Healthy Aging: Is Smaller Better? – A Mini-Review

Andrzej Bartke

Departments of Internal Medicine and Physiology, Southern Illinois University School of Medicine, Springfield, Ill., USA; Department of Physiology, King Saud University College of Medicine, Riyadh, Saudi Arabia

Key Words

Laron dwarfism • Growth hormone • Longevity

Abstract

A recent report of virtually complete protection from diabetes and cancer in a population of people with hereditary dwarfism revived interest in elucidating the relationships between growth, adult body size, age-related disease and longevity. In many species, smaller individuals outlive those that are larger and a similar relationship was shown in studies of various human populations. Adult body size is strongly dependent on the actions of growth hormone (GH) and the absence of GH or GH receptor in mice leads to a remarkable extension of longevity. Many mechanisms that may account for, or contribute to, this association have been identified. It is suggested that modest modifications of the diet at different ages may extend human healthspan and lifespan by reducing levels of hormones that stimulate growth.

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Introduction

It was recently reported that Laron dwarfism, a rare genetic disorder of endocrine function, provides a striking, virtually complete protection from diabetes and cancer [1]. In individuals with this syndrome, the actions of

growth hormone (GH) are disrupted and as a result, growth and adult stature are severely reduced. Individuals with this or other dwarfing syndromes were also reported to have little atherosclerosis in spite of unfavorable serum lipid profiles. At first glance, the co-existence of major health benefits with severe defects in endocrine function is contradictory, or at the very least, exceedingly unlikely. However, the notion that smaller body size can offer advantages in terms of health and longevity is not new. Although not universally accepted, the concept is supported by a considerable amount of evidence. Genetic alterations that block GH secretion or action delay aging and impressively extend longevity in laboratory mice. In this mini-review, we will bring together some of the evidence that suggests that, at least in terms of healthy aging, ‘smaller is better.’ We will also identify mechanisms that are most likely to explain the surprising benefits of being small.

Early Reports of Negative Association of Body Size and Longevity

In 1935, McCay et al. [2] first reported that rats given reduced amounts of food were smaller and lived longer than fully fed control animals. Since that time, several reports have provided evidence that in comparison of different stocks, inbred strains or selected lines of mice, the

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0304-324X/12/0584-0337\$38.00/0

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Andrzej Bartke, PhD
Department of Internal Medicine, Division of Geriatric Research
Southern Illinois University School of Medicine
801 N. Rutledge, Room 4389, PO Box 19628
Springfield, IL 62794-9628 (USA), Tel. +1 217 545 7655, E-Mail abartke@siu.edu

average lifespan of smaller animals was longer [reviewed in 3]. Studies of Samaras et al. [4] provided numerous examples of a similar, that is, negative association of body size and longevity in humans. The significance of these observations for understanding the mechanisms that control aging was, until recently, largely overlooked. This may have been due to the fact that in comparisons between rather than within a species, it is the larger animals that generally live longer. Moreover, during the last 50–100 years, many human populations experienced parallel increases in adult stature and longevity. However, the positive association of body size and lifespan in different species is by no means universal. Thus, humans live much longer than larger mammals, with elephants and whales being the only exceptions. Many species of bats live much longer than mice or other small rodents even though they weigh less and birds live much longer than mammals of the same body weight. Recent impressive gains in average life expectancy in technologically advanced countries were largely due to improvements in public health measures (e.g., safe drinking water supply, vaccinations against multiple diseases) and to progress in medicine. The huge impact of these advances on life expectancy overshadows the consequences of concomitant changes in nutrition that tend to increase growth and adult stature.

In 1972, a paper dealing with osteoarthritis reported a remarkably long lifespan and a delay of age-related pathological changes in the joints in Snell dwarf mice [5]. Snell dwarfs have hereditary deficiencies of several hormones including GH, and diminutive body size (approximately 1/3 of normal). This rather striking observation appears to have been completely missed by gerontologists. In 1996, Brown-Borg et al. [6] reported major increases in average and maximal longevity in Ames dwarf mice, diminutive mutants with endocrine defects identical (or nearly identical) to those in Snell dwarf mice. Because deficiency of GH leads to profound suppression of circulating levels of insulin-like growth factor 1 (IGF-1) and to a reduction in the levels of insulin, it was soon realized that findings in Ames and Snell dwarf mice relate in most interesting ways to the evidence that reduction in the actions of homologous hormones (insulin/IGF-like signaling; IIS) extends longevity in a microscopic roundworm, *Caenorhabditis elegans*, and in a fruit fly, *Drosophila melanogaster* [reviewed in 7, 8]. Studies in the Ruvkun laboratory provided evidence that *daf-2*, the key ‘longevity gene’ in *C. elegans*, is homologous to gene coding for mammalian IGF-1 and insulin receptors [9] and *age-1*, the first gene shown to control longevity in *C. el-*

