Published in final edited form as:
Mech Ageing Dev. 2007 January ; 128(1): 58–63.

Extended longevity mechanisms in short-lived progeroid mice: identification of a preservative stress response associated with successful aging

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Abstract

Semantic distinctions between “normal” aging, “pathological” aging (or age-related disease) and “premature” aging (otherwise known as segmental progeria) potentially confound important insights into the nature of each of the complex processes. Here we review a recent, unexpected discovery: the presence of longevity-associated characteristics typical of long-lived endocrine-mutant and dietary-restricted animals in short-lived progeroid mice. These data suggest that a subset of symptoms observed in premature aging, and possibly normal aging as well, may be indirect manifestations of a beneficial adaptive stress response to endogenous oxidative damage, rather than a detrimental result of the damage itself.

Definitions of aging: current focus on lifespan

Most definitions of aging attempt to capture the irreversible, degenerative nature of the process by focusing on quite apparent symptoms like wrinkled skin and gray hair that affect different people in different ways as they age. A more general definition of aging avoids such individual variation and focuses on the one constant, the time-dependent increase in the probability of dying. The problem with this latter definition is that lifespan is only one component of aging and says nothing about a potentially more important aspect, the quality of life up until the point of death.

In the so-called “premature aging” disorders, or segmental progerias, lifespan is shortened and a number of characteristics, or “segments”, of aging (in addition to a number of disease-specific pathologies) appear early or in exacerbated form (Martin and Oshima, 2000). The relation between progeria and “normal” aging is controversial, largely because there are so many ways to shorten lifespan that have nothing to do with the normal aging process (Miller, 2004). Also poorly defined is the connection between “normal” and “pathological” aging. Cancer or

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Alzheimer's both increase with age, but some people become very old without either and still die of "old age".

On the opposite side of premature or pathological aging, the connection between lifespan extension and "normal" aging is most often taken for granted. But perhaps it should not be. An increase in maximum lifespan can be achieved by slowing the rate of aging or merely by delaying its onset, with different implications for the underlying mechanism (Barger et al., 2003). Restricting the diet by reducing the total amount of food eaten (Weindruch and Walford, 1988) achieves both. Genetic models of lifespan extension, however, may simply delay the onset of ageing-related pathologies, some of which otherwise would limit lifespan (Barger et al., 2003).

What then is aging, and does broadening its definition beyond lifespan reveal anything useful about its nature? We gained an unexpected insight into this problem by performing detailed phenotypic analyses of segmental progeroid mice engineered with various defects in DNA damage repair.

Progeroid NER syndrome: longevity-associated traits in short-lived mice

Nucleotide excision repair (NER) is an evolutionarily conserved mechanism for the removal of bulky, helix-distorting lesions from DNA such as UV-induced damage. It functions by a "cut-and-patch" mechanism in which the damage is recognized, the DNA helix unwound, the damaged strand excised, and the remaining single-stranded region patched (Hoeijmakers, 2001). In humans, congenital defects in NER-associated components are uniformly associated with UV (sun) hypersensitivity. Specific defects in a subset of these components can also lead to the segmental progeroid disorders Cockayne syndrome and trichothiodystrophy (Bootsma et al., 2002). These recessive disorders display postnatal onset of progressive neurodevelopmental pathology with overlapping progeroid features including reduced subcutaneous fat and small size (together known as cachectic dwarfism), sensorineural deafness, retinal degeneration, white matter hypomyelination and CNS calcification sometimes accompanied with premature appearance of neurofibrillary tangles (Itin et al., 2001;Nance and Berry, 1992;Rapin et al., 2000).

Mouse models of these diseases (Table 1 and references therein) display an overlapping set of progressive symptoms including cachectic dwarfism, reduced bone mineral density resembling osteoporosis, curvature of the spine (lordokyphosis) and failure to thrive. Cerebellar ataxia, a disease-specific pathology not associated with normal aging in mice, is sometimes accompanied by the loss of Purkinje neurons late in disease progression. Death usually occurs before weaning at about three weeks of age.

