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Sealing the gap between nuclear DNA damage and longevity

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ABSTRACT

A number of progeroid syndromes with defects in the cellular response to DNA damage suggest that progressive genome instability represents an important aspect of the aging process. Here, we review a number of mouse models for progeroid syndromes that are caused by inherited defects in nucleotide excision repair and are characterized by rapid onset of aging symptoms and premature death. We argue that alterations in genome maintenance pathways impact complex physiological processes that may affect the onset of clinically defined age-related pathologies, including cancer as well as pathways that are normally associated with longevity.

1. The DNA damage hitch

Preservation of genetic information is of prime importance to all living systems. However, the integrity of the genome is continuously threatened by a variety of environmental and endogenous agents that damage the DNA, as well as by intrinsic instability of chemical bonds in DNA itself. Oxidative stress, X-rays, ultraviolet (UV) light and numerous chemicals induce a wide mélange of lesions in DNA. Obviously, this affects the proper functioning of vital DNA-metabolizing transactions. Immediate effects of DNA damage include a physical block of transcription and replication. As DNA lesions interfere with the process of transcription, they also affect gene expression and consequently vital responses for the survival of a cell against hazardous threats that could also lead to cell death (Jans et al., 2006; Garinis et al., 2005, 2006). Long-term effects of DNA damage involve induction of mutations via replication of damaged DNA, which ultimately provides a major initiating and driving step in the process of carcinogenesis. A substantial body of evidence argues that DNA damage and mutations accumulate with age in mammalian cells (Vijg, 2000). However, one should distinguish between mutations in the genome and the DNA damage itself. Whereas DNA damage is an undesired chemical alteration in the base, sugar or phosphate that alters the properties of DNA, mutations represent fixed errors in the coding sequence of otherwise chemically unaffected DNA (Hoeijmakers, 2007). Eventually, the effects of distinct types of lesions diverge with respect to helix distortion, ability to pause or obstruct DNA replication, block ongoing transcription or else hamper the battery of repair systems and other caretakers that continuously safeguard the genome. Lesions such as spontaneous deaminations, depurinations and certain oxidized bases are predominantly responsible for mutations and contribute to carcinogenesis (mutagenic). On the other hand, lesions such as double strand breaks and DNA interstrand cross-links [ICLs], uncapped telomeres and certain oxidized bases are thought to predominantly cause apoptosis (cytotoxic) or senescence (cytostatic), thereby contributing to aging (Mitchell et al., 2003). That being said, however, mutagenic lesions can become cytotoxic (in case the damage is excessive) whereas upon faulty repair, cytotoxic lesions may also turn into mutagenic ones. This simplified distinction between cytotoxic/cytostatic and mutagenic lesions appears to support, to some extent, the notion that DNA repair systems that primarily patch mutagenic lesions prevent cancer while repair pathways that primarily attack cytotoxic lesions combat aging. Either way, the strong cancer predisposition observed in certain inherited human disorders with malfunctioning genome care-taking systems (i.e. Xeroderma pigmentosum [XP], Li-Fraumeni, hereditary non-polyposis colorectal cancer, ataxia telangiectasia [AT] as well as the increasing number of progeroid syndromes with defects in DNA repair (e.g. Cockayne syndrome [CS], trichothiodystrophy [TTD] or XPF-ERCC1 [XFE] syndrome) emphasize the biological impact of genome care-taking mechanisms in both cancer and aging (Friedberg et al., 1995; Bootsma et al., 1998; de Boer et al., 2002; Niedernhofer et al., 2006; van der Pluijm et al., 2006).

2. Nucleotide excision repair: at the cross-road of cancer and aging

To withstand the harmful effects of (persisting) DNA lesions, cells are equipped with a set of complementary repair pathways