egans that acts downstream from *daf-2*, is homologous to PI3 kinase, an enzyme involved in transmission of IGF-1 and insulin signals in mammalian cells [10]. It is now accepted that the IIS pathway is an evolutionarily conserved mechanism that controls aging in organisms ranging from yeast to mammals [7, 8, 11]. Interestingly, some of the long-lived *D. melanogaster* mutants are smaller than the corresponding normal (‘wild-type’) animals.

Findings Linking Reduced Growth with Delayed Aging and Extended Longevity Are Confirmed and Expanded

During the past 15 years, association of extended longevity and reduced body size was described in a number of mouse mutants with various defects in the so-called ‘somatotropic’ (GH/IGF-1) signaling [reviewed in 12]. The best example of the positive impact of reduced somatotropic signaling on healthy aging and longevity was provided by studies of mice created in the laboratory of John Kopchick [13] by disrupting the GH receptor gene. Extended longevity of these mutants was documented in independent studies in different laboratories using diets of different composition and breeding the animals on different genetic backgrounds [13–15]. Importantly, many indices of biological aging were shown to be delayed and/or attenuated and the maximal lifespan is increased in Snell dwarf, Ames dwarf and GH-receptor deleted (*Ghr*^{–/–}, often referred to as GHRKO or Laron dwarf) mice [3, 5, 16, 17]. This indicates that increased longevity of these mutants reflects delayed and/or slower aging and this, in turn, may prevent age-related disease.

Richard Miller’s laboratory provided important evidence that the negative association of somatotropic signaling with longevity applies not only to comparisons of mutant and normal mice but also to individual differences between genetically normal animals. Thus, in a genetically heterogeneous population of mice derived from crosses of four inbred strains, body weight of young adults and serum IGF-1 levels were shown to be negative predictors of lifespan of individual animals. Results of this study were published under a title that says it all: ‘Big Mice Die Young’ [18]. Further evidence for the association of lower levels of IGF-1 with longer life was obtained by Yuan et al. [19] who analyzed differences in plasma IGF-1 concentration and in longevity between 31 inbred strains of mice.

Studies in dogs, rats and horses provided strong evidence that the negative association of body size and longevity is not limited to laboratory stocks of mice [20–22]. In fact, the widely known and well-documented differences in the average lifespan of various dog breeds or mixed-breed dogs of different size provide some of the most striking examples of small animals living longer than larger individuals from the same species [21, 23] and link this relationship specifically to genetic differences in IGF-1 levels.

In 2007, Samaras and Rollo [24] published a book that compiles numerous datasets showing negative association of body size and longevity in various human populations. Although results of some studies do not support this association, there is very strong evidence that taller people are at greater risk of developing various kinds of cancer [25, 26]. However, body size of some long-lived *Drosophila* and mouse mutants is normal or only slightly reduced.

Human Dwarfism Protects from Some Age-Related Diseases

Suppression of somatotrophic signaling caused by genetic GH deficiency or GH resistance leads to reduced growth and adult stature along with obesity and serum lipid profiles that in genetically normal individuals predict increased risk of cardiovascular disease (CVD). Increased CVD-related mortality and reduced lifespan were reported in a population of GH-deficient individuals in Switzerland in comparison to their normal relatives [27]. In contrast to these observations, no increase in atherosclerosis was detected in a population of GH-deficient individuals in Brazil in spite of similar ‘unfavorable’ serum lipid profiles [28]. Moreover, arterial function was not impaired in obese, hyperlipidemic individuals with Laron dwarfism, hereditary GH resistance due to absence or loss of function of GH receptors [29]. A recent study of Laron dwarfs in Ecuador revealed a complete absence of diabetes and only 1 case of cancer among 99 individuals, and no record of deaths due to either of these diseases [1]. Moreover, meta-analysis of data from several populations of GH-resistant individuals confirmed virtually complete protection from cancer [30].

