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OPINION

Is rate of skin wound healing associated with aging or longevity phenotype?

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Abstract Wound healing (WH) is a fundamental biological process. Is it associated with a longevity or aging phenotype? In an attempt to answer this question, we compared the established mouse models with genetically modified life span and also an altered rate of WH in the skin. Our analysis showed that the rate of skin WH in advanced ages (but not in the young animals) may be used as a marker for biological age, i.e., to be indicative of the longevity or aging phenotype. The ability to preserve the rate of skin WH up to an old age appears to be associated with a longevity phenotype, whereas a decline in WH—with an aging phenotype. In the young, this relationship is more complex and might even be inversed. While the aging process is likely to cause wounds to heal slowly, an altered WH rate in younger animals could indicate a different cellular proliferation and/or migration capacity, which is likely to affect other major processes such as the onset and progression of cancer. As a point for future studies on WH and longevity, using only young animals might yield confusing or misleading results, and therefore including older animals in the analysis is encouraged.

Keywords Wound healing · Skin · Aging · Longevity · Genes · Mouse models

Abbreviations

KO	Knockout
LAGs	Longevity-associated genes
WH	Wound healing
WT	Wild type
Agtr1a	Angiotensin II receptor, type 1a
Arhgap1	Rho GTPase activating protein 1
Bub1b	Budding uninhibited by benzimidazoles 1 homolog, beta (*S. cerevisiae*)
Cav1	Caveolin, caveolae protein 1
Dmd	Dystrophin, muscular dystrophy
Fn1	Fibronectin 1
Igf1	Insulin-like growth factor 1 (somatomedin C)
Igf1r	Insulin-like growth factor 1 receptor
Nos3	Nitric oxide synthase 3, endothelial cell
Plau (*uPa*)	Plasminogen activator, urokinase
Tert	Telomerase reverse transcriptase
Trp53	Transformation related protein 53

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Definition of the problem: is there an association between WH and aging/longevity?

Wound healing (WH) is a fundamental biological process. Deviations from regular WH could lead to diverse age-related pathological conditions, from slow or ineffective tissue repair to fibroproliferative responses, thus representing major biomedical challenges (Singer and Clark 1999; Ferguson and O'Kane 2004). The optimal outcome of WH response to damage is the complete regeneration of tissue structure and function, as occurs in several species from diverse taxa (e.g., salamander, axolotle, hydra, planaria) and in early mammalian embryos (Gardiner 2005). In postnatal mammals, tissue repair is usually achieved by a combination of an inflammatory response with rapid scarring repair, instead of the full albeit slower tissue regeneration (Gurtner et al. 2008). Such a trade-off, favoring speed of restoration over functionality, is probably imperative in a variety of mammalian tissues, especially such as the skin. Indeed, the skin is the first and foremost natural barrier of the organism against foreign threats and therefore "any break in it must be rapidly and efficiently mended" (Martin 1997). Not surprisingly, in the wild, a quick repair of damaged skin is vital for the protection of the organism from pathogen invasion (Baker et al. 2004), and thus could have some survival value with a potential impact on longevity. It could also be questioned whether life span extension is accompanied by accelerated skin repair, or alternatively, is premature aging accompanied by deterioration in the healing process? Here we address a principal issue of whether WH is associated with a longevity or aging phenotype. Since our knowledge on WH in species with different life span is very limited, we took advantage of the accumulated data on mouse models with genetically modified life span and WH in the skin.