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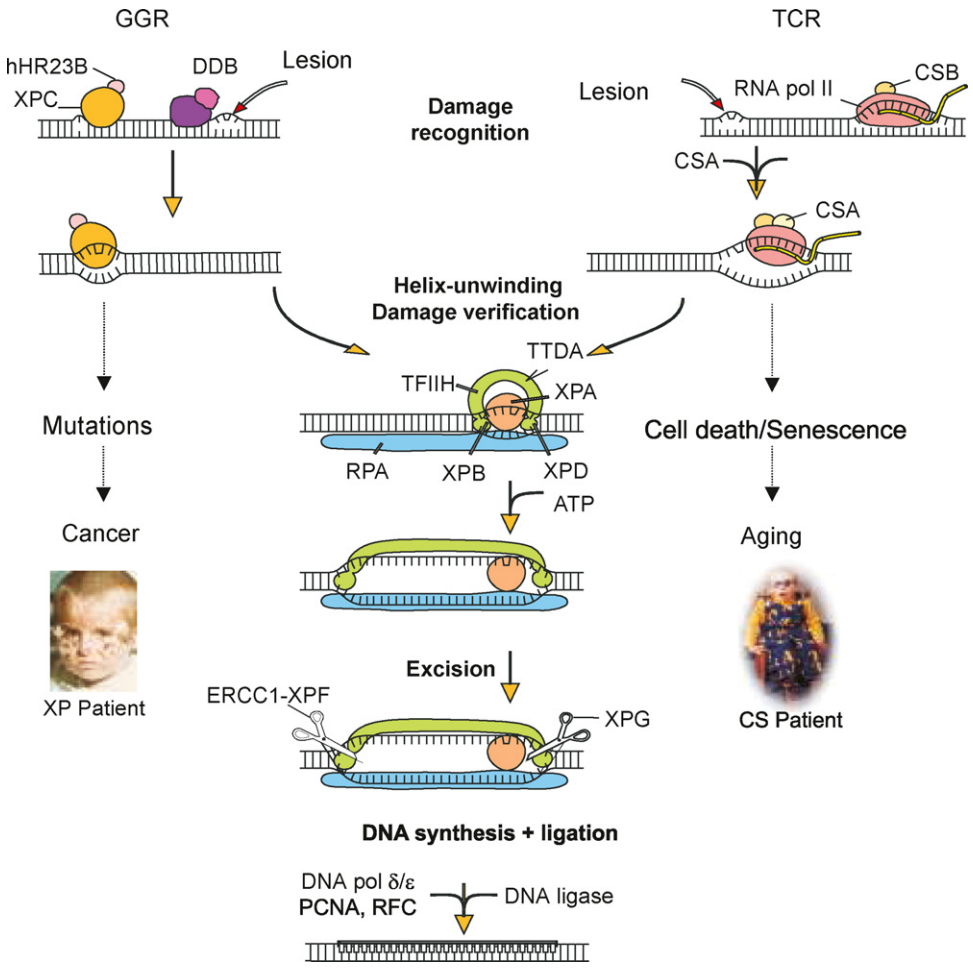

Fig. 1. Two modes of nucleotide excision repair (NER) can be distinguished: repair of lesions over the entire genome, referred to as global genome NER (GGR), and repair of transcription-blocking lesions present in the actively transcribed DNA strand of genes, referred to as transcription-coupled repair (TCR). GGR is dependent on the activity of the GGR-specific complex XPC-hHR23B to recognize mutagenic lesions that are usually small changes to the base-pairing region of DNA bases. Such lesions often obstruct replication, interfering with replication fidelity, which in turn causes mutations and contributes to carcinogenesis. XP-C patients carrying inborn errors in the GGR-specific *XPC* gene are characterized by highly increased risk of skin cancer but importantly show no signs of progeria. Instead, in TCR, damage is detected by the elongating RNA polymerase II complex when it encounters a transcription blocking lesion (e.g. DNA double-strand breaks, UV-induced bulky adducts, DNA ICLs, uncapped telomeres, thymine glycols and cyclopurines). If left unrepaired, such lesions are thought to be cytotoxic as they can block transcription and replication, leading to proliferative arrest/senescence or cell death and thus to functional decline in affected tissues and organs with aging. The causal role of TCR and relevance of cytotoxic DNA lesions in tissue-specific premature ageing (without cancer) is highlighted by the progeroid Cockayne syndrome (CS).

with specific (partially) overlapping substrate specificity and control mechanisms that arrest cell cycle progression, thereby providing a time window for repair (Friedberg et al., 1995; Hoeijmakers, 2001). Base excision repair (BER) or nucleotide excision repair (NER) and its subpathways are predominantly employed to repair DNA lesions that affect only one DNA strand. However, although BER has a vital role in the repair of oxidative lesions, mutations in genes associated with this pathway are either lethal or, when redundant, confer no obvious phenotypes. By contrast, mutations in distinct NER factors lead to premature aging or increased cancer predisposition (Andressoo et al., 2006; Mitchell et al., 2003). NER responds to a bewildering range of lesions that distort the helical DNA structure, via the concerted action of 25 or so proteins that sequentially execute damage recognition, chromatin remodeling, local opening of the DNA double helix, incision of the damaged DNA strand on both sides of the lesion, excision of the 27–29mer oligonucleotide containing the damage, and gap-filling DNA synthesis followed by strand ligation (Hoeijmakers, 1994; de Laat et al., 1999; Wood, 1996; Friedberg et al., 1995).

