2008). WS patients have an increased incidence of melanoma, particularly acral lentiginous melanoma of mucosal surfaces, as well as of skin ulcers on the ankles and elbows (Goto *et al.*, 1996). As one of five RecQ helicase proteins, WRN (*RECQL3*) is a 180-kDa tumor suppressor with ATPase, helicase, exonuclease, and single-stranded DNA annealing activities (Oshima *et al.*, 1996; Yu *et al.*, 1996). It is involved in DNA repair, replication initiation, establishment of replication foci, resolution of stalled replication forks, and recombination (Kusumoto *et al.*, 2007). Most *WRN* mutations result in the production of a truncated version of WRN that lacks its nuclear localization signal and thus cannot find its way to the nucleus to perform its usual functions (Matsumoto *et al.*, 1997). WS cells have telomere shortening, chromosomal rearrangements, increased susceptibility to malignant transformation, and frequent telomere fusions. In all individuals, WRN is involved in the processing of telomeric DNA and subsequent activation of DNA damage responses (Eller *et al.*, 2006), thus it is not surprising that WRN is epigenetically inactivated in numerous human cancers and it is required for proper telomere maintenance (Agrelo *et al.*, 2006).

Two of the other RecQ helicases are the mutated proteins of RTS (encoded by *RECQL4*) and BS (BLM, encoded by *RECQL2* or *BLM*). BS is characterized by a dramatically increased susceptibility to all types of cancers, UV hypersensitivity, hyper- and hypopigmented

skin changes, decreased subcutaneous fat, immune deficiency, anemia, increased susceptibility to type II diabetes mellitus, severe growth retardation, and death by the age of 30 usually due to cancer (Table S1) (Ellis *et al.*, 1995; Hanada and Hickson, 2007; Ouyang *et al.*, 2008). BLM colocalizes and appears to work in concert with WRN during DNA repair. BLM is necessary for normal double-stranded break repair (Langland *et al.*, 2002). It was very recently discovered that BLM is stabilized by the protein RMI2, and that the two proteins form a complex to suppress sister-chromatid exchange (Singh *et al.*, 2008; Xu *et al.*, 2008). In the absence of this properly functioning complex, homologous recombination events occur at a ten-fold increased level. This hyper-recombination and defective DNA repair leads to a 150- to 300-fold increased risk of cancer. Underscoring the conserved and central role of these proteins in genome stability and aging, yeast lacking the WRN and BLM homolog, SGS1, also undergo premature age-related changes, including cell-cycle arrest defects, more frequent chromosomal rearrangements, and an age-related increase in DNA mutations (Madia *et al.*, 2008).

Clinically, RTS is characterized by poikiloderma, sparse hair, small stature, skeletal abnormalities, cataracts, and an increased risk of cancer (Figure 1 and Table S1) (Jin *et al.*, 2008). Compared with WRN and BLM, less is known about RecQ4, the protein mutated in RTS, though it shares structural similarity to WRN and BLM, as well as very recently demonstrated helicase activity (Xu and Liu, 2009). The end result is also similar as RTS cells exhibit marked genomic instability and chromosomal rearrangements. Studies in both RTS fibroblasts as well as in model organisms have demonstrated that RecQ4 is necessary for initiating DNA replication and proliferation (Sangrithi *et al.*, 2005; Wu *et al.*, 2008), and is also involved in the repair of DNA damage induced by UV irradiation (Fan and Luo, 2008). It is speculated that the increased sensitivity to oxidant damage seen in RTS induces premature senescence and is also responsible for the increased susceptibility to osteosarcomas and cutaneous epithelial neoplasms such as squamous and basal cell carcinomas (Stinco *et al.*, 2008).

CS, characterized by neurological abnormalities as well as atrophic skin, loss of subcutaneous fat, sparse hair, and increased sun sensitivity, is due to mutations in *CSA* or *CSB*, which encode CSA and CSB, components of the transcription-coupled nucleotide excision repair system (TC-NER) (Table S1) (Stevnsner *et al.*, 2008). Approximately 80% of CS cases are due to mutations in CSB (Mallery *et al.*, 1998). TC-NER, which along with global genome nucleotide excision repair (GG-NER), make up the two subpathways of nucleotide excision repair, recognizes damage marked by stalled RNA polymerase II complexes. TC-NER then removes the damaged or erroneous oligonucleotide and allows RNA synthesis to resume (Puzianowska-Kuznicka and Kuznicki, 2005). During the unwinding step of TC-NER, CSA, and CSB work in concert with TFIIH, a transcription factor protein complex consisting of 10 subunits required for both NER and transcription. Upon exposure to UV irradiation, TFIIH and CSB allow TC-NER to occur by bringing about the necessary alterations in chromatin structure at the RNA polymerase II stall site and the transport of CSA to the nuclear matrix (Saijo *et al.*, 2007). Beyond these critical functions, CSB also plays a key role in mediating the hypoxic response pathway (Filippi *et al.*, 2008) as well as in chromatin structure (Stevnsner *et al.*, 2008).