Recently we reported a surprising finding in *Xpd/Xpa* double homozygous mutant mice (van de Ven et al., 2006). In addition to the progeroid features listed above, these mice display characteristics usually associated with good health and extended lifespan, as in endocrine-deficient or dietary-restricted animals (Bartke and Brown-Borg, 2004). These characteristics, measured at two weeks of age when the pups are still nursing, include reduced weight, hypoglycemia, hypoinsulinemia, reduced serum insulin-like growth factor-1 (IGF-1) and reduced body temperature. In addition, a number of genes involved in the postnatal growth axis are downregulated in the livers of these animals, including growth hormone receptor. These features are observed in a variety of progeroid NER mice, including two different *Xpd/Xpa* (van de Ven et al., 2006) mutants, *Csb/Xpa* (van der Pluijm et al., 2006) and *Ercc1* (Niedernhofer et al., 2006) and are likely to be common to all of the progeroid NER mutants.

Adaptive response vs. constitutive defect

Constitutive defects in endocrine-mediated insulin signaling and dietary restriction can both extend longevity in a number of model organisms. In mice, both result in reduced size, hypoglycemia, hypoinsulinemia, reduced serum IGF-1 and reduced temperature (Bartke and Brown-Borg, 2004;Koubova and Guarente, 2003). One clear difference, however, is that these phenotypes are permanent in endocrine-deficient animals but reversible in dietary restricted animals. In short-lived progeroid NER mice, normal pituitaries (van der Pluijm et al., 2006) and normal growth hormone (Niedernhofer et al., 2006;van de Ven et al., 2006;van der Pluijm et al., 2006) are inconsistent with defects in hypothalamic or pituitary function. A more attractive hypothesis is that the alteration of energy metabolism via dampening of the growth hormone/IGF-1 axis in progeroid NER mice reflects an adaptive response in which reduction of mitochondrial ROS-derived oxidative DNA damage is the intended consequence. However, such a hypothesis is difficult to test in mice with an early onset, irreversible condition as in progeroid NER syndrome in which animals die within three weeks after birth.

Fortuitously, one particular combination of mutant alleles ($Xpd^{R722W/G602D}/Xpa^{-/-}$, Table 1) resulted in mice with each of the longevity-associated traits of dietary restriction in addition to all of the pathologies of progeroid NER syndrome, save one: instead of a three week lifespan, mutants survived past weaning with 80% penetrance. We hypothesize this to be due to complementation between the two different mutant *Xpd* alleles (Andressoo et al., 2006a). This allowed us to study these animals past early development and into adulthood. We noted additional phenotypes including normal to elevated food intake per gram body mass (like hypopituitary Ames dwarf mice (Bartke et al., 2001)) despite continuing dwarfism, time-dependent reduction in the mass of both white and brown adipose tissue deposits relative to total mass, progressive lordokyphosis, frequent loss of balance and a mean lifespan of approximately 5 months of age.

Blood glucose and serum IGF-1 levels of adult mutants gave us an unexpected clue about the nature of the effect on growth and metabolism observed at the earlier age of 2 weeks. By ten weeks of age, when control animals are past postnatal development and have reached sexual maturity, blood glucose and serum IGF-1 levels in the mutants are once again normal despite the remaining dwarfism (van de Ven et al., 2006).This is further evidence against any constitutive alteration of the growth hormone/IGF-1 axis or glucose homeostasis and strongly in favor of the interpretation that the downregulation of these components at two weeks of age reflects an adaptive response to stress.

SIRT6 KO mice: similar adaptive response to a common DNA repair defect?

SIRT6 deficiency results in a phenotype strongly overlapping progeroid NER syndrome. Like progeroid NER mice, SIRT6 KO mice are born normally but display early postnatal onset of growth retardation followed by lordokyphosis, cachexia and failure to thrive, with a maximum lifespan of 24 days (Mostoslavsky et al., 2006).

Beginning at postnatal day 12, animals become increasingly hypoglycemic despite evidence of normal eating (milk in the stomach) and a normal ability to absorb glucose (R. Mostoslavsky, personal communication). Like in the NER progeroid mice, reduced serum IGF-1 (Mostoslavsky et al., 2006) despite normal growth hormone levels (D. Lombard, personal communication), suggestive of growth hormone insensitivity, is also present. Furthermore, ablation of the DNA damage response protein p53 does not affect lifespan in SIRT6 deficient mice (D. Lombard, R. Mostoslavsky, personal communication) or progeroid NER *Csb/Xpa* mice (H. van Steeg, unpublished observation).