Two subpathways of NER can be distinguished that differ primarily in how the damage is initially recognized: the global genome repair (GGR) subpathway is responsible for the removal of lesions from the entire genome (Fig. 1). A major limitation of this system, however, is that certain types of damage (like UV-induced CPDs) are less well recognized and accordingly less efficiently repaired. To avoid that such lesions hamper transcription by stalling RNA polymerase II, a distinct NER subpathway has evolved, called Transcription-Coupled Repair (TCR). This system directs the repair machinery preferentially to the template strand of actively transcribed DNA and operates as a fast backup system for lesions that are slowly repaired by GGR (Fig. 1). In man, the clinical consequences of defective NER are illustrated by the phenotype of four rare, autosomal recessive disorders: xeroderma pigmentosum (XP; affected proteins: *XPA-XPG*), Cockayne syndrome (CS; affected proteins: *CSB*, *CSA*), trichothiodystrophy (TTD; affected proteins: *XPB*, *XPD*, *TTDA* that are subunits of TFIIH) and XPF-ERCC1 syndrome (XFE; affected proteins: *XPF*, *ERCC1*) (Bootsma et al., 2001; Giglia-Mari et al., 2004; Jaspers et al., 2007; Niedernhofer et al., 2006). The common hallmark of these pleiotropic disorders is pronounced hypersensitivity to solar (UV) light. Most XP patients are defective in both GGR and TCR and suffer from pigmentation anomalies and a 2000-fold elevated risk of developing skin cancer in sun-exposed

areas of the body, often in combination with progressive neurological degeneration. CS patients are defective in the TCR subpathway of NER and present with cachexia, dwarfism, neurological abnormalities, impaired sexual development, kyphosis, osteoporosis and severely reduced lifespan (mean age of death: 12.5 years) (Nance and Berry, 1992; Bootsma et al., 2002). TTD patients are partially defective in TCR, as well as GGR, and share the symptoms associated with CS. The only patient documented so far with XPF-ERCC1 syndrome carries a TCR defect as well as a defect in the repair of DNA interstrand cross-links (Jaspers et al., 2007). Many of the CS and TTD features are progressive and resemble premature aging. However, as most of these patients develop some, but not all, aspects of normal aging in an accelerated manner, CS, TTD or XPF-ERRC1 are considered "segmental progeroid syndromes" (Martin, 2005). In essence, congenital defects in TCR can lead to premature aging syndromes (CS, TTD) but show no cancer predisposition. Instead, defects in GGR may give rise to disorders with greatly elevated cancer rates (e.g. XP) but no progeria (Fig. 1). Besides NER progeroid syndromes, however, a series of additional syndromes with accelerating features of aging exist based on defects in other repair pathways than NER (not reviewed here).

3. NER progeria: from humans to mice

At present, a comprehensive series of mouse mutants are available with defects in NER demonstrating either progeria or increased cancer predisposition. Mice with a homozygous point mutation in the *Xpd* gene encoding a DNA helicase that functions in both repair and transcription recapitulated most of the features seen in TTD patients (de Boer et al., 1998), including brittle hair, osteoporosis, osteosclerosis, kyphosis, cachexia and a reduced lifespan (de Boer et al., 2002). These findings provided the first substantial evidence that aging in TTD mice is likely caused by unrepaired DNA damage compromising transcription that leads to functional inactivation of critical genes and consequently to age-related pathology. Similarly, mice with defects in CSA and CSB genes consistently mimic the sensitivity of CS patients to solar (UV) irradiation and show accelerated retinal photoreceptor loss (Gorgels et al., 2007), reduced body weight, and mild neurodegeneration (van der Horst et al., 1997; van der Horst et al., 2002). Notably, complete NER inactivation (by concurrent inactivation of the *Xpa* gene) substantially enhances the severity of CS features of TCR-compromised TTD or CSB mice. For instance, $Xpd^{TTD}/^{TTD}/Xpa^{-/-}$ double-mutant animals display dramatic postnatal growth attenuation, kyphosis, ataxia, abnormal locomotor activity, as well as progressive weight loss and died prematurely before weaning (de Boer et al., 2002). In a similar fashion, newborn $Csb^{m/m}/Xpa^{-/-}$ mice exhibit very similar progeroid features and, like the $Xpd^{TTD}/^{TTD}/Xpa^{-/-}$, die at ~1 month of age (van der Pluijm et al., 2006). These findings put forward the notion that an increase in the total DNA damage load on the transcribed strand of active genes likely underlies the cytotoxicity and dramatic progeria seen in TCR-deficient animals. Interestingly, the double-mutant mice ($Xpd^{TTD}/^{TTD}/Xpa^{-/-}$ or $Csb^{m/m}/Xpa^{-/-}$) are both defective in TCR and GGR. Even so, these mice only show greatly accelerated ageing but no enhanced cancer predisposition. Obviously, the lack of cancer predisposition in these mice is likely due to their extremely short lifespan (~1 month). But no signs of enhanced tumor incidence is also seen in the case of progeroid $Xpd^{-/-}$ mice that leave substantially longer (>1.5 years). This indicates that either the effect of cytotoxic/cytostatic lesions override mutagenic lesions when the repair of both is compromised as cells might undergo apoptosis before DNA lesions can result in mutations, or else that tumors need considerably more time to develop than the extremely short lifespan of double mutant animals. However, the latter seems rather unlikely as TTD mice have relatively long lifespans (>1.5 years), yet they develop cancer less frequently than wild-type littermates. The recent discovery of a novel syndrome, designated XFE (XPF-ERCC1) progeria (Niedernhofer et al., 2006) has further expanded the spectrum of lesions that can interfere with DNA metabolism and lead to progeria. $Ercc1^{-/-}$ mice (carrying a defect in an endonuclease required for NER as well as for repair of cytotoxic DNA interstrand cross-links) mimic the XPF-ERCC1 syndrome and demonstrate most of the progeroid features described above but also others that are, in part, distinct from mice only deficient TCR such as dramatic liver, kidney and bone marrow pathology (Niedernhofer et al., 2006). Hence, different types of lesions and defects in repair systems might differentially obstruct vital biological processes such as transcription and/or replication leading preferentially to cell death or senescence of particular cell types, tissues or organs and ultimately to "segments" of "age-related deterioration" over time (Hasty et al., 2003; de Boer and Hoeijmakers, 2000; Mitchell et al., 2003).