Further highlighting the overlapping basic mechanisms and phenotypes of these conditions, mutations in some components of TFIIH can lead to TTD (Stefanini *et al.*, 1993; Vermeulen *et al.*, 2000; Giglia-Mari *et al.*, 2004). TTD is characterized by sulfur and cystine-deficient brittle hair, developmental delay or intellectual impairment, short stature, ichthyosis, ocular abnormalities, photosensitivity, infections, and defective DNA repair of oxidative lesions (Table S1) (Liang *et al.*, 2006; Faghri *et al.*, 2008). Most cases of TTD are due to mutations in the XPD component of TFIIH. The structure of XPD was recently determined and has demonstrated that XPD's main function is in catalyzing DNA duplex opening at either transcriptional start sites or sites of DNA damage (Fan *et al.*, 2008; Liu *et al.*, 2008a). In TTD cells, mutated subunits of TFIIH prevent it from accessing UV-induced DNA damage in regions of closed chromatin (Chigancas *et al.*, 2008). A mouse model of TTD that display many of the phenotypic characteristics of TTD, such as brittle hair, UV sensitivity, and premature aging, suggests that the disease is caused by unrepaired DNA damage that ultimately compromises transcription, leading to functional inactivation of critical genes and enhanced apoptosis (de Boer *et al.*, 2002). For example, reduced levels of transcription of cystine and sulfur-rich matrix proteins, which are expressed late in terminal differentiation of the hair follicle may be responsible for the brittle nature of hair seen in both TTD patients and mice (Price *et al.*, 1980; de Boer *et al.*, 1998; Liang *et al.*, 2006).

XP often presents with an unusual susceptibility to prolonged sunburn and is characterized by a more than 1000-fold increased susceptibility to sun-induced skin cancers due to deficient GG-NER (Table S1) (Kraemer *et al.*, 1987; Garinis *et al.*, 2008). Clinically, all XP patients exhibit increased freckle-like pigmentation with minimal sun exposure, usually first appearing in children before 2 years of age (Figure 1). Just as strikingly, skin cancer has an onset at a mean age of less than 10 in XP (Kraemer *et al.*, 2007). XP is autosomal recessive and associated with seven genes (*XPA* through *XPG*) (Sugasawa, 2008), as well as a variant form (''XP-V'') due to mutations in the DNA polymerase eta, leading to defective translesion synthesis (Masutani *et al.*, 1999). In addition to CSA and CSB, all the XP gene products (types A–G) are likewise involved in TC-NER, and in addition to the distinct phenotypic entities of XP, CS, and TTD, there are combined syndromes such as XP-CS and XP-TTD caused by mutations in certain XP genes (for example, *XPB*, *XPD*, and *XPG*). Characterizing the various phenotypic presentations of these overlapping conditions has assisted in dissecting out the

mechanisms of disease. For instance, although CS involves neurodegeneration but not an increased risk of skin cancer, the reverse is true in XPA, suggesting that although neoplastic transformation entails global genome instability comprised of copy number changes and aneuploidy, neurodegeneration results from precise transcriptional alterations and protein modifications (Cleaver, 2005). Defects in TC-NER may thus be anti-cancer, but pro-aging, leading to cell death or senescence when transcription is unable to go on (Garinis *et al.*, 2008). Interestingly, it has been noted that in HGPS, XPA localizes with double-strand breaks caused by accumulation of the permanently farnesylated progerin (Liu *et al.*, 2008b).