Mouse models with genetically modified life span and skin wound healing

Studies on genetically engineered mice have brought about several dozens of mouse models, in which single gene manipulations (gene deletion, full or partial loss-of-function mutations or gene overexpression) result in either longevity or premature aging phenotype (de Magalhães et al. 2009, Human Aging Genomic Resources—GenAge Database, http://genomics.senescence.info/genes). Under the same criteria, comprehensive data mining of scientific literature with subsequent manual curation revealed 207 genetic mouse models with altered WH in the skin. This data has recently been organized by us in RESOLVE–Wound Healing and Fibrosis-related Genes database (Tacutu et al. 2010, http://www.resolve-whfg.appspot.com). We further compared the list of WH-associated genes with those reported as being involved in regulation of life span in mice (LAGs, $n = 94$, update of GenAge Database). The comparison yielded ten genetic mouse models of extended (longevity phenotype) or reduced life span (premature aging phenotype) with an altered rate of skin WH. We also add to this list our recent data on long-lived αMUPA transgenic mice of different ages (unpublished data). The results are summarized in Table 1 (for more details, see Online Resource 1).

Association between wound healing and longevity potential manifests in advanced age

As depicted in Table 1, most of mutant mouse models ($n = 7$) under the present analysis displayed a reduction in median life span (by 20–60% versus WT) with characteristic signs of premature aging (shorter reproduction period, earlier development of osteoporosis, kyphosis, and cataracts, diminished stress response, etc.; Online Resource 1). In four of the above studies (*Arhgap1*, *Bulb1*, *Fn1*, and *Trp53*), the rate of skin wound closure was used as a phenotypic marker, providing a priori that slower WH is indicative of an aging phenotype. Indeed, in these studies, the negative effect of gene targeting on life span coincided well with the expected effect on the rate of skin WH. The important point is that this effect was clearly noted only in the groups of older mutant mice which were either obviously old (24 months) or had the features of an aging phenotype as early as 8–12 months. The same, concordant relation between longevity and WH rate was also observed in long-lived αMUPA mice: the old αMUPA mice healed the skin wounds much faster than their parental age-matched FVB mice (unpublished data). However, the results were less consistent

Table 1 Comparison of the effects of genetic interventions on skin wound healing and longevity in mice

Target gene	Type of genetic intervention	Genetic background	Age of wounding[a] (months)	Effect on rate of skin WH	Effect on life span
Agtr1a	Knockout	C57BL/6	2	(−)	+
Arhgap1[b]	Knockout	C57BL/6	8	(−)	−
Bub1b[b]	Partial loss-of-function mutation	C57BL/6	2	(+)	−
			12	(−)	
Cav1	Knockout	C57BL/6	2	(+)	−
Dmd	Knockout	C57BL/10S	2	(+)	−
Fn1[b]	Partial loss-of-function mutation	C57BL/6	2–3	(−)	−
			11	(−)	
Igf1[c]	Overexpression	FVB	2	(+)	+
Igf1r[d]	Heterozygous KO	C57BL/6–129/Sv	N/A	N/A	+
Nos3	Knockout	C57BL/6	2	(−)	−
Tert[b]	Overexpression	C57BL/6	2-4	(+)	+
Trp53[b]	Enhanced function mutation	C57BL/6	3	(=)	−
			24	(−)	
Plau	Overexpression	FVB	4	(=)	+
			24	(+)	

(+), (−), (=) the increased, decreased, or unaltered rate of skin WH, respectively (compared with age-matched WT mice)

+ Longevity phenotype, − Premature aging phenotype

[a] Full thickness head excision punch was exploited in transgenic αMUPA mice and their WT counterparts, FVB mice (our unpublished data). In all other mouse models, the full thickness back excision punch was utilized

[b] The effects on WH and on aging/longevity were explored in the same studies (*Bub1b*, Baker et al. 2004; *Fn1*, Muro et al. 2003; *Trp53*, Tyner et al. 2002; *Arhgap1*, Wang et al. 2007) or by the same research group (*Tert*, González-Suárez et al. 2001, 2005). In other cases, the effects were evaluated in independent studies by different research groups (WH: *Agtr1a*, Kurosaka et al. 2009, Yahata et al. 2006; *Cav1*, Lizarbe et al. 2008; *Dmd*, Straino et al. 2004; *Igf1*, Semenova et al. 2008; *Nos3*, Muangman et al. 2009; *Plau*, our unpublished data on WH; Longevity: *Agtr1a*, Benigni et al. 2009; *Cav1*, Park et al. 2003; *Dmd*, Chamberlain et al. 2007; *Igf1*, Li and Ren 2007; *Nos3*, Li et al. 2004; *Plau*, Miskin and Masos 1997)

