Somatic growth, aging, and longevity

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Although larger species of animals typically live longer than smaller species, the relationship of body size to longevity within a species is generally opposite. The longevity advantage of smaller individuals can be considerable and is best documented in laboratory mice and in domestic dogs. Importantly, it appears to apply broadly, including humans. It is not known whether these associations represent causal links between various developmental and physiological mechanisms affecting growth and/or aging. However, variations in growth hormone (GH) signaling are likely involved because GH is a key stimulator of somatic growth, and apparently also exerts various “pro-aging” effects. Mechanisms linking GH, somatic growth, adult body size, aging, and lifespan likely involve target of rapamycin (TOR), particularly one of its signaling complexes, mTORC1, as well as various adjustments in mitochondrial function, energy metabolism, thermogenesis, inflammation, and insulin signaling. Somatic growth, aging, and longevity are also influenced by a variety of hormonal and nutritional signals, and much work will be needed to answer the question of why smaller individuals may be likely to live longer.

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INTRODUCTION

There is considerable evidence that developmental events, including pre-natal and post-natal growth, can have a profound impact on adult phenotypes and risk of chronic disease. In this context, it is interesting to consider to what extent somatic growth and adult body size can influence the trajectory of aging and life expectancy. Pioneering studies of Samaras and his colleagues provided numerous examples of negative association of human height and lifespan. Other investigators emphasized a positive, rather than a negative, association of human stature with various health outcomes, including longevity. However, some of the reported associations are controversial. Importantly, studies from several laboratories reported reduced age mortality and exceptional longevity in individuals with shorter stature and reduced somatotropic signaling. Evidence from genetic studies supports the negative association of somatotropic signaling and height with human longevity. A recent study revealed that the total 24-hour secretion of GH was lower in middle-aged offspring of long-lived families than in their partners.

Deciphering relationships between growth and longevity in human populations is difficult because both can be powerfully influenced by environmental factors including nutrition, numerous public health measures, access to medical interventions and lifestyle factors such as smoking, alcohol, and drug use. In this article, we will briefly review evidence for the links between somatic growth, aging, and longevity in experimental animals and discuss the most likely underlying mechanisms.

“LONGEVITY GENES” AND SOMATIC GROWTH

The very exciting and largely unexpected discoveries of mutations that significantly extend longevity in a worm (Caenorhabditis elegans) or in a fly (Drosophila melanogaster) are an important part of the present understanding of the genetic control of aging. The striking effects of mutations of a single gene on longevity of heterothermic invertebrates led to the question of whether identifiable “longevity genes” also influence aging and lifespan in mammals, including our own species. Studies conducted during the last 25 years in laboratory stocks of house mice (Mus musculus) demonstrated that longevity of these animals can be extended by a natural loss-of-function mutation or targeted deletion of a single gene. With very few exceptions, the genetic modifications which produced a significant and reproducible extension of longevity in both females and males disrupted the so-called “somatotropic axis,” that is, biosynthesis or action of the pituitary growth hormone (GH) and/or the insulin-like growth factor I (IGF-1), an important mediator of GH actions. Since in mammals the somatotropic axis is a key regulator of postnatal growth, these long-lived mutants exhibit major reductions in growth rate and in adult body size. It should be emphasized that the remarkably extended longevity of GH-deficient and GH-resistant mice is associated with multiple signs of delayed aging and with the extension of “healthspan,” the period of life free of functional deficits and chronic disease. This includes maintenance of normal cognitive function (learning and memory) into advanced age. The rate of aging of these long-lived mutants was initially reported to be either reduced or unaltered, with life extension being due to a delay, rather than a slowing, of age-related mortality. However, a more recent analysis using what we believe is a more pertinent methodology suggests that the rate of aging of long-lived, GH-deficient and GH-resistant mice is initially slower than in genetically normal (control) animals and accelerates only later in their life, after most of the control animals have died.

Extended longevity and phenotypic characteristics of animals with deletion of genes acting downstream from the IGF-1 receptor such as IRS-1, IRS-2, or Akt and the well-documented anti-aging effects of calorie restriction, provide additional examples of...
the negative association of somatotropic signaling and growth with healthy aging and lifespan.