In the context of the increasing evidence that GH deficiency or resistance and the consequent reduction of circulating IGF-1 levels can protect from cancer, diabetes and atherosclerosis, it is interesting to compare these findings to the consequences of pathological hyperfunc-

tion of the somatotrophic axis. In acromegalics, GH-secreting tumors produce a chronic excess of GH and IGF-1 and affected individuals are at increased risk of diabetes, CVD and cancer and have a reduced life expectancy [31]. Transgenic mice overexpressing GH are much larger than normal animals, insulin resistant, hyperinsulinemic, prone to cancer, short-lived and prematurely exhibit many phenotypic features that are normally associated with aging [32].

Lifespan of Humans with Various Dwarfism Syndromes

As was mentioned earlier, hereditary GH deficiency in one human population was significantly associated with increased CVD and reduced life expectancy [27]. However, it was also reported that some individuals with hypopituitarism and dwarfism due to mutation of the *Prop1* gene (the same gene that is mutated in Ames dwarf mice) or with dwarfism due to GH resistance can reach very advanced age [30, 33]. There are no reports of increased average longevity in any of the examined populations of human dwarfs. Apparently the beneficial effects of protection against cancer, diabetes and atherosclerosis are counterbalanced by the increased risk of death from other causes, which in Laron dwarfs in Ecuador include accidents, seizures and alcohol abuse [1] and by differential impact of dwarfism on early versus late mortality in the examined populations [1, 28]. Nevertheless, protection from diabetes, cancer and atherosclerosis in individuals with mutations that lead to obesity, hyperlipidemia and severe suppression of growth provides evidence that some of the benefits of reduced somatotrophic signaling discovered in mice, dogs and other animals apply also to our species. Indeed, studies of polymorphism of genes related to somatotrophic signaling support the association of reduced levels of GH or IGF-1 receptors with exceptional longevity in the human [34, 35].

A negative correlation of height and longevity in various studies of genetically normal people was mentioned earlier in this article. It appears exceedingly unlikely that short stature or small body size per se may confer advantages in terms of healthspan and lifespan. Instead, the negative association of body size with longevity in mice, rats, dogs, horses and some human datasets likely reflects the fact that these characteristics share dependence on the same controlling mechanism or mechanisms. From the available evidence it can be postulated that somatotrophic signaling is such a common mechanism. Because

GH deficiency or resistance can slow aging and protect from some age-related diseases, we hypothesize that GH actions accelerate aging. Since GH is a major regulator of somatic growth and adult body size, this hypothesis would explain the longevity advantage of smaller individuals. It also leads to an obvious question, namely how GH signaling can influence aging and longevity. In the remainder of this mini-review, we will identify mechanisms that are likely to account for the impact of reduced GH/IGF-1 actions on aging, age-related disease and longevity.

How Can Somatotrophic Signaling Affect Aging?

Improved Stress Resistance

Increased stress resistance has been associated with increased lifespan in many organisms. Oxidative stress damage to nucleic acids, proteins and lipids is believed to represent an important mechanism of aging across species although some recent findings question various implications of the oxidative theory of aging. Long-lived Ames dwarf mice have increased levels and activity of several antioxidant enzymes, reduced production of reactive oxygen species and reduced oxidative damage in various organs [36]. Dermal fibroblasts derived from these animals or from other mutants lacking GH or GH receptors are more resistant to a variety of oxidative or other cytotoxic insults than cells derived from genetically normal, control animals [37 and references cited therein]. Importantly, stress resistance is severely attenuated in cells from Ames dwarfs that had been injected with GH for several weeks [37]. Furthermore, Ames dwarfs have reduced susceptibility to the toxic effects of Paraquat, an insecticide that produces massive oxidative stress [38].

Reduced Insulin Levels and Improved Insulin Signaling

Somatotropic and insulin signaling pathways interact at multiple levels. Both GH and IGF-1 promote development of insulin-producing pancreatic β cells. While IGF-1 mimics many of insulin's effects, GH is generally anti-insulinemic and promotes insulin resistance. Insulin stimulates fat deposition while GH is lipolytic. Long-lived mouse mutants with GH deficiency or resistance are hypoinsulinemic and very sensitive to insulin actions. The combination of reduced insulin levels and improved insulin sensitivity in these animals resembles the effects of calorie restriction (CR) in both animals and humans.