[c] WH was evaluated in transgenic mice with skin-specific overexpression of *Igf1* (Semenova et al. 2008), whereas in the longevity study, mice with cardiac-specific *Igf1* overexpression were investigated (Li and Ren 2007)

[d] The $Igf1r^{+/-}$ mouse model (Holzenberger et al. 2003) was included as supportive data for *Igf1*

among the young (2–4 month-old) mutant or transgenic animals. Compared with their age-matched WT, they showed slower (*Fn1* mutants), unaltered (*Trp53* mutants, αMUPA mice), or even accelerated WH (*Bub1b* mutants). Similar "inconsistencies" were also observed in studies where the skin WH was investigated only in young animals and independently of the impact of genetic manipulations on mouse life span, i.e., without regard to aging or longevity. Moreover, the analysis showed that in the mouse aging/longevity models, the difference in skin WH rate, whatever the cause, is much more prominent in older animals than in the young.

Thus, as follows from our analysis, when assessed in advanced age, a slower or faster skin WH could indeed be indicative of an aging or longevity phenotype, respectively. Most likely, this is primarily attributed to an overall effect on organismal aging rather than to a skin-specific action of the targeted genes, otherwise, similar changes would be expected in the young animals as well. This assumption is strongly exemplified by our study on the long-lived αMUPA mice which preserve their skin WH capacity up to an old age. In this unique model (for review see: Miskin et al. 2005), the *uPa* (*Plau)* transgene is expressed in the ocular lens and the brain *but not in the skin* (Miskin and Masos 1997), thus excluding the gene-specific effects on skin WH. Another line of evidence linking WH capacity to longevity comes from the fact that endogenous sex hormones

profoundly influence both longevity and the response to cutaneous injury (Gilliver et al. 2008). As a result, female mice live longer and heal better than males. Likewise, castration of male mice extends their life span and improves wound repair. With regard to the pivotal role of fibroblasts in skin WH (Gurtner et al. 2008), it is also interesting to note that primary cultures of human fibroblasts derived from patients with Hutchinson-Gilford progeria syndrome showed attenuated cell migration and proliferation in an in vitro wound healing model (Verstraeten et al. 2008).

Linking wound healing, cancer, and longevity

In several mouse models (*Agtr1a*, *Bub1b*, *Cav1* and *Dmd*), the effect on the rate of skin WH *in young age* was opposite to the effect on life span (Table 1). To some extent, this could be explained by the inherent links between WH and cancer and its role in the determination of mouse longevity. Indeed, cancer is the main cause of death in mice (Anisimov 2001) and on the other hand has so much in common with WH that Schäfer and Werner (2008) even consider "cancer as an overhealing wound". Notably, in another pilot analysis, we found that in most cases, genetic manipulations leading to accelerated cutaneous WH in young mice are also associated with earlier and more frequent development of cancer (15 of 18 models; 85%, $P < 0.05$, chi-test; unpublished data). With regard to the genetic models presented in Table 1, for example, the partial inactivation of *Bub1b*, an important component of the spindle checkpoint, results in a rapid healing of skin wounds but also in an increased susceptibility to cancer (Dai et al. 2004). Tumor suppressor-like action was also observed for *Cav1* (Mercier et al. 2009) and *Dmd* (Chamberlain et al. 2007), and accordingly, KO of these genes promotes both cancer and WH (Lizarbe et al. 2008; Straino et al. 2004). In contrast, the *Agtr1a*-deficient mice healed slower in young age (Yahata et al. 2006) but lived longer than their WT littermates (Benigni et al. 2009). Concerning its possible role in cancer, high expression of *Agtr1a* was observed in radiation-induced carcinomas in rats (Imaoka et al. 2008). Interestingly, αMUPA mice, whose rate of skin WH in the young group did not differ from that of the young FVB (WT) mice, showed a significantly reduced rate of spontaneous and induced tumorigenesis (Tirosh et al. 2003, 2005). Spontaneously arising tumors were observed only in 16% of 24–28-month-old female αMUPA mice, whereas in old FVB mice, this value was approximately four times higher (66%, Mahler et al. 1996; 62%, Tirosh et al. 2003).