Elucidating the precise pathways through which DNA damage leads to organismal aging has been challenging. Niedernhofer *et al.* (2006) described a patient with a severe mutation in *XPF*, which encodes XPF-ERCC1, an endonuclease required for the repair of helix-distorting DNA lesions and cytotoxic DNA interstrand cross-links. Mild mutations in *XPF* cause XP. However, in this case, the patient had severe progeroid symptoms. Upon creating a mouse model of this syndrome, they demonstrated that the mice displayed a survival response marked by increased cell death and anti-oxidant defenses, a shift towards anabolism and suppression of growth hormone/insulin-like growth factor 1 (GH/IGF1) signaling. Similar changes were seen in wild-type mice in response to chronic genotoxic stress, calorie restriction, and aging. As this response is also seen in a mouse model of CS, as well as in wild-type mice exposed to low doses of genotoxic stress (van der Pluijm *et al.*, 2007), the authors concluded that unrepaired cytotoxic DNA damage induces a highly conserved metabolic response mediated by the IGF1/insulin pathway, which reallocates resources from growth to somatic preservation and lifespan extension, uncovering a direct link between DNA damage and aging (Niedernhofer *et al.*, 2006). Similarly, reduced expression of IGF1 has also been reported in skin from aged individuals, and some work suggests that this reduced signaling might contribute to the increased prevalence of ultraviolet-B-induced skin cancer seen in aged individuals (Lewis *et al.*, 2009).

AT is characterized by early onset cerebellar ataxia, oculocutaneous telangiectasias, and increased vulnerability to pulmonary disease, and lymphoid tumors (Table S1) (Boder, 1985). It is caused by mutations in the AT-mutated gene (*ATM*), encoding ATM, a serine/threonine protein kinase, which along with ''ATM and Rad3-related protein'' (ATR), serves to recognize and respond to DNA double-strand breaks to maintain genome stability and thus inhibit neoplastic transformation and neurodegeneration. AT cells display cell-cycle checkpoint defects such as a failure to activate the G1-S checkpoint through the inability to stabilize p53, one of ATM's many substrates (Lavin, 2008), and the often-termed ''guardian of the genome'' (Lane, 1992) (discussed further in the next section). Again, underscoring the many overlapping basic mechanisms of disease, expressing numerous progeroid mutations (including the common HGPS mutation, *LMNA* G608G) in different cell lines compromises the ability of DNA repair foci to form in response to cisplatin or UV radiation and results in mislocalization of ATR, a key sensor in the response to DNA damage (Manju *et al.*, 2006).

OLD AND BEYOND REPAIR: TUMOR SUPPRESSORS AND CELLULAR SENESCENCE

With all of the possible damage to cells that can accrue with age, it is not surprising that mechanisms have evolved for removal of this damage. Similarly, these processes doubly serve as protection against uncontrolled cellular growth or cancer. Among these mechanisms, the one most closely implicated with cancer and aging is irreversible cell-cycle arrest, or cellular senescence.

Age-related increases in the number of senescent dermal fibroblasts and epidermal keratinocytes have been observed (Dimri *et al.*, 1995), as well as increases in markers of the senescence phenotype in the skin (Francis *et al.*, 2004). Similarly, recent work suggests that fibroblast dysfunction secondary to oxidative stress and marked by premature senescence may be responsible for age-related phenotypes such as decreased wound healing capabilities (Wall *et al.*, 2008). Considering that progerin is more abundant in late-passage cells and in the dermis of aged individuals, it is suggestive of a possible role for progerin in age-related increases in cellular senescence (McClintock *et al.*, 2007). Likewise, in addition to senescence, recent data from the study of a mouse model of progeria show that the permanently farnesylated lamin A precursor leads to a chronically overactive induction of autophagy, and opens up a new area of exploration of the role of this catabolic pathway in aging (Marino *et al.*, 2008; Vellai, 2009).

Concerning senescence, mouse models of HGPS and other laminopathies, as well as HGPS cells, are notable for undergoing a period hyperproliferation prior to senescing prematurely (Bridger and Kill, 2004). Others have shown that exogenous expression of progerin leads to reduced cellular proliferation and premature senescence (Kudlow *et al.*, 2008). These effects were reversible upon either suppressing p53 expression or inducing the expression of the catalytic subunit of telomerase. These results were significant as they supported previous findings in a mouse model of HGPS of a correspondence between an upregulation of p53 target genes and the senescent phenotype at both the cellular and organismal level (Varela *et al.*, 2005). Likewise, they suggested a possible role of progerin in causing defective telomere structure or metabolism (Grove and Kligman, 1983; Kudlow *et al.*, 2008). Both activated p53 (Choudhury *et al.*, 2007) and oxidative DNA damage (d'Adda di Fagagna *et al.*, 2003) have been shown to accelerate telomere shortening and promote senescence. It should be noted, however, that the role of progerin in causing defective telomere function has never been proven directly in a physiological setting. Recent work demonstrates that overexpression of even wild-type lamin A can lead to accelerated telomere loss

and shortened replicative lifespan (Huang *et al.*, 2008), supporting the previously suggested hypothesis that progerin might exert some of its deleterious effects simply by altering the normal ratio and segregation of the nuclear lamins A and B (Delbarre *et al.*, 2006). Notably, altered lamin expression levels have been observed in both premalignant as well as malignant lesions of the skin (Oguchi *et al.*, 2002; Tilli *et al.*, 2003), as well as in other common neoplasms (Willis *et al.*, 2008).