Differences between SIRT6 deficiency and progeroid NER disorder also exist, but are minor compared to the overall similarities. These differences appear mainly in the end-of-life pathology. SIRT6 KO mice lose splenocytes, thymocytes and peripheral lymphocytes as the result of a systemic, non-cell autonomous defect, which may be attributable in part to the sensitivity of these cells to hypoglycemia and low IGF-1 (Alves et al., 2006;Mostoslavsky et al., 2006). The loss of Purkinje neurons typical of progeroid NER mice may be due to a cell-type specific hypersensitivity to oxidative DNA damage combined with the systemic effects of reduced IGF-1, a neuronal survival factor. Decreased serum IGF-1 levels are associated with cerebellar ataxias of various etiologies in both humans and experimental rodent models (Busiguina et al., 2000;Torres-Aleman et al., 1996), and Purkinje neurons are hypersensitive to oxidative stress accompanying ischemic injury although relatively resistant to other types of stress such as hypoglycemia (Mohseni, 2001). Interestingly, different gene-specific pathologies also exist amongst progeroid NER disorders (Table 1). For example, liver- and kidney-specific pathologies exclusively in XPF- and ERCC1-deficient mice are probably due to the particular roles of these proteins outside of NER, such as interstrand crosslink repair or telomere maintenance; brittle hair is specific to the R722W-encoding mutation in *Xpd*, probably due to transcriptional deficiencies particular to this mutation (de Boer et al., 1999). Despite these differences, the overlapping phenotype of progeroid NER syndrome and SIRT6 deficiency is consistent with a common adaptive response to genotoxic stress during development.

Is there any evidence that this hypothetical shared adaptive response is triggered by a common genotoxic stress? SIRT6-deficient cells are hypersensitive to the effects of ROS generated by ionizing radiation or H_2O_2, and monoadducts by the alkylating agent MMS, but not to ultraviolet radiation, consistent with a defect in the base excision repair (BER) system (Mostoslavsky et al., 2006) or in other DNA damage response pathways. Although BER is functionally distinct from NER, there is recent genetic and biochemical evidence of a partial functional overlap between components previously thought to be specific to one system (NER components XPG and CSB) or the other (BER components OGG-1 and PARP-1)(Dianov et al., 2000;Licht et al., 2003;Osterod et al., 2002;Thorslund et al., 2005;Tuo et al., 2002). Although much further evidence is required, it is tempting to speculate that such a shared DNA repair defect can elicit a common adaptive response.

Adaptive stress response is not a general characteristic of genome instability

In addition to progeroid NER syndrome and SIRT6 deficiency, a number of genetically engineered mice have progeroid characteristics (reviewed in (Lombard et al., 2005)). At face value, these progeroid conditions appear to have much in common. The engineered mutations are mostly in genes involved in nucleic acid metabolism, for example, other types of DNA repair (Espejel et al., 2004), telomere maintenance (Lee et al., 1998), chromosome segregation (Baker et al., 2004), DNA methylation (Sun et al., 2004), mitochondrial DNA replication fidelity (Trifunovic et al., 2004), and the DNA damage response (Maier et al., 2004;Tyner et al., 2002). Also, the progeroid phenotypes have an overlapping set of characteristics including cachectic dwarfism, reduced fertility, hair loss and graying, curvature of the spine, cancer predisposition and shortened lifespan.

We asked whether other forms of genome instability in addition to excision repair defects could trigger a preservative organismal response through the postnatal growth/energy metabolism axis. We chose KU80-deficient mice, with a defect in repairing DNA double-strand breaks via the non-homologous endjoining pathway. These animals are cachectic dwarfs throughout their lives and display many characteristics of premature senescence on both the cellular and organismal levels (Vogel et al., 1999). In two-week-old animals, however, we found no

difference in blood glucose, serum IGF-1, or gene expression from the postnatal growth axis in the liver as there is in progeroid NER syndrome (van de Ven et al., 2006).

Together these data suggest that whatever the apparent similarities amongst genomically unstable progeroid mice, on both the molecular and organismal levels different mechanisms, or possibly similar mechanisms with very different kinetics, are at work. In support of this conclusion, a different form of genome instability related to short telomeres produces a related subset of progeroid symptoms including hair loss and graying, osteoporosis and fingernail atrophy in a variety of otherwise unrelated progerias (Hofer et al., 2005).