**GROWTH VS. LONGEVITY IN TRANSGENIC AND IN GENETICALLY NORMAL ANIMALS**

The reciprocal relationship of longevity to growth rate and adult body size discovered in various dwarf mutants also applies to animals in which somatic growth and adult body size are experimentally enhanced. Transgenic mice, chronically expressing heterologous (in most cases bovine or human) GH in liver and other organs under control of metallothionein I or phosphoenolpyruvate carboxykinase promoters, grow faster than normal animals and achieve a greater adult body size, often exhibiting a very striking giant phenotype. These animals have much shorter lives than their normal siblings and exhibit multiple characteristics of early (premature) aging. Experimental animals with extreme phenotypes, such as encountered in genetic dwarfs and giant transgenics, are useful for identifying the underlying mechanisms and previously unsuspected physiological relationships. However, it is of obvious importance to determine whether the associations and causal relationships described in these animals apply to organisms that have not been genetically altered and to genetic and phenotypic variations within the normal range. In fact, the negative association of longevity with adult body weight has been demonstrated in comparisons of normal ("wild type") animals from different stocks, inbred strains and selected lines in studies going back to the '60s, and, more recently, in comparisons of individual animals from a normal, genetically heterogeneous population.

Importantly, the negative association of body size and longevity extends to other mammalian species, with differences in longevity between different breeds of domestic dogs, and between individual dogs differing in size providing the most striking example. It is interesting, but currently difficult to explain, why these relationships within species are opposite to the fairly consistent trend for large species of mammals and birds living longer than smaller species. One could speculate that because smaller species are more vulnerable to predation and other environmental hazards, they have developed life-course strategies for early reproduction and high fecundity. This, in turn, may divert available resources away from repair and maintenance and thus lead to a shorter lifespan. The surprising tendency of circulating IGF-1 levels to be lower, rather than higher, in large species may also prove to be a contributing factor to their longevity.

**SEARCH FOR MECHANISMS LINKING SOMATIC GROWTH WITH AGING AND LONGEVITY**

The (very consistent) negative association of adult body size and longevity in laboratory mice and other mammalian species brings up the questions of causality and underlying mechanisms. Available data can be interpreted as evidence that normal growth involves some intrinsic "costs" in terms of aging and longevity. Thus, faster or longer growth, and the consequent attainment of greater body size, somehow predispose the organism to earlier and/or faster aging and a shorter lifespan. The underlying mechanisms could be envisaged to influence growth with a secondary impact on aging and lifespan, or to independently influence both growth and aging, possibly via different signaling pathways or cellular processes (Fig. 1). In either case, identifying the mechanisms involved is an important goal of our research and work in other laboratories. Comparing gene expression and phenotypic characteristics of long-lived mutants which have various defects in the somatotropic axis with the same characteristics of age-matched and sex-matched normal animals from the same strain identified a number of suspected mechanisms of extended longevity. Defining the role of these mechanisms in the extension of healthspan and lifespan in the examined mutants is complicated by the fact that many of the differences between mutant and control ("wild type") animals...
could represent either mechanisms or markers of delayed and/or slower aging. For example, long-lived Ames dwarf and growth hormone receptor knockout (GHRKO) mice are more insulin sensitive than their normal siblings, but insulin sensitivity generally declines during aging. Thus, this difference could simply confirm the fact that at the same chronological age, the long-lived dwarf mice are biologically younger. This difficult issue was addressed in one of our studies by comparing gene expression data in long-lived mutants to two groups of normal animals that were either of the same chronological age or a comparable "biological age," that is their age represented a similar percent of their life expectancy. In this particular study, differences in hepatic expression of the examined genes in GHRKO vs. normal mice were shown to be due to the differences in genotype rather than in biological age. However, we are not aware of a similar analysis being performed in other long-lived mutants or in studies examining other candidate mechanisms of aging.