A more complicated and less clear case is that of telomerase (*Tert*)-transgenic mice. González-Suárez et al. (2001) found that the increased rate of wound closure in young mice was also accompanied by an increased susceptibility to induced tumorigenesis in the skin. Later on, the authors found that *Tert*-transgenic and WT mice do not significantly differ in median life span, but display distinct survival patterns in young adult and advanced ages. Namely, the transgenic mice display a high incidence of cancer and increased mortality in the first half of life, while in the second half the survivors live longer than their WT littermates, perhaps because of the delayed onset of other age-related pathologies (González-Suárez et al. 2005).

Activation of cell proliferation and migration is critical for both WH and cancer. *Igf1* is a potent mitogen and also enhances cell motility, thus promoting wound repair and tumorigenesis (Fürstenberger and Senn 2002; Sekharam et al. 2003) As expected, mice overexpressing *Igf1* specifically in the skin, healed cutaneous wounds much faster than WT mice (Semenova et al. 2008). However, this does not yet mean that the same would take place in the case of *Igf1* overexpression in the whole body, though it seems quite plausible. Unfortunately, there is neither survival nor cancer data on this model. In the only known *Igf1*-transgenic mice where longevity was studied, *Igf1* was overexpressed specifically in the heart (Li et al. 2007). The extended life span in this model obviously results from local *Igf1* activity in the heart where the development of tumors is extremely rare. More accurately reflecting the relationship between *Igf1* and longevity, is the observation that an inverse correlation exists between plasma *Igf1* level measured at 6 months of age and median life span in 31 genetically-diverse inbred mouse strains (Yuan et al. 2009), which coincides well with the notion that *Igf1* or *Igf1* receptor deficiency contributes to a longevity phenotype by protecting from cancer (Holzenberger et al. 2003; Laron 2008). If so, it is likely that overexpression of *Igf1* would be associated with an

accelerated skin WH, cancer promotion, and reduced longevity.

Further evidence strengthening the links between WH, cancer, and longevity comes from the naked mole rat. Having a comparable body size and incomparably longer life span (ca. eight-fold increase in maximum life span vs. mice), the naked mole rat possesses extraordinary resistance to cancer (Buffenstein 2008), and as reported by Ruttencutter et al. (2009), displays a relatively slow skin WH compared with mice. Inhibition of both cancer and WH in this animal may be attributed to the phenomenon of "early contact inhibition" described by Seluanov et al. (2009).

Concluding remarks

Our analysis shows a positive correlation between the rate of skin WH and the longevity of mice when tested at advanced ages. It therefore appears that the rate of skin WH in older animals (but not in the young) may be used as a marker for biological age, i.e., to be indicative of the longevity or aging phenotype. The ability to preserve the rate of skin WH is associated with a longevity phenotype, whereas a decline in WH is associated with an aging phenotype. In young adults, the relationship between WH and the "longevity potential" is more complex and might even be inversed, so that, for example, faster WH in the young might be linked to reduced life span. Alternatively, an unaltered or slower WH rate in the young might be in favor of longevity. It is likely that the aging process causes wounds to heal slower in the aged, but in younger animals that do not yet show signs of aging, an altered WH rate could indicate dysregulation in cellular homeostasis, such as changes in apoptosis, proliferation and/or migration capacity. Such alterations probably affect not just WH but also other major processes such as the onset and progression of cancer which resembles wound healing in many aspects and is the main cause of death in mice. Altogether, this shows that the relationships between wound healing (especially when evaluated in the young) and longevity could not be put down as a simple "the better WH, the higher longevity" and warrants further study.