Evolution of the preservative stress response

An adaptive stress response involving downregulation of growth and alteration of energy metabolism in favor of conservation may have evolved to cope with periods of reduced food availability or life-threatening disease. It may be thus best defined as a preservative stress response rather than a longevity stress response, because its primary purpose is to help animals through a period of stress that could occur during any stage of life (and thus could be selected for) rather than to extend lifespan past the reproductive years. A developmental stage-specific version of this response is also conserved in the worm *C. elegans*. During early larval development, food inadequacy triggers an adaptive response known as dauer formation in which metabolism is altered via the insulin-signaling pathway in an attempt to survive until environmental conditions are once again favorable (Kenyon et al., 1993).

The phenotypes of progeroid NER syndrome and SIRT6 deficiency suggest another way to trigger this response: a particular type of oxidative genotoxic stress during early development. The rapid postnatal onset suggests that birth stress, which involves an increase in ROS levels (Randerath et al., 1997a;Randerath et al., 1997b) may trigger it and that rapid postnatal growth may further exacerbate it. Combined with the inability to repair certain endogenous lesions as in SIRT6 or NER deficiency, oxidative genotoxic stress may trigger an adaptive response intended to reduce generation of ROS through mitochondrial respiration and thus prevent further damage.

This stress response may also not be limited to aging or aging-related pathology, but may also occur in response to acute stress. In support of this, we have data implicating downregulation of IGF-1 and growth hormone receptor on the mRNA level in response to the acute oxidative stress of renal ischemia reperfusion injury (J. Mitchell, unpublished observation). Furthermore, chronic exposure of mice to a peroxisome proliferator (resulting in elevated oxidative DNA damage (de Waard et al., 2004)) induces a similar response in the gene expression profile of livers of wild-type mice (van der Pluijm et al., 2006). A reduction of the growth hormone/IGF-1 may thus be a more general marker of both chronic and acute oxidative stress. However, as is clear from the shortened lifespan of progeroid NER and SIRT6 deficient mice, reduced IGF-1 on its own cannot ensure a beneficial outcome; the nature and duration of the stress must also be taken into consideration (Figure 1).

Terminal senescent weight loss: an adaptive stress response to normal aging?

If the reaction to certain types of genome instability resembles a stress response, does the oxidative DNA damage that accumulates with age also trigger such a beneficial response? There is some evidence that normal aging evokes a similar response to stress. In the absence of age-related disease such as cancer or diabetes, people at advanced age often enter a period of weight loss culminating in death. This syndrome is known as geriatric failure to thrive (Sarkisian and Lachs, 1996). The cause of the weight loss is currently unknown. Rats that live

to advanced age also display a related phenomenon known as senescent terminal weight loss. Although originally believed to be caused by decreased food intake, new data indicate this not to be the case (Black et al., 2003). The growth hormone/IGF-1 axis is already greatly reduced by this age, and thermoregulation and blood glucose may also be altered in this terminal senescent period (Black et al., 2003;van de Ven et al., 2006). In light of the data reviewed here, perhaps its not surprising then that rats (Black et al., 2003) (and probably mice (Miller et al., 2005)) that experience this senescent terminal weight loss "syndrome" actually live significantly *longer* than those that do not. In other words, we propose that terminal senescent weight loss and geriatric failure to thrive, despite their foreboding names, are probably components of a beneficial, adaptive response triggered very late in life in response to the accumulated oxidative damage to macromolecules including DNA.

Conclusions

Everything changes with age, and few of them for the better. Most things, from our muscles to our short-term memory, deteriorate over time. Here we emphasize the potential importance of another component of the aging process: the body's own response to deterioration. This adaptive response probably evolved to combat other stresses such as starvation early in life, but may be activated in cases of premature, pathological and natural aging. A more nuanced and useful definition of aging should thus include at least four basic components: underlying mechanisms including molecular oxidation (Harman, 1988), genetic background (from progeroid to centenarian) defining susceptibility to such damage, time-dependent primary effects of stochastic oxidative macromolecular damage, and secondary adaptive organismal attempts to counterbalance these effects. In the future, a better understanding of these components and their interactions will tell us more, not just about how we age, but about how we function at all stages of our lives.

Acknowledgements

The authors would like to thank Joris Pothof, David Lombard and Raul Mostoslavsky for informative discussions and critical reading of the manuscript. This work was supported in part by the following grants: National Institutes of Health (1PO1 AG17242-02); Association of International Cancer Research Grant Award (05-280); and Netherlands Organization for Health Research and Development, Research Institute for Diseases in the Elderly (60-60400-98-004).