Suppression of GH release by CR may contribute to these effects. In studies of interactive effects of CR and longevity genes in mice, these alterations in insulin release and actions were consistently associated with extension of longevity [15, 39].

Altered Distribution and Secretory Function of Adipose Tissue

In the mouse, as in the human, suppression of GH signaling leads to increased adiposity. In GH-deficient and GH-resistant mouse mutants, white adipose tissue (WAT) accumulation is increased primarily in the subcutaneous depots with less of an effect on the accumulation of visceral fat. In spite of increased adiposity and leptin, the profile of circulating adipokines is shifted from pro- to anti-inflammatory with a significant increase in adiponectin levels [40]. Adiponectin is a product of WAT that promotes insulin sensitivity, exerts anti-inflammatory and anti-atherogenic actions and is associated with increased longevity in both mice and humans. Increased levels of adiponectin were reported in centenarians and in the offspring of exceptionally long-lived people [41; R. Westendorp, pers. commun.]. Recent studies in our laboratory provided evidence for increased secretion of adiponectin by visceral fat of Ghr-/- ('Laron dwarf') as compared to normal mice [M. Masternak, unpubl. data].

Reduced Mammalian Target of Rapamycin (mTOR) Signaling

There is considerable evidence that the TOR pathway is importantly involved in the regulation of mRNA translation, protein synthesis and growth, in mediating responses to CR and in regulation of aging and longevity in organisms ranging from yeast to mammals. The lifespan of mice can be increased by pharmacological suppression of mTOR signaling or by genetic deletion of its key target ribosomal protein S6 kinase [42, 43]. Signaling via mTOR pathway is reduced in Ames dwarf and Laron dwarf mice, and this undoubtedly contributes to a reduction in cell size and somatic growth in these animals, as well as their increased sensitivity to insulin actions [39, 44]. Together with profound suppression of circulating IGF-1, reduced activity of this pathway is among the most likely reasons for a reduced incidence and severity of neoplastic diseases in these dwarfs [45].

Other Mechanisms

Somatotropic signaling and its effects on growth and adult body size appears to be linked with the regulation of aging and longevity by multiple mechanisms. Studies

in mouse mutants characterized by dwarfism and increased longevity indicate that these mechanisms include those listed in the preceding paragraphs as well as shifts in mitochondrial function and metabolism including increased β -oxidation of lipids as energy substrates [46], reduced body temperature [47], improved maintenance of stem cell populations [48], better genome maintenance as suggested by reduced mutation rate [49], enhanced expression of genes involved in metabolism of xenobiotics [50], as well as multiple alterations in the profiles of gene expression in different organs, leading to metabolic adaptations yet to be identified.

Discussion and Conclusions

The common tendency to associate taller stature with physical attractiveness, authority, leadership and social and professional success leads to the perception that, in the realm of human growth similar to economic growth, bigger is better. However, many observations led scientists to question this perception. It has been known for decades that smaller dogs, mice, and horses outlive their larger counterparts and genetically dwarfed mice are remarkably long-lived. This relationship was detected also in studies of some human populations, and taller stature is now regarded as a risk for several common types of cancer. Recent reports indicate that several types of human hereditary dwarfism provide striking protection from major age-related diseases. These findings may appear counterintuitive but fit with the current understanding of the genetic causes of aging and with the concept of 'tradeoffs' between longevity and various phenotypic characteristics reflecting evolutionary fitness.

The reader may ask whether these intriguing relationships have any practical implications for lifestyle recommendations, clinical practice or public health issues. Severely reduced postnatal growth and adult body size in

humans with an absence of GH or GH receptors is clearly not an optimal or a desired phenotype. Moreover, reduced prenatal growth and low birth weight have been associated with an increased risk of chronic disease in adult life. However, an argument can be made that a modest reduction of food intake below the level of current average food consumption in developed countries could provide a measure of protection from diabetes and cancer and likely improve life expectancy by reducing the activity of the somatotrophic axis. In mice, reducing the supply of pre-weaning nutrients by increasing the number of pups per litter slightly reduced adult body size and significantly increased longevity [51]. Modifications of the macronutrient composition of the diet could specifically target IGF-1 and/or mTOR which have been linked to cancer. These considerations may be particularly timely now, when many societies face catastrophic increases in the incidence of obesity and contemplate various means to promote healthier diets and better balance between caloric intake and energy expenditure. There are also exciting prospects that further research into the relationships of the somatotrophic axis, growth and body size to health-span and lifespan will improve our understanding of the developmental and physiological processes that control aging and identify targets for development of novel anti-aging interventions.