Detailed discussion of all the mechanisms that appear to be involved in linking reduced somatotropic signaling to slower aging and extended longevity is outside the scope of this review. Interested readers are referred to several recent review articles. Mechanisms most likely related to the negative association of somatic growth and longevity and to the opposite effects of GH signaling on these processes are briefly discussed below.

MECHANISTIC TARGET OF RAPAMYCIN (mTOR)
The ability of GH to directly or indirectly activate the mTOR signaling pathway provides one of the most likely explanations of how this hormone can exert positive effects on somatic growth and negative effects on the lifespan. Mechanistic TOR (mTOR) pathway integrates somatotropic, nutritional and stress signals and plays a role in the control of autophagy and cell senescence. While activation of mTOR signaling prevents cell death, promotes protein synthesis, growth and cell divisions, it apparently also accelerates aging. Blagosklonny and his colleagues suggested that aging can be viewed as "a continuation of developmental growth driven by genetic pathways such as mTOR". These investigators also proposed that gender differences in longevity of mice may be related to greater mTOR activity in males and that conversion of reversible cell cycle arrest to senescence (termed "geroconversion") represents one of the mechanisms by which mTOR promotes aging. The excess "developmental" growth driven by mTOR presumably contributes to the accumulation of unfolded proteins, endoplasmic reticulum (ER) stress, and reactive oxygen species (ROS) production, and leads to inhibition of autophagy and promotion of cell senescence.

Pharmacological or genetic suppression of mTOR signaling pathways results in extended longevity in organisms ranging from yeast to mice. mTOR exerts its function via two complexes: mTORC1 and mTORC2. There is increasing evidence that the "anti-aging" effect of mTOR suppression is due to inhibition of mTORC1 signaling. For example, long-lived mice with disrupted somatotropic axis have diminished mTORC1 signaling, while mTORC2 activity may be increased.

mTORC2 appears to act to prevent, rather than promote aging, and consequently, its inhibition can reduce longevity. The evidence for anti-aging effects of mTORC2 signaling includes demonstration that genetic deletion of Rictor, a mediator of mTORC2 signaling, reduces longevity in male mice. Interestingly, body weight and accumulation of white adipose tissue (WAT) in these animals were increased, suggesting that mTORC2, in contrast to mTORC1, may normally act as a negative regulator of growth. Further support of the role of TORC-2 in the control of aging, adipose-specific deletion of Rictor leads to increases in body size, weight of non-adipose organs and levels of IGF-1, IGFBP3, and insulin with a concomitant decrease of adiponectin, i.e., produces phenotypic characteristics generally associated with accelerated aging.

ENERGY METABOLISM AND THERMOGENESIS
Another mechanism which may contribute to the longevity benefits of small body size involves adjustments in mitochondrial function and energy metabolism in response to greater heat loss and increased demand for thermogenesis. Smaller individuals have a greater body surface to body mass ratio and, thus, lose heat faster. Therefore, they have to increase thermogenesis to maintain body temperature. This physiological response is of particular significance in laboratory mice whose thermoneutral temperature is ~30 °C (86 °F) and, thus, housing at a "standard" animal room temperature (~22 °C, or 72 °F) represents a chronic mild cold stress. The long-lived diminutive GHRKO and hypopituitary dwarf mice, in fact, exhibit increases in the mass and activity of brown adipose tissue (BAT), the key site of non-shivering thermogenesis, along with evidence for thermogenic activation, the so-called "browning" of BAT. Reduced body temperature in these animals is reflected in increased consumption of oxygen per gram of body weight and is accompanied by a marked reduction in respiratory quotient (RQ, equivalent to respiratory exchange ratio). Reduced RQ implies increased reliance on fatty acids as a metabolic fuel which is generally considered a marker of improved mitochondrial efficiency leading to generation of smaller amounts of noxious ROS. In fact, reduced RQ in long-lived dwarf mice is associated with increased expression of genes involved in β-oxidation of free fatty acids (Sun L, Darcy J, and Bartke A, unpublished) and with reduced ROS generation. These alterations, together with improved anti-oxidant defenses, probably account for less oxidative damage to DNA and other macromolecules in these long-lived animals. Although it remains to be conclusively proven which of these associations are causally related to aging, we believe that improvements in mitochondrial function in response to increased demand for thermogenesis represent one of the mechanisms linking reductions in somatotropic signaling, growth and adult body size to slower (and/or delayed) aging and extended longevity.