It is noteworthy to mention that, though differing in specific mechanisms, WH has much in common across a variety of wounded tissues/organs. For example, the sequence of events and tissue dysfunction that follow skin burns are remarkably similar to that following myocardial infarction or a spinal-cord injury (Gurtner et al. 2008).

As points for further investigation, it would be interesting to examine:

- Is there an association between longevity and the rate or quality of WH in other organs?
- Is the rate of WH affected in organs with a high frequency of cancer incidence?
- Do species with different longevity also differ in their WH capacity?

As follows from our analysis, the age factor should be taken into account when answering the above questions. An important point for future studies on WH and longevity is that using *only* young animals might yield confusing or misleading results, thus including older animals in the analysis is encouraged.

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References

Anisimov VN (2001) Mutant and genetically modified mice as models for studying the relationship between aging and carcinogenesis. Mech Ageing Dev 122:1221–1255

Baker DJ, Jeganathan KB, Cameron JD, Thompson M, Juneja S, Kopecka A, Kumar R, Jenkins RB, de Groen PC, Roche P, van Deursen JM (2004) BubR1 insufficiency causes early onset of aging-associated phenotypes and infertility in mice. Nat Genet 36:744–749

Benigni A, Corna D, Zoja C, Sonzogni A, Latini R, Salio M, Conti S, Rottoli D, Longaretti L, Cassis P (2009) Disruption of the Ang II type 1 receptor promotes longevity in mice. J Clin Invest 119:524–530

Buffenstein R (2008) Negligible senescence in the longest living rodent, the naked mole-rat: insights from a successfully aging species. J Comp Physiol B 178:439–445

Chamberlain JS, Metzger J, Reyes M, Townsend D, Faulkner JA (2007) Dystrophin-deficient mdx mice display a reduced life span and are susceptible to spontaneous rhabdomyosarcoma. FASEB J 21:2195–2204

Dai W, Wang Q, Liu T, Swamy M, Fang Y, Xie S, Mahmood R, Yang YM, Xu M, Rao CV (2004) Slippage of mitotic

arrest and enhanced tumor development in mice with BubR1 haploinsufficiency. Cancer Res 64:440–445

de Magalhães JP, Budovsky A, Lehmann G, Costa J, Li Y, Fraifeld V, Church GM (2009) The human ageing genomic resources: online databases and tools for biogerontologists. Aging Cell 8:65–72

Ferguson MW, O'Kane S (2004) Scar-free healing: from embryonic mechanisms to adult therapeutic intervention. Philos Trans R Soc Lond B 359:839–850

Fürstenberger G, Senn HJ (2002) Insulin-like growth factors and cancer. Lancet Oncol 3:298–300

Gardiner DM (2005) Ontogenetic decline of regenerative ability and the stimulation of human regeneration. Rejuvenation Res 8:141–153

Gilliver SC, Ruckshanthi JP, Hardman MJ, Nakayama T, Ashcroft GS (2008) Sex dimorphism in wound healing: the roles of sex steroids and macrophage migration inhibitory factor. Endocrinology 149:5747–5757

González-Suárez E, Samper E, Ramírez A, Flores JM, Martín-Caballero J, Jorcano JL, Blasco MA (2001) Increased epidermal tumors and increased skin wound healing in transgenic mice overexpressing the catalytic subunit of telomerase, mTERT, in basal keratinocytes. EMBO J 20:2619–2630

González-Suárez E, Geserick C, Flores JM, Blasco MA (2005) Antagonistic effects of telomerase on cancer and aging in K5-mTert transgenic mice. Oncogene 24:2256–2270

Gurtner GC, Werner S, Barrandon Y, Longaker MT (2008) Wound repair and regeneration. Nature 453:314–321

Holzenberger M, Dupont J, Ducos B, Leneuve P, Géloën A, Even PC, Cervera P, Le Bouc Y (2003) IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. Nature 421:182–187

Imaoka T, Yamashita S, Nishimura M, Kakinuma S, Ushijima T, Shimada Y (2008) Gene expression profiling distinguishes between spontaneous and radiation-induced rat mammary carcinomas. J Radiat Res 49:349–360

Kurosaka M, Suzuki T, Hosono K, Kamata Y, Fukamizu A, Kitasato H, Fujita Y, Majima M (2009) Reduced angiogenesis and delay in wound healing in angiotensin II type 1a receptor-deficient mice. Biomed Pharmacother 63:627–634

Laron Z (2008) The GH-IGF1 axis and longevity. The paradigm of IGF1 deficiency. Hormones (Athens) 7:24–27

Li Q, Ren J (2007) Influence of cardiac-specific overexpression of insulin-like growth factor 1 on lifespan and aging-associated changes in cardiac intracellular Ca^{2+} homeostasis, protein damage and apoptotic protein expression. Aging Cell 6:799–806

Li W, Mital S, Ojaimi C, Csiszar A, Kaley G, Hintze TH (2004) Premature death and age-related cardiac dysfunction in male eNOS-knockout mice. J Mol Cell Cardiol 37:671–680

Lizarbe TR, Garcia-Rama C, Tarin C, Saura M, Calvo E, Lopez JA, Lopez-Otin C, Folgueras AR, Lamas S, Zaragoza C (2008) Nitric oxide elicits functional MMP-13 protein-tyrosine nitration during wound repair. FASEB J 22:3207–3215

Mahler JF, Stokes W, Mann PC, Takaoka M, Maronpot RR (1996) Spontaneous lesions in aging FVB/N mice. Toxicol Pathol 24:710–716

Martin P (1997) Wound healing–aiming for perfect skin regeneration. Science 276:75–78

Mercier I, Casimiro MC, Zhou J, Wang C, Plymire C, Bryant KG, Daumer KM, Sotgia F, Bonuccelli G, Witkiewicz AK, Lin J, Tran TH, Milliman J, Frank PG, Jasmin JF, Rui H, Pestell RG, Lisanti MP (2009) Genetic ablation of caveolin-1 drives estrogen-hypersensitivity and the development of DCIS-like mammary lesions. Am J Pathol 174:1172–1190

Miskin R, Masos T (1997) Transgenic mice overexpressing urokinase-type plasminogen activator in the brain exhibit reduced food consumption, body weight and size, and increased longevity. J Gerontol A Biol Sci Med Sci 52:B118–B124

Miskin R, Tirosh O, Pardo M, Zusman I, Schwartz B, Yahav S, Dubnov G, Kohen R (2005) AlphaMUPA mice: a transgenic model for longevity induced by caloric restriction. Mech Ageing Dev 126:255–261

Muangman P, Tamura RN, Muffley LA, Isik FF, Scott JR, Xie C, Kegel G, Sullivan SR, Liang Z, Gibran NS (2009) Substance P enhances wound closure in nitric oxide synthase knockout mice. J Surg Res 153:201–209

Muro AF, Chauhan AK, Gajovic S, Iaconcig A, Porro F, Stanta G, Baralle FE (2003) Regulated splicing of the fibronectin EDA exon is essential for proper skin wound healing and normal lifespan. J Cell Biol 162:149–160

Park DS, Cohen AW, Frank PG, Razani B, Lee H, Williams TM, Chandra M, Shirani J, De Souza AP, Tang B (2003) Caveolin-1 null (−/−) mice show dramatic reductions in life span. Biochemistry 42:15124–15131

Ruttencutter JA, Gajendrareddy P, Park TJ, Laurito CE, Maruch PT (2009) Sensory neuropeptides and wound healing in a naked mole-rat. J Dent Res 88A:3443