4. Impaired genome maintenance, metabolism and longevity

A number of NER-deficient mice that show numerous progeroid features and die prematurely have recently shed light on the link between impaired genome maintenance and changes in gene expression related to metabolic and growth parameters that have previously been associated with delayed aging and longevity in dwarf mutant and calorie restricted mice (Schumacher et al., 2008; Niedernhofer et al., 2006; van der Pluijm et al., 2006).

Transcriptome analysis of the liver of progeroid $Csb^{m/m}/Xpa^{-/-}$ and $Ercc1^{-/-}$ mice, combined with a number of physiological endpoints in these as well as the $Xpd^{TTD}/Xpa^{-/-}$ mouse mutants, demonstrated a widespread decrease in the expression of genes associated with the somatotroph, thyrotroph and lactotroph axes, mitogenic signals and several catabolic pathways including the glycolysis, tricarboxylic acid cycle, the cytochrome P450 monooxygenases, the NADH dehydrogenase complex and the NADPH-dependent oxidative metabolism. In parallel, the same studies revealed a significant upregulation of genes associated with glycogen synthesis, i.e. *Gyg1* and *Gys2* and downregulation of glycogen phosphorylase (*Pygl*), involved in the breakdown of glycogen into its constitutive glucose monomers and the substantial downregulation in the expression of genes coupled to peroxisomal metabolism and biosynthesis. These data provided ample evidence that the complete catabolic metabolism is likely restrained in the liver of progeroid mice carrying predominantly a TCR defect ($Csb^{m/m}/Xpa^{-/-}$ and $Xpd^{TTD}/Xpa^{-/-}$ mice) as well as defects associated with the repair of DNA interstrand cross-links ($Ercc1^{-/-}$ mice). Unexpectedly, these expression profiles suggested that progeroid mice likely store rather than burn glucose monomers for derivation of energy, an observation that appeared, at first, contradictory with their early age at a time when healthy wild-type mice would rather maximize instead of suppress the utilization of energy reserves for growth and development.

Additional expression changes were also noticed such as the broad upregulation in the expression of genes associated with fatty acid synthesis and transport, the adipocyte hormone leptin receptor (*Lplr*) and the central fat regulator peroxisome proliferator-activated receptor-gamma (*Pparγ*). Thus, short-lived, TCR-defective mice demonstrated similar to the previously observed limited glucose utilization a propensity to store rather than burn fat. Finally, the upregulation of genes encoding key enzymatic and non-enzymatic low molecular mass scavengers and antioxidant defense enzymes revealed an attempt of progeroid mice to minimize further induction of DNA damage by counteracting free radicals.