INDIRECT LINKS BETWEEN SOMATIC GROWTH AND LONGEVITY
In addition to the mechanisms discussed above, the negative association of body size and longevity within a species likely reflects several indirect, but important, mechanisms. These include pleiotropic actions of GH which affect both body size and aging, acting through different, but likely physiologically related mechanisms. Growth hormone is a key regulator of hepatic IGF-1 expression, circulating IGF-1 levels, growth and adult body size, but it also appears to promote aging by a variety of actions such as inducing insulin resistance promoting cell senescence and chronic low grade inflammation, as well as favoring differentiation and depletion of at least one type of stem cell. Thus, the spectrum of known biological actions of GH could explain why growth and adult body size would tend to be negatively associated with longevity.

Another indirect link between body size and longevity concerns alterations in disease risk. Growth hormone and IGF-1, as well as stature, have been related to cancer incidence on the basis of numerous in vitro, in vivo and epidemiological studies. Severe GH resistance in the syndrome of Laron dwarfism produces a remarkable degree of protection from cancer. Neoplastic disease may have little if any influence on aging, but it has an obvious and major impact on longevity. This is particularly striking in laboratory mice in which cancer is an important and, in many strains, by far...
the most common cause of death. The fact that GH induces insulin resistance, an important element of the metabolic syndrome, prediabetes and diabetes, should also be mentioned in this context. The risk of diabetes is increased in association with abnormally elevated GH levels in acromegaly.83 and reduced in the GH-resistant individuals with Laron syndrome.84

Impacts of nutrition on growth, body composition, disease risk and aging are outside of the scope of this brief article, but can provide yet another indirect mechanism for the observed associations. Thus, both pre-natal and post-natal overnutrition can stimulate growth, as well as obesity and also increase risk of various chronic diseases in adulthood.85,86 Rapid growth in response to food availability after a period of nutrient shortage, the so-called “catch-up growth”, may be particularly important in this context.87–89 Increased risk of chronic disease in adult life can obviously reduce longevity and it also may represent a symptom of accelerated aging.90,91 Results of recent and ongoing studies in our laboratory indicate that treatment of hypopituitary Ames dwarf mice with GH injections during a relatively brief period (6 weeks) during development increases adult body size and significantly reduces the remarkably long lifespan of these animals.92,93 Importance of early (peripubertal) GH actions in the control of longevity is indirectly supported by the recent report that disruption of the GH receptor gene in adult mice produces a relatively modest increase in lifespan only in females.94

It should also be mentioned that the endocrine basis of the complex relationships between growth-related processes and aging is not limited to the somatotropic axis. Ames and Snell dwarfs, which represent some of the extremes of mouse longevity, are both GH- and thyroid stimulating hormone-deficient and, thus, profoundly hypothyroid.18,19 Chronic thyroid treatment can shorten longevity of Snell dwarf mice,95 as well as normal rats96 while subclinical hypothyroidism was associated with exceptional longevity in women.97,98 However, treatment of dwarf mice with thyroxine limited to the peripubertal period did not alter their longevity.93,99

The relationships between the activity of the hypothalamic-pituitary-adrenal axis and aging are complex and poorly understood.100 However, chronic elevation of glucocorticoid levels can promote age-related pathology, and is suspected of contributing to accelerated aging of GH transgenic mice.101 Much more work will be needed to determine whether the association of reduced body size with extended longevity is truly causal, and to identify the mechanisms underlying this association.

CONCLUSIONS

Negative association of longevity with GH signaling, somatic growth and adult body size discovered in GH-deficient and GH-resistant mutant mice applies also to genetically normal individuals and to other mammalian species. Stimulation of mTORC1 singling by the somatotropic axis could explain this association but many other mechanisms appear to be involved.

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AUTHOR CONTRIBUTION

A.B. searched the literature, reviewed unpublished data, and wrote the article.

ADDITIONAL INFORMATION

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