As discussed further in the next section, in addition to p53, another tumor suppressor, $p16^{INK4A}$, helps to tie together the concepts of age-related genome instability, cancerous transformation, senescence, and stem-cell dysfunction. It has been shown that both senescing human skin fibroblasts and aging mice accumulate DNA lesions with irreparable double-strand breaks (Sedelnikova *et al.*, 2004). More specifically, dermal fibroblasts from both aged human and baboon skin display DNA damage foci as represented by γ-H2AX, activated ATM kinase, and 53BP1 (a marker of DNA double-strand breakage) (Herbig *et al.*, 2006). The ATM-signaling pathway is activated and leads to extensive formation of heterochromatin, a hallmark of cellular senescence, along with upregulation of $p16^{INK4A}$ (Herbig *et al.*, 2006). Levels of $p16^{INK4A}$ increase with the replicative lifespan of cells in culture and in human skin (7-fold induction). Conversely, Bmi1, which is a repressor of $p16^{INK4A}$, decreases in skin with age (Ressler *et al.*, 2006). As key responders in the early response to UV irradiation (Abd Elmageed *et al.*, 2009), it is not surprising that disrupting either the p53 or $p16^{INK4A}$ pathways can lead to melanoma and non-melanoma skin cancers (Sharpless and DePinho, 1999; Ouhtit *et al.*, 2000a, b; Recio *et al.*, 2002).

Beyond the skin, the increase of reactive oxygen species with age also activates the *INK4A/ARF* locus (Ito *et al.*, 2006), leading to impaired regeneration of pancreatic islets, neuronal progenitors, and the hematopoietic system (Janzen *et al.*, 2006; Krishnamurthy *et al.*, 2006; Molofsky *et al.*, 2006; Nishino *et al.*, 2008). Thus, while preventing cancers, these proteins may be promoting senescence, and thus aging (Collado *et al.*, 2007). This mechanism, a hypothesis known as antagonistic pleiotropy, has been suggested to be evolution's way of protecting organisms from cancer early in life, but in doing so, promoting aging phenotypes, perhaps providing an explanation for why cancer is so rarely seen in HGPS (Campisi, 2005).

REGENERATION AND RENEWAL: STEM-CELL BIOLOGY

When the damage has been extensive and the cell is forced to undergo senescence or apoptosis, how does the organism replace these cells and go on? A reservoir of adult stem cells appears to serve in this function, though it is clear that stem-cell function and the regenerative ability of different tissues, such as the skin, declines with age. Establishing whether this decline is due to intrinsic stem-cell aging or reduced function due to the aged skin environment in which they reside remains an open question (Rando, 2006; Sharpless and DePinho, 2007). How exactly this might occur is an area of intense interest and another area from which insight can be gained from HGPS and the progeroid syndromes.

Following the observation that the Notch-signaling pathway, a major regulator of stem-cell maintenance and differentiation, was upregulated in cells expressing progerin, Scaffidi and Misteli (2008) examined the effects of progerin expression on human mesenchymal stem cells, as the tissues affected in progeria are of mesenchymal origin. The introduction of progerin into mesenchymal stem cells not only induced the Notch pathway, it caused the mesenchymal stem cells to undergo sporadic, undirected differentiation into all three germ layers. This effect may lead to premature exhaustion of stem-cell pools, diminishing the ability to regenerate damaged cells and tissues, and therefore resulting in premature aging of tissues such as the skin and vasculature (Gotzmann and Foisner, 2006). Consistent with this, another group has shown that disruption of the nuclear lamina disturbs normal retinoblastoma protein function and leads to inefficient cell-cycle arrest and misregulation of the balance between proliferation and differentiation of epidermal progenitor cells (Naetar *et al.*, 2008).