Serum measurements and immunoassays in serial liver tissue sections further confirmed these findings, demonstrating substantially lower insulin-like growth factor (IGF)1, insulin and glucose serum levels, a lower enzymatic activity of citrate synthase as well as enhanced accumulation of glycogen in unusually large vesicles and triacylglycerides in the 2-week old progeroid mouse livers as compared to littermate controls. Overnight fasting in the $Csb^{m/m}/Xpa^{-/-}$ pups and littermate controls (by taking away the lactating mother as well as food pellets) resulted in a near-to-complete depletion of liver glycogen. This indicates that the increased glycogen accumulation observed in the progeroid mouse livers did not derive from an inherent inability to split glycogen into its glucose monomers but was either reflecting a response or impaired regulation of upstream physiological/hormonal pathways. With respect to the suppression of the somatotropic axis comprised of growth hormone (GH)/IGF1 that regulates somatic growth, and the subsequent decrease in IGF1 serum levels observed in 15-day-old progeroid mice, no pituitary dysfunction was detected in both $Csb^{m/m}/Xpa^{-/-}$ and $Ercc1^{-/-}$ mice as both the histological examination and TUNEL staining of sections (in the case of $Csb^{m/m}/Xpa^{-/-}$ mice) from the pituitary pars distalis, intermedia, and nervosa appeared normal. Even more, GH levels were found to be normal, if not increased as in $Ercc1^{-/-}$ mice, likely reflecting a compensatory feedback response to the decreased expression of Ghr in the liver of short-lived animals, indicating that these progeroid mice show GH resistance.

Evidently, one could ask whether the majority of expression changes observed in NER progeroid mice can also be seen in naturally aged animals. Indeed, comparative gene expression analysis revealed broad genome-wide parallels between the transcriptomes of 2-week-old $Csb^{m/m}/Xpa^{-/-}$ and $Ercc1^{-/-}$ mice and naturally aged tissues (Schumacher et al., 2008; Niedernhofer et al., 2006; van der Pluijm et al., 2006) supporting the notion that similar changes are intrinsic to natural aging as well as NER progeria. Thus, NER progeroid mice appeared to recapitulate to a great extent the age-related hormonal and metabolic changes seen during the natural course of aging. Yet these studies failed to identify an upregulation of antioxidant responses in naturally aged animals – as seen before with NER progeroid pups – thereby leaving the relevance of oxidative lesions to age-related deterioration an open question.

Paradoxically, however, similar expression changes (i.e. the suppression of the somatotroph, lactotroph and thyrotroph axes, along with the concomitant suppression of oxidative metabolism and the upregulation of antioxidant responses) seen in short-lived NER progeroid mice are also manifested by long-lived Snell and Ames dwarf and calorie-restricted animal models (Carter et al., 2002a; Longo and Finch, 2003). This led to the hypothesis that impaired genome instability and the ensuing rapid accumulation of lesions in the mammalian genome may be capable of triggering a series of conserved, physiological homeostatic responses that likely favor longevity, a notion that also conforms to the nematode longevity paradigm (Longo and Finch, 2003), the long-lived dwarf mutant and calorie restricted mice (Bartke and Brown-Borg, 2004; Carter et al., 2002b; Brown-Borg, 2003) (Fig. 2). Remarkably, a response previously only associated with prolonged lifespan could now also be induced upon genotoxic stress, early in life. If so, NER-deficient mice could benefit from such a response by minimizing the harmful effects of metabolism and consequently genome instability itself. GH and IGF1 are both potent mitogens; during early organismal development, they promote (oxidative) metabolism that drives organismal growth (Carter et al., 2002b; Bartke, 2003; Chandrashekar et al., 2004). However, an intense metabolic activity may lead to higher oxygen consumption (Carter et al., 2002b) and potentially to the parallel increase in the generation of free radicals through the concerted increased activity of mitochondrial electron transport, peroxisomal fatty acid metabolism and/or microsomal cytochrome *P-450* enzymes (Beckman and Ames, 1998). As a first

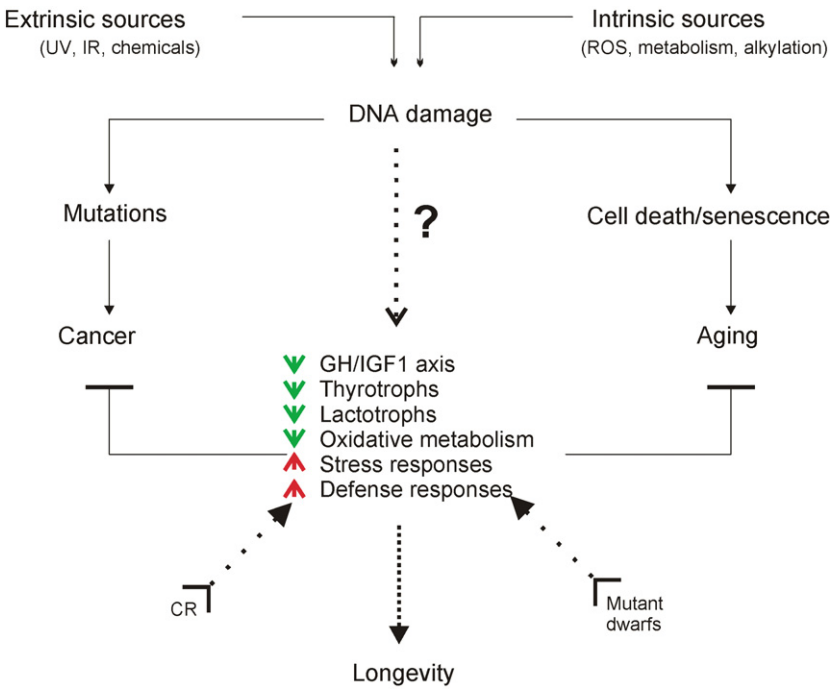

Fig. 2. Although nuclear DNA must last the lifetime of a cell, its physicochemical constitution cannot guarantee life-long stability. Environmental agents (e.g. the ultraviolet component of sunlight, ionizing radiation and genotoxic chemicals) or intrinsic sources of DNA damage (metabolic by-products, spontaneous disintegration of DNA structure) can damage our genome. DNA damage may lead to mutations, a primary step into cancer initiation or else to transcriptional stress, impaired replication, cellular senescence, malfunction or death and eventually to progressive loss of tissue homeostasis and organismal decline. Recent findings on premature aging mice deficient in NER disclosed a novel link between inherent genome instability and an adaptive "survival" response similar to that seen in long-lived mutant dwarfs and wild-type animals; CR included the suppression of GH/IGF1, thyrotroph and lactotroph axes and oxidative metabolism as well as the upregulation of stress and defense responses.

attempt, cells would try to lessen the harmful effects of radical oxygen species (ROS) by surmounting a battery of antioxidant, defense and DNA repair mechanisms. However, DNA damage is still expected to accumulate obstructing transcription and replication, thereby leading to cellular senescence, malfunction or death, and eventually to progressive loss of tissue homeostasis and organismal decline. It is tempting to assume that NER progeroid mice initiate an adaptive response (reduction of metabolic activity through downregulation of the GH/IGF1 axis and other mitogenic signals) to relieve the pressure on their genome (Fig. 2). This response, futile as it may be in view of the repair defect in progeroid mice, could likely extend the limited lifespan of NER-deficient animals, revealing a link between damage to the genome and regulation of the GH/IGF1 hormonal axis. The initially physiological pace of growth diminishes soon after birth (as levels of key hormones decline), eventually leading to severe growth retardation and ultimately to dramatically accelerated progeria. Alternatively, in view of the damage accumulated in their genome, a continuous activity of mitogenic signals is expected to greatly increase the chance of tumor initiation and dramatic tissue pathology rapidly after birth. However, more definite conclusions can only be derived once the metabolic rate in these and other progeroid mice with repair defects is fully determined.

At present, supportive evidence for the role of DNA damage in instigating the enormity of observed metabolic changes is found in the fact that exposure of wild-type mice to low chronic doses of genotoxic agents (e.g. DEHP or mitomycin that induces oxidative stress or cross-links, respectively) triggers a similar suppression of the somatotroph, thyrotroph and lactotroph axes along with the upregulation of antioxidant responses, indicating a link between genome instability and the age-related decline of the GH/IGF1 somatotroph axis. However, whether such responses are the result of an otherwise indirect cytotoxicity that could hamper the endocrine function systemically or else a direct outcome of nuclear DNA damage has yet to be determined. It also remains unknown how and what type of DNA lesions might trigger such a response, what are the possible signal mediators and how such adaptive responses could be fine-tuned in each tissue type. Future research is needed to delineate the specific pathways connecting nuclear DNA damage to complex processes such as the GH/IGF1 hormonal response and to explore potential interventions of the dramatic pace of aging in the repair-compromised mouse mutants. It would also be important to examine whether the suppression of physiological/hormonal pathways (e.g. the GH/IGF1 axis) is unique to the NER progeroid mice or is also seen in other mouse models with documented progerias, for example, the telomerase null mice ($Terc^{-/-}/Atm^{-/-}$ or $Terc^{-/-}/Wrn^{-/-}$).