Schäfer M, Werner S (2008) Cancer as an overhealing wound: an old hypothesis revisited. Nat Rev Mol Cell Biol 9:628–638

Sekharam M, Zhao H, Sun M, Fang Q, Zhang Q, Yuan Z, Dan HC, Boulware D, Cheng JQ, Coppola D (2003) Insulin-like growth factor 1 receptor enhances invasion and induces resistance to apoptosis of colon cancer cells through the Akt/Bcl-x(L) pathway. Cancer Res 63:7708–7716

Seluanov A, Hine C, Azpurua J, Feigenson M, Bozzella M, Mao Z, Catania KC, Gorbunova V (2009) Hypersensitivity to contact inhibition provides a clue to cancer resistance of naked mole-rat. Proc Natl Acad Sci USA 106:19352–19357

Semenova E, Koegel H, Hasse S, Klatte JE, Slonimsky E, Bilbao D, Paus R, Werner S, Rosenthal N (2008) Overexpression of mIGF-1 in keratinocytes improves wound healing and accelerates hair follicle formation and cycling in mice. Am J Pathol 173:1295–1310

Singer AJ, Clark RA (1999) Cutaneous wound healing. N Engl J Med 341:738–746

Straino S, Germani A, Di Carlo A, Porcelli D, De Mori R, Mangoni A, Napolitano M, Martelli F, Biglioli P, Capogrossi MC (2004) Enhanced arteriogenesis and wound repair in dystrophin-deficient mdx mice. Circulation 110:3341–3348

Tacutu et al. (2010) RESOLVE—wound healing and fibrosis-related genes database. http://www.resolve-whfg.appspot.com

Tirosh O, Aronis A, Zusman I, Kossoy G, Yahav S, Shinder D, Abramovitz R, Miskin R (2003) Mitochondrion-mediated apoptosis is enhanced in long-lived alphaMUPA transgenic mice and calorically restricted wild-type mice. Exp Gerontol 38:955–963

Tirosh O, Pardo M, Schwartz B, Miskin R (2005) Long-lived alphaMUPA transgenic mice show reduced SOD2 expression, enhanced apoptosis and reduced susceptibility to the carcinogen dimethylhydrazine. Mech Ageing Dev 126:1262–1273

Tyner SD, Venkatachalam S, Choi J, Jones S, Ghebranious N, Igelmann H, Lu X, Soron G, Cooper B, Brayton C (2002) P53 mutant mice that display early ageing-associated phenotypes. Nature 415:45–53

Verstraeten VL, Ji JY, Cummings KS, Lee RT, Lammerding J (2008) Increased mechanosensitivity and nuclear stiffness in Hutchinson-Gilford progeria cells: effects of farnesyltransferase inhibitors. Aging Cell 7:383–393

Wang L, Yang L, Debidda M, Witte D, Zheng Y (2007) Cdc42 GTPase-activating protein deficiency promotes genomic instability and premature aging-like phenotypes. Proc Natl Acad Sci USA 104:1248–1253

Yahata Y, Shirakata Y, Tokumaru S, Yang L, Dai X, Tohyama M, Tsuda T, Sayama K, Iwai M, Horiuchi M, Hashimoto K (2006) A novel function of angiotensin II in skin wound healing. Induction of fibroblast and keratinocyte migration by angiotensin II via heparin-binding epidermal growth factor (EGF)-like growth factor-mediated EGF receptor transactivation. J Biol Chem 281:13209–13216

Yuan R, Tsaih SW, Petkova SB, Marin de Evsikova C, Xing S, Marion MA, Bogue MA, Mills KD, Peters LL, Bult CJ, Rosen CJ, Sundberg JP, Harrison DE, Churchill GA, Paigen B (2009) Aging in inbred strains of mice: study design and interim report on median lifespans and circulating IGF1 levels. Aging Cell 8:277–287