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Growth Hormone and Aging: New Findings

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Complex relationships between growth hormone (GH) signaling and mammalian aging continue to attract attention of many investigators. Recent results include evidence that the impact of GH on genome maintenance (DNA damage and repair) is drastically different in normal as compared to cancer cells, consistent with GH promoting aging and cancer progression. Impact of GH on DNA methylation was studied as a possible mechanism linking actions of GH during early life to the trajectory of aging. Animals with reduced or enhanced GH signaling and novel animals with adipocyte-specific deletion of GH receptors were used to elucidate the effects of GH on white and brown adipose tissue, including the impact of this hormone on lipolysis, fibrosis, and thermogenesis. Effects of GH on adipose tissue related to lipid and energy metabolism emerge as mechanistic links between GH, healthspan, and lifespan. Treatment of healthy men with a combination of GH, dehydroepiandrosterone, and metformin was reported to restore thymus function and reduce epigenetic age. Studies of human subjects with deficiency of GH or GH receptors and studies of mice with the same endocrine syndromes identified several phenotypic changes related (positively or negatively) to the previously reported predisposition to healthy aging. Results of these and other recent studies advance present understanding of the mechanisms by which GH influences aging and longevity and of the trade-offs involved.

Keywords: Aging; DNA methylation; Growth hormone; Healthy aging; Longevity

INTRODUCTION

In an article published in this journal in January 2019, we presented the evidence that growth hormone (GH) has an important role in the control of aging and longevity [1]. Much of the evidence for this role of GH was derived from studies of mice with spontaneous or experimentally induced mutations affecting the somatotropic axis and transgenic mice with chronic increase in circulating GH levels. Results of these studies indicated that (i) major elevation of GH levels accelerates aging and shortens life; (ii) stimulatory actions of normal (physiological) GH levels on growth, maturation, and fecundity involve costs in terms of the rate of aging and average as well as maximal longevity; and (iii) suppression of GH signaling slows the process of aging, increases healthspan, and remarkably extends longevity at the expense of reduced growth, delayed puberty, diminutive adult body size, and reduced fecundity. Importantly, these effects of GH on aging as well as the associated trade-offs were shown to apply to normal mice (animals without genetic modifications)

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and to other mammalian species.

In humans, familial longevity is associated with reduced GH secretion, and height, a strongly GH-dependent trait, is negatively correlated with longevity in many (although not all) of the examined populations. Hereditary conditions of isolated GH deficiency (IGHD) or GH resistance do not extend human longevity, but appear to extend healthspan and provide strong, and in some cases complete, protection from age-associated diseases. Pathological elevation of GH levels in the syndrome of acromegaly reduces both healthspan and life expectancy, likely reflecting acceleration of the aging process.

Paradoxically, recombinant GH treatment of middle aged or elderly subjects, in whom secretion of GH is naturally reduced, can have beneficial effects on body composition along with subjective improvement in various aspects of the quality of life. Beneficial effects of insulin-like growth factor I (IGF-I), a key mediator of GH actions on various aging-associated traits, support the notion that GH can act as an anti-aging agent. However, age is not among the approved indications for GH therapy and side effects and risks of GH therapy are generally believed to outweigh known or hoped-for benefits.

Available evidence indicates that most of the aging-related effects of GH which were discovered in laboratory mice apply to other mammals, including humans, but important species differences also exist. We speculate that differences in the impact of GH on longevity in mice *versus* people stem from major differences in life history, energy partitioning, and reproductive strategy between species with a different pace-of-life. The slow pace-of-life of humans combined with the impacts of social organization, public health measures, and medical advances, favors longevity and makes it difficult to induce further increase in lifespan.

In this update of the topic of GH and aging, we will discuss recent findings related to this issue with focus on the mechanism linking GH signaling with aging and on aging related traits of humans with major alterations of GH signaling.

GROWTH HORMONE EFFECTS ON DNA DAMAGE AND REPAIR

Damage to DNA, including single- and double-strain breaks, along with accumulation of somatic mutations, is involved in aging and in carcinogenesis. Repair of DNA damage and genome maintenance are crucially important in prevention of premature aging [2,3], and both GH and IGF-I are involved in these processes. Actions of both GH and IGF-I have been linked to development and progression of neoplastic disease [4-6]. Moreover, there is considerable epidemiological evidence for a positive association of height, a GH and IGF-I dependent trait, with various types of cancer in women and men [7-9]. Cancerous cells can be affected not only by the pituitary derived (endocrine) GH, but also by the autocrine GH produced by tumors, including GH secreted by senescent cells within the tumor tissue [4]. Recent work provided new evidence for divergent actions of GH in cancer as compared to normal cells. In various types of cancer cells, GH supports DNA damage repair and protects from death induced by radiation or drugs used in chemotherapy [6,10-12]. Consistent with these effects, genetic suppression on GH signaling in mice reduces incidence and progression of neoplastic lesions [13,14], slows growth of chemically-induced cancers [15], and increases effectiveness of chemotherapy [6].