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References

Andressoo, J.O., Hoeijmakers, J.H., Mitchell, J.R., 2006. Nucleotide excision repair disorders and the balance between cancer and aging. Cell Cycle 5, 2886–2888.
Bartke, A., 2003. Is growth hormone deficiency a beneficial adaptation to aging? Evidence from experimental animals. Trends Endocrinol Metab. 14, 340–344.
Bartke, A., Brown-Borg, H., 2004. Life extension in the dwarf mouse. Curr. Top. Dev. Biol. 63, 189–225.
Beckman, K.B., Ames, B.N., 1998. The free radical theory of aging matures. Physiol. Rev. 78, 547–581.
Bootsma, D., Kraemer, K.H., Cleaver, J.E., Hoeijmakers, J.H.J., 1998. Nucleotide excision repair syndromes: xeroderma pigmentosum, cockayne syndrome and trichothiodystrophy. In: Vogelstein, B., Kinzler, K.W. (Eds.), The Genetic Basis of Human Cancer. McGraw-Hill, New York, pp. 245–274.
Bootsma, D., Cleaver, K.H., Hoeijmakers, J.H.J., 2001. The Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill, New York.
Bootsma, D., Cleaver, K.H., Hoeijmakers, J.H.J., 2002. Nucleotide Excision Repair Syndromes: Xeroderma Pigmentosum, Cockayne Syndrome and Trichthiodystrophy. McGraw-Hill Medical Publishing Division, New York.
Brown-Borg, H.M., 2003. Hormonal regulation of aging and life span. Trends Endocrinol. Metab. 14, 151–153.
Carter, C.S., Ramsey, M.M., Ingram, R.L., Cashion, A.B., Cefalu, W.T., Wang, Z.Q., Sonntag, W.E., 2002a. Models of growth hormone and igf-1 deficiency: applications to studies of aging processes and life-span determination. J. Gerontol. A: Biol. Sci. Med. Sci. 57, B177–188.
Carter, C.S., Ramsey, M.M., Sonntag, W.E., 2002b. A critical analysis of the role of growth hormone and igf-1 in aging and lifespan. Trends Genet. 18, 295–301.
Chandrashekar, V., Zaczek, D., Bartke, A., 2004. The consequences of altered somatotropic system on reproduction. Biol. Reprod. 71, 17–27.
de Boer, J., Andressoo, J.O., de Wit, J., Huijmans, J., Beems, R.B., van Steeg, H., Weeda, G., van der Horst, G.T., van Leeuwen, W., Themmen, A.P., Meradji, M., Hoeijmakers, J.H., 2002. Premature aging in mice deficient in DNA repair and transcription. Science 296, 1276–1279.
de Boer, J., Donker, I., de Wit, J., Hoeijmakers, J.H., Weeda, G., 1998. Disruption of the mouse xeroderma pigmentosum group d DNA repair/basal transcription gene results in preimplantation lethality. Cancer Res. 58, 89–94.
de Boer, J., Hoeijmakers, J.H., 2000. Nucleotide excision repair and human syndromes. Carcinogenesis 21, 453–460.
de Laat, W.L., Jaspers, N.G., Hoeijmakers, J.H., 1999. Molecular mechanism of nucleotide excision repair. Genes Dev. 13, 768–785.
Friedberg, E., Walker, G., Siede, W., 1995. DNA Repair and Mutagenesis. American Society of Microbiology Press, Washington.
Garinis, G.A., Jans, J., van der Horst, G.T., 2006. Photolyases: capturing the light to battle skin cancer. Future Oncol. 2, 191–199.
Garinis, G.A., Mitchell, J.R., Moorhouse, M.J., Hanada, K., de Waard, H., Vandeputte, D., Jans, J., Brand, K., Smid, M., van der Spek, P.J., Hoeijmakers, J.H., Kanaar, R., van der Horst, G.T., 2005. Transcriptome analysis reveals cyclobutane pyrimidine dimers as a major source of UV-induced DNA breaks. EMBO J. 24, 3952–3962.
Giglia-Mari, G., Coin, F., Ranish, J.A., Hoogstraten, D., Theil, A., Wijgers, N., Jaspers, N.G., Raams, A., Argentini, M., van der Spek, P.J., Botta, E., Stefanini, M., Egly, J.M., Aebersold, R., Hoeijmakers, J.H., Vermeulen, W., 2004. A new, tenth subunit of fifth is responsible for the DNA repair syndrome trichothiodystrophy group a. Nat. Genet. 36, 714–719.
Gorgels, T.G., van der Pluijm, I., Brandt, R.M., Garinis, G.A., van Steeg, H., van den Aardweg, G., Jansen, G.H., Ruijter, J.M., Bergen, A.A., van Norren, D., Hoeijmakers, J.H., van der Horst, G.T., 2007. Retinal degeneration and ionizing radiation hypersensitivity in a mouse model for cockayne syndrome. Mol. Cell Biol. 27, 1433–1441.
Hasty, P., Campisi, J., Hoeijmakers, J., van Steeg, H., Vijg, J., 2003. Aging and genome maintenance: lessons from the mouse? Science 299, 1355–1359.
Hoeijmakers, J.H., 1994. Human nucleotide excision repair syndromes: molecular clues to unexpected intricacies. Eur. J. Cancer. 30A, 1912–1921.
Hoeijmakers, J.H., 2001. Genome maintenance mechanisms for preventing cancer. Nature 411, 366–374.
Hoeijmakers, J.H., 2007. Genome maintenance mechanisms are critical for preventing cancer as well as other aging-associated diseases. Mech. Ageing Dev. 128, 460–462.
Jans, J., Garinis, G.A., Schul, W., van Oudenaren, A., Moorhouse, M., Smid, M., Sert, Y.G., van der Velde, A., Rijksen, Y., de Gruijl, F.R., van der Spek, P.J., Yasui, A., Hoeijmakers, J.H., Leenen, P.J., van der Horst, G.T., 2006. Differential role of basal keratinocytes in UV-induced immunosuppression and skin cancer. Mol. Cell Biol. 26, 8515–8526.
Jaspers, N.G., Raams, A., Silengo, M.C., Wijgers, N., Niedernhofer, L.J., Robinson, A.R., Giglia-Mari, G., Hoogstraten, D., Kleijer, W.J., Hoeijmakers, J.H., Vermeulen, W., 2007. First reported patient with human ercc1 deficiency has cerebro-oculo-facio-skeletal syndrome with a mild defect in nucleotide excision repair and severe developmental failure. Am. J. Hum. Genet. 80, 457–466.
Longo, V.D., Finch, C.E., 2003. Evolutionary medicine: from dwarf model systems to healthy centenarians? Science 299, 1342–1346.
Martin, G.M., 2005. Genetic modulation of senescent phenotypes in homo sapiens. Cell 120, 523–532.
Mitchell, J.R., Hoeijmakers, J.H., Niedernhofer, L.J., 2003. Divide and conquer: nucleotide excision repair battles cancer and ageing. Curr. Opin. Cell Biol. 15, 232–240.
Nance, M.A., Berry, S.A., 1992. Cockayne syndrome: review of 140 cases. Am. J. Med. Genet. 42, 68–84.
Niedernhofer, L.J., Garinis, G.A., Raams, A., Lalai, A.S., Robinson, A.R., Appeldoorn, E., Odijk, H., Oostendorp, R., Ahmad, A., van Leeuwen, W., Theil, A.F., Vermeulen, W., van der Horst, G.T., Meinecke, P., Kleijer, W.J., Vijg, J., Jaspers, N.G., Hoeijmakers, J.H., 2006. A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis. Nature 444, 1038–1043.
Schumacher, B., van der Pluijm, I., Moorhouse, M.J., Kosteas, T., Robinson, A.R., Suh, Y., Breit, T.M., van Steeg, H., Niedernhofer, L.J., van Ijcken, W., Bartke,