Acknowledgements

Our current studies of this topic and preparation of this chapter were supported by National Institute on Aging grants, RO1 AG019899, PO1 AG031736 and R21 AG038850 and Southern Illinois University School of Medicine Geriatrics Research Initiative. The author would like to thank S. Sandstrom and P. Schafer for help in manuscript preparation and apologize to those whose work pertinent to the subject was not cited because of inadvertent omission or space limitations.

References

- 1 Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M, Wei M, Madia F, Cheng CW, Hwang D, Martin-Montalvo A, Saavedra J, Ingles S, de Cabo R, Cohen P, Longo VD: Growth hormone receptor deficiency is associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans. *Sci Transl Med* 2011;3:70ra13.
- 2 McCay CM, Crowell MF, Maynard LA: The effect of retarded growth upon the length of the life span and upon the ultimate body size. *J Nutrition* 1935;10.
- 3 Bartke A, Coschigano K, Kopchick J, Chandrasekar V, Mattison J, Kinney B, Hauck S: Genes that prolong life: relationships of growth hormone and growth to aging and life span. *J Gerontol A Biol Sci Med Sci* 2001;56:B340–349.
- 4 Samaras TT, Elrick H, Storms LH: Height, health and growth hormone. *Acta Paediatr* 1999;88:602–609.
- 5 Silberberg R: Articular aging and osteoarthritis in dwarf mice. *Pathol Microbiol (Basel)* 1972;38:417–430.
- 6 Brown-Borg HM, Borg KE, Meliska CJ, Bartke A: Dwarf mice and the ageing process. *Nature* 1996;384:33.

- 7 Tatar M, Bartke A, Antebi A: The endocrine regulation of aging by insulin-like signals. *Science* 2003;299:1346–1351.
- 8 Kenyon CJ: The genetics of ageing. *Nature* 2010;464:504–512.
- 9 Kimura KD, Tissenbaum HA, Liu Y, Ruvkun G: *daf-2*, an insulin receptor-like gene that regulates longevity and diapause in *Caenorhabditis elegans*. *Science* 1997;277:942–946.
- 10 Tissenbaum H, Ruvkun G: An insulin-like signaling pathway affect both longevity and reproduction in *Caenorhabditis elegans*. *Genetics* 1998;148:703–717.
- 11 Longo VD, Finch CE: Evolutionary medicine: from dwarf model systems to healthy centenarians? *Science* 2003;299:1342–1346.
- 12 Russell SJ, Kahn CR: Endocrine regulation of ageing. *Nat Rev Mol Cell Biol* 2007;8:681–691.
- 13 Coschigano KT, Holland AN, Riders ME, List EO, Flyvbjerg A, Kopchick JJ: Deletion, but not antagonism, of the mouse growth hormone receptor results in severely decreased body weights, insulin, and insulin-like growth factor I levels and increased life span. *Endocrinology* 2003;144:3799–3810.
- 14 Bartke A, Peluso MR, Moretz N, Wright C, Bonkowski M, Winters TA, Shanahan MF, Kopchick JJ, Banz WJ: Effects of soy-derived diets on plasma and liver lipids, glucose tolerance, and longevity in normal, long-lived and short-lived mice. *Horm Metab Res* 2004;36:550–558.
- 15 Bonkowski MS, Rocha JS, Masternak MM, Al-Regaiey KA, Bartke A: Targeted disruption of growth hormone receptor interferes with the beneficial actions of calorie restriction. *Proc Natl Acad Sci USA* 2006;103:7901–7905.
- 16 Flurkey K, Papaconstantinou J, Miller RA, Harrison DE: Lifespan extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production. *Proc Natl Acad Sci USA* 2001;98:6736–6741.
- 17 Kinney BA, Coschigano KT, Kopchick JJ, Bartke A: Evidence that age-induced decline in memory retention is delayed in growth hormone resistant GH-R-KO (Laron) mice. *Physiol Behav* 2001;72:653–660.
- 18 Miller RA, Harper JM, Galecki A, Burke DT: Big mice die young: early life body weight predicts longevity in genetically heterogeneous mice. *Aging Cell* 2002;1:22–29.
- 19 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: Aging in inbred strains of mice: study design and interim report on median lifespans and circulating IGF1 levels. *Aging Cell* 2009;8:277–287.
- 20 Rollo CD: Growth negatively impacts the life span of mammals. *Evol Dev* 2002;4:55–61.
- 21 Patronek GJ, Waters DJ, Glickman LT: Comparative longevity of pet dogs and humans: implications for gerontology research. *J Gerontol A Biol Sci Med Sci* 1997;52A:B171–B178.
- 22 Paradis MR: Demographics of health and disease in the geriatric horse. *Vet Clin North Am Equine Pract* 2002;18:391–401.
- 23 Eigenmann JE, Amador A, Patterson DF: Insulin-like growth factor I levels in proportionate dogs, chondrodystrophic dogs and in giant dogs. *Acta Endocrinol (Copenh)* 1988;118:105–108.
- 24 Samaras TT: Human Body Size and the Laws of Scaling: Physiological, Performance, Growth, Longevity and Ecological Ramifications, ed I. New York, Nova Science, 2007.
- 25 Batty GD, Barzi F, Woodward M, Jamrozik K, Woo J, Kim HC, Ueshima H, Huxley RR: Adult height and cancer mortality in Asia: the Asia Pacific Cohort Studies Collaboration. *Ann Oncol* 2010;21:646–654.
- 26 Sung J, Song YM, Lawlor DA, Smith GD, Ebrahim S: Height and site-specific cancer risk: a cohort study of a Korean adult population. *Am J Epidemiol* 2009;170:53–64.
- 27 Besson A, Salemi S, Gallati S, Jenal A, Horn R, Mullis PS, Mullis PE: Reduced longevity in untreated patients with isolated growth hormone deficiency. *J Clin Endocrinol Metab* 2003;88:3664–3667.
- 28 Oliveira JL, Aguiar-Oliveira MH, D'Oliveira A Jr, Pereira RM, Oliveira CR, Farias CT, Barreto-Filho JA, Anjos-Andrade FD, Marques-Santos C, Nascimento-Junior AC, Alves EO, Oliveira FT, Campos VC, Ximenes R, Blackford A, Parmigiani G, Salvatori R: Congenital growth hormone (GH) deficiency and atherosclerosis: effects of GH replacement in GH-naïve adults. *J Clin Endocrinol Metab* 2007;92:4664–4670.
- 29 Shechter M, Ginsberg S, Scheinowitz M, Feinberg MS, Laron Z: Obese adults with primary growth hormone resistance (Laron syndrome) have normal endothelial function. *Growth Horm IGF Res* 2007;17:165–170.
- 30 Steerman R, Shevah O, Laron Z: Congenital IGF1 deficiency tends to confer protection against post-natal development of malignancies. *Eur J Endocrinol* 2011;164:485–489.
- 31 Jadresic A, Banks LM, Child DF, Diamant L, Doyle FH, Fraser TR, Joplin GF: The acromegaly syndrome. *Quart J Med* 1982;202:189–204.
- 32 Bartke A: Can growth hormone (GH) accelerate aging? Evidence from GH-transgenic mice. *Neuroendocrinology* 2003;78:210–216.
- 33 Krzisnik C, Kolacio Z, Battelino T, Brown M, Parks JS, Laron Z: The 'little people' of the island of Krk – revisited. Etiology of hypopituitarism revealed. *J Endocr Genet* 1999;1:9–19.
- 34 Van Heemst D, Beekman M, Mooijaart SP, Heijmans BT, Brandt BW, Zwaan BJ, Slagboom PE, Westendorp RG: Reduced insulin/IGF-1 signalling and human longevity. *Aging Cell* 2005;4:79–85.
- 35 Suh Y, Atzmon G, Cho MO, Hwang D, Liu B, Leahy DJ, Barzilai N, Cohen P: Functionally significant insulin-like growth factor I receptor mutations in centenarians. *Proc Natl Acad Sci USA* 2008;105:3438–3442.
- 36 Brown-Borg HM, Rakoczy SG, Sharma S, Bartke A: Long-living growth hormone receptor knockout mice: potential mechanisms of altered stress resistance. *Exp Gerontol* 2009;44:10–19.
- 37 Panici JA, Harper JM, Miller RA, Bartke A, Spong A, Masternak MM: Early life growth hormone treatment shortens longevity and decreases cellular stress resistance in long-lived mutant mice. *FASEB J* 2010;24:5073–5079.
- 38 Bokov AF, Lindsey ML, Khodr C, Sabia MR, Richardson A: Long-lived Ames dwarf mice are resistant to chemical stressors. *J Gerontol A Biol Sci Med Sci* 2009;64:819–827.
- 39 Bonkowski MS, Dominici FP, Arum O, Rocha JS, Al-Regaiey KA, Westbrook R, Spong A, Panici J, Masternak MM, Kopchick JJ, Bartke A: Disruption of growth hormone receptor prevents calorie restriction from improving insulin action and longevity. *PLoS One* 2009;4:e4567.
- 40 Berryman DE, List EO, Palmer AJ, Chung MY, Wright-Piekarski J, Lubbers E, O'Connor P, Okada S, Kopchick JJ: Two-year body composition analyses of long-lived GHR null mice. *J Gerontol A Biol Sci Med Sci* 2010;65:31–40.
- 41 Atzmon G, Pollin TI, Crandall J, Tanner K, Schechter CB, Scherer PE, Rincon M, Siegel G, Katz M, Lipton RB, Shuldiner AR, Barzilai N: Adiponectin levels and genotype: a potential regulator of life span in humans. *J Gerontol A Biol Sci Med Sci* 2008;63:447–453.
- 42 Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, Nadon NL, Wilkinson JE, Frenkel K, Carter CS, Pahor M, Javors MA, Fernandez E, Miller RA: Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* 2009;460:392–395.
- 43 Selman C, Tullet JM, Wieser D, Irvine E, Lingard SJ, Choudhury AI, Claret M, Al-Qassab H, Carmignac D, Ramadani F, Woods A, Robinson IC, Schuster E, Batterham RL, Kozma SC, Thomas G, Carling D, Okkenhaug K, Thornton JM, Partridge L, Gems D, Withers DJ: Ribosomal protein S6 kinase 1 signaling regulates mammalian life span. *Science* 2009;326:140–144.