Taking another approach, Espada *et al.* (2008) examined the relatively well-described stem-cell niche of the hair follicle and its bulge cells in the progeroid *Zmpste24*-knockout mouse model. Here, corresponding to the levels of unprocessed and permanently farnesylated lamin A, they found altered nuclear architecture in the bulge cells and increased numbers of resident epidermal stem cells which had decreased proliferative potential. There was also an increase in apoptosis of supporting cells in the hair bulb region. Analogous to the Notch findings described above, Espada *et al.* (2008) found a virtually complete absence of transcriptionally active β-catenin, the regulator of the Wnt-signaling pathway, and Mitf, which is known to bind β-catenin and regulate melanocyte stem cells. As the Wnt pathway is a master regulator of stem-cell self-renewal and cancer, and a promoter of stem-cell proliferation in various stem-cell niches, including the epidermis (Reya and Clevers, 2005; Lowry and Richter, 2007), the decreased epidermal stem-cell proliferation in these cells is likely the result of the absence of Wnt signaling. Most interestingly, all of these cellular and organismal phenotypes are completely rescued in *Zmpste24−/−Lmna+/−* mice; in other words, with one less copy of *Lmna* and thus 50% less unprocessed and permanently farnesylated lamin A around, all phenotypes were normalized, a direct correlation of mutant lamin A and defective stem-cell regeneration (Espada *et al.*, 2008). Along these lines, levels of normal lamin A are reduced significantly in aged hematopoietic stem cells (Chambers *et al.*, 2007).

With increasing age, numerous changes in the skin take place due to both intrinsic and extrinsic forces (McCullough and Kelly, 2006). Epidermal turnover, which occurs in approximately 28 days in young adults, requires 40–60 days in the elderly (Grove and Kligman, 1983). This

diminished renewal alters the appearance of the skin, which may become rougher, scalier, and more transparent. The cellular content of the dermis (mast cells, fibroblasts, and macrophages) decreases, as does the number and function of antigen-presenting cells (Langerhans cells, mast cells) (Swift *et al.*, 2001). The decreased numbers and function of melanocytes leads to mottled pigmentation, and the decrease both in melanocytes and in Langerhans cells may increase the risk of skin cancers as well (McCullough and Kelly, 2006). A loss of subdermal fat, seen clearly in HGPS, as well as misregulation of normal collagen and elastin production, leads to wrinkling, sagging, and a general loss of support and elasticity (Rabe *et al.*, 2006). Thus, might the increased levels of progerin with age in human skin be impairing regeneration and allowing for intrinsic skin aging and all of its associated defects?

In unaffected individuals, the case for stem-cell dysfunction as a cause of age-related changes in the skin has been building. For instance, hair graying, a classic part of the aging phenotype, has been linked to decreased melanocyte stem-cell maintenance, possibly in association with melanoblast senescence (Nishimura *et al.*, 2005). Likewise, an age-related decline in the ability to heal wounds has long been recognized. It has been shown recently that hair follicles in wounds regenerate *de novo* from epithelial cells outside the hair follicle stem-cell niche, suggesting that epidermal cells assume a hair follicle stem-cell phenotype and that this is dependent upon Wnt signaling (Ito *et al.*, 2007). Similarly, Wnt can induce mesenchymal stem cells and these contribute to wound healing and regeneration, contributing to many cell components of the skin (Sasaki *et al.*, 2008). Once again, the age-related accumulation of progerin in the skin might negatively impact stem-cell maintenance through both direct effects on stem cells and upon normal stem cell-signaling pathways such as Wnt and Notch. Similarly, aberrant DNA damage repair may also lead to cancer or senescence and aging. In an elegant study bringing together many of these concepts, Rossi *et al.* (2007) demonstrated that stem-cell function declines with age in mice because of DNA damage and that these aged stem cells show dramatic epigenetic changes and alterations in gene expression, damage and instability that may also lead to increased chances of transformation into cancer.

CONCLUSIONS

Recent advances made in the study of rare progeroid syndromes, particularly HGPS, have been groundbreaking, though the questions and uncertainties that remain are extensive. For instance, what role does progerin play in the skin? Is it a cause or byproduct of aging? One thing that is certain, however, is that the study of these conditions has provided novel insights and opened up new avenues of exploration into some of the most basic and fundamental aspects of molecular and cellular biology, with implications for processes of vital importance to human health, namely aging and cancer. As Paget noted so long ago, by stopping and looking for a moment at these most rare and seemingly unique conditions, we might yet be surprised at the ubiquity of what they teach us.

CONFLICT OF INTEREST

The authors state no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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