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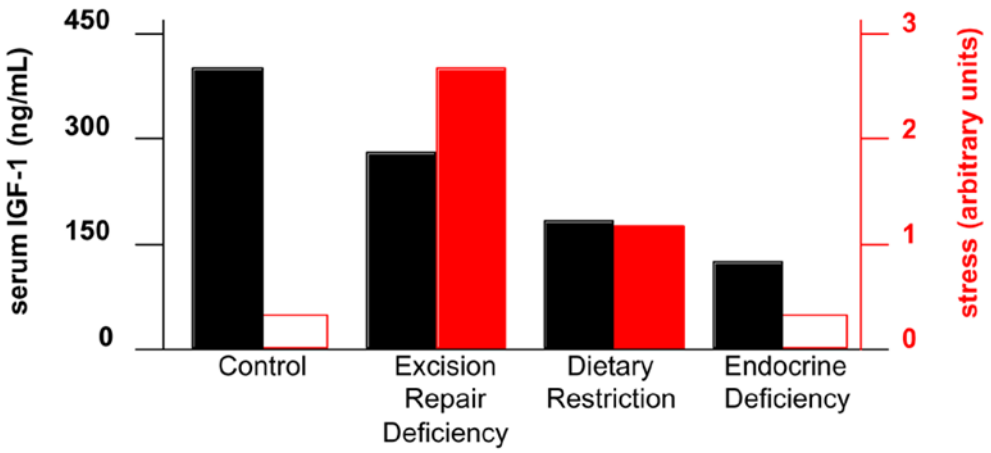

Figure 1.

Correlations between serum IGF-1, genotoxic stress and lifespan. In dietary restricted and endocrine-deficient mice, reduced serum IGF-1 (black bars; y axis on the left) correlates with increased longevity. In progeroid NER and SIRT6 knockout (excision repair deficient) mice, this correlation doesn't hold. To explain this apparent paradox, we add the presumed cause of the reduced IGF-1 in excision repair deficient and dietary restricted animal: stress (red bars; y axis on the right). Different shadings indicate the different nature of the stressors (unrepaired endogenous DNA damage, dark red; reduced energy intake, light red; baseline stress in control and endocrine-deficient animals, empty). Constitutive unrepaired genotoxic stress may overrule the efficacy of reduced IGF-1 signalling in excision repair-deficient progeroid mice, while in dietary restriction or endocrine deficiency the stress is either of a different nature, or absent relative to controls as in constitutive endocrine deficiency.

Table 1

Overlapping characteristics of excision repair deficiencies in man and mouse

Human Progeroid syndrome	Mouse Mutant	DNA repair defect	Lifespan	Genotype specific pathology
XFE	*Ercc1*$^{-/-}$ (McWhir et al., 1993;Weeda et al., 1997)	NER/TCR; ICLR; telomere maintenance (Zhu et al., 2003)	~3 wk	Liver/kidney polyploidy; reduced hematopoietic reserves (Prasher et al., 2005)
	Xpf$^{-/-}$ (Tian et al., 2004)	NER/TCR; ICLR; telomere maintenance (Zhu et al., 2003)	~3 wk	Liver/kidney polyploidy
XPCS	*Xpg*$^{-/-}$ (Harada et al., 1999;Sun et al., 2001)	NER/TCR	~2–3 wk	undeveloped small intestines
	Xpa$^{-/-}$|*Csb*$^{-/-}$ (Murai et al., 2001;van der Pluijm et al., 2006)	NER/TCR	~3 wk	n.d.
	Xpa$^{-/-}$|*Xpd*$^{G602D/G602D}$ (Andressoo et al., 2006b)	NER/TCR	~3 wk	n.d.
XPTTD	*Xpa*$^{-/-}$|*Xpd*$^{R722W/R722W}$ (de Boer et al., 2002)	NER/TCR	~3wk; survivors 4, 12 mos	cutaneous abnormalities, brittle hair
XPCS (Mild)	*Xpa*$^{-/-}$|*Xpd*$^{R722W/G602D}$ (Andressoo et al., 2006b;van de Ven et al., 2006)	NER/TCR	~22 wk	n.d.
?	*SIRT6*$^{-/-}$ (Mostoslavsky et al., 2006)	BER	~3 wk	osteopenia, lymphopenia

n.d. none determined

NER: Nucleotide excision repair

TCR: Transcription coupled repair

ICRL: Interstrand cross-link repair

BER: Base excision repair