A., Spindler, S.R., Hoeijmakers, J.H., van der Horst, G.T., Garinis, G.A., 2008. Delayed and accelerated aging share common longevity assurance mechanisms. PLoS Genet. 4 (8), e1000161.
van der Horst, G.T., Meira, L., Gorgels, T.G., de Wit, J., Velasco-Miguel, S., Richardson, J.A., Kamp, Y., Vreeswijk, M.P., Smit, B., Bootsma, D., Hoeijmakers, J.H., Friedberg, E.C., 2002. Uvb radiation-induced cancer predisposition in cockayne syndrome group a (csa) mutant mice. DNA Rep. (Amst.) 1, 143–157.
van der Horst, G.T., van Steeg, H., Berg, R.J., van Gool, A.J., de Wit, J., Weeda, G., Morreau, H., Beems, R.B., van Kreijl, C.F., de Gruijl, F.R., Bootsma, D., Hoeijmakers, J.H., 1997. Defective transcription-coupled repair in cockayne syndrome b mice is associated with skin cancer predisposition. Cell 89, 425–435.
van der Pluijm, I., Garinis, G.A., Brandt, R.M., Gorgels, T.G., Wijnhoven, S.W., Diderich, K.E., de Wit, J., Mitchell, J.R., van Oostrom, C., Beems, R., Niedernhofer, L.J., Velasco, S., Friedberg, E.C., Tanaka, K., van Steeg, H., Hoeijmakers, J.H., van der Horst, G.T., 2006. Impaired genome maintenance suppresses the growth hormone—insulin-like growth factor 1 axis in mice with cockayne syndrome. PLoS Biol. 5, e2.
Vijg, J., 2000. Somatic mutations and aging: a re-evaluation. Mutat. Res. 447, 117–135.
Wood, R.D., 1996. DNA repair in eukaryotes. Annu. Rev. Biochem. 65, 135–167.