- 44 Sharp ZD, Bartke A: Evidence for down-regulation of phosphoinositide 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR)-dependent translation regulatory signaling pathways in Ames dwarf mice. *J Gerontol A Biol Sci Med Sci* 2005;60:293–300.
- 45 Ikeno Y, Hubbard GB, Lee S, Cortez LA, Lew CM, Webb CR, Berryman DE, List EO, Kopchick JJ, Bartke A: Reduced incidence and delayed occurrence of fatal neoplastic diseases in growth hormone receptor/binding protein knockout mice. *J Gerontol A Biol Sci Med Sci* 2009;64:522–529.
- 46 Westbrook R, Bonkowski MS, Strader AD, Bartke A: Alterations in oxygen consumption, respiratory quotient, and heat production in long-lived GHRKO and Ames dwarf mice, and short-lived bGH transgenic mice. *J Gerontol A Biol Sci Med Sci* 2009;64A:443–451.
- 47 Hauck SJ, Hunter WS, Danilovich N, Kopchick JJ, Bartke A: Reduced levels of thyroid hormones, insulin, and glucose, and lower body core temperature in the growth hormone receptor/binding protein knockout mouse. *Exp Biol Med* 2001;226:552–558.
- 48 Ratajczak J, Shin DM, Wan W, Liu R, Masternak MM, Piotrowska K, Wiszniewska B, Kucia M, Bartke A, Ratajczak MZ: Higher number of stem cells in the bone marrow of circulating low IGF-1 level Laron dwarf mice – novel view on IGF-1, stem cells and aging. *Leukemia* 2011;25:729–733.
- 49 Garcia AM, Busuttill RA, Calder RB, Dollé MET, Diaz V, McMahan CA, Bartke A, Nelson J, Reddick R, Vijg J: Effect of Ames dwarfism and caloric restriction on spontaneous DNA mutation frequency in different mouse tissues. *Mech Ageing Dev* 2008;129:528–533.
- 50 Amador-Noguez D, Dean A, Huang W, Setchell K, Moore D, Darlington G: Alterations in xenobiotic metabolism in the long-lived Little mice. *Aging Cell* 2007;6:453–470.
- 51 Sun L, Sadighi Akha AA, Miller RA, Harper JM: Life-span extension in mice by preweaning food restriction and by methionine restriction in middle age. *J Gerontol A Biol Sci Med Sci* 2009;64:711–722.