In contrast to the effects of GH on DNA damage and repair in cancers, GH was shown to induce DNA damage in normal (non-transformal) cells and tissues, increase sensitivity to DNA-damaging agents, and reduce DNA repair [16-19]. Mechanisms of these effects include oxidative stress, altered phosphorylation of ataxia-telangiectasia-mutated kinase and p53 protein, and changes in the expression of genes related to stress response or to repair pathways [16,20-22]. Reduced levels of DNA damage and enhanced capacity for DNA repair undoubtedly contribute to extended healthspan and lifespan of GH-deficient and GH-resistant mice and to the remarkable protection of GH-resistant individuals from cancer [23].

THE RATE OF EPIGENETIC AGING IS RELATED TO BODYWEIGHT, A GROWTH HORMONE-DEPENDENT TRAIT

Recent work provided considerable evidence that analysis of DNA methylation can be used to develop a very accurate "epigenetic clock" of aging [24-27]. In addition to creating a novel biomarker of aging, this approach allows estimating the biological (as opposed to the chronological) age and detecting changes in the

rate of aging. This includes deceleration of aging by calorie restriction or life-extending mutations and acceleration of aging by obesity [28,29].

Sandoval-Sierra et al [30] analyzed epigenetic aging of female mice from a group of recombinant inbred strains that differ in multiple phenotypic characteristics including bodyweight and longevity. Recombinant inbred strains are produced by crossing animals from two different inbred strains (in this case, C57BL6 and DBA2) and then inbreeding their progeny by repeated brother X sister mating. The resulting strains (also referred to as "lines") represent genetically homogenous populations of animals homozygous for different combinations of genes derived from parental strains. Mice used for this study included animals from three short-lived lines with mean lifespans ranging from 417 to 585 days and from five long-lived lines with mean lifespans ranging from 771 to 993 days. Epigenetic age was calculated from age-related differentially methylated regions and age acceleration (negative or positive) was calculated by relating epigenetic age to chronological age. The results revealed age-accelerating effect of greater adult bodyweight [30]. These findings relating epigenetic aging to bodyweight represent a significant addition to previous evidence for a negative association of body size and longevity among members of the same species [1,31]. Apparently, differences in the rate of biological aging are responsible for the impact of body size on life expectancy. These results also suggest an exciting possibility that further analysis of the expression of genes in differentially methylated regions will identify a mechanism linking DNA methylation to growth, aging, and trade-offs between these processes.

IMPACT OF GROWTH HORMONE ON ADIPOSE TISSUE; RECENT ADVANCES

GH influences the amount and function of both white and brown adipose tissue (WAT and BAT). Many of the effects of GH on adipose tissue have been related to aging and longevity. Severe suppression or absence of GH signals in long-lived Prop1^{df} and Ghr-/- mice is associated with reduced expression of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α [32,33], and increased expression of adiponectin which exerts anti-inflammatory and anti-atherogenic effects and improves insulin sensitivity [34,35]. Curiously, these shifts in the secretory profile of WAT coexist with an increase in adiposity. This association is opposite to what is usually seen in comparisons of lean, normal weight, and obese individuals. Similar association of increased obesity and increased levels of adiponectin was described in subjects with IGHD from the Itabaianinha cohort in Brazil [31].

In mice with genetic GH deficiency or resistance, the amount and thermogenic activity of BAT is increased and there is increased "beiging" of subcutaneous WAT along with increased utilization of fats (as opposed to carbohydrates) as an energy substrate [34,36]. These characteristics almost certainly contribute to healthy aging and extension of longevity in these animals. Yet another link between the actions of GH on adipose tissue and aging concerns the lipolytic actions of this hormone, with reduction of adiposity in middle-aged and elderly individuals seen as signs of rejuvenation that is anti- (rather than pro-) aging effects of GH [37].

In a paper published in 2018, Householder and her colleagues reported novel evidence for promotion of WAT fibrosis by GH [38]. The role of GH in the control of collagen content in WAT was documented using transgenic mice expressing GH or a GH antagonist, and mice in which GH levels are elevated due to deletion of GH receptor in the liver and consequent disruption of the IGF-I mediated negative feedback control of GH release. Moreover, GH-stimulated increase in the expression of the collagen gene was shown *in vitro* in cultured 3T3-Li cells [38].

Recent advances in the studies of the actions of GH on adipose tissue included characterization of a novel animal model for such studies, a mouse with deletion of GH receptor specific to adipocytes, FaGHRKO [39]. These animals have increased size of all major WAT depots (except for epididymal fat pads in males), increased size of adipocytes, reduced WAT fibrosis, improved glucose homeostasis, and reduced triglyceride content of the liver. These findings imply that some of the important beneficial effects of whole body (germline) GHR deletion described previously in Ghr-/- animals were due to suppression of GH signaling in adipose tissue. Curiously, adiponectin levels in adipocyte-specific GHR null mice are reduced; a change opposite to that seen in response to global GHR deletion [34].

Another novel animal model developed in the same laboratory is a mouse with disruption of the GH gene [40]. These GH-/- animals with IGHD have the expected

severe reduction of IGF-I levels, somatic growth, and adult body size, along with increased adiposity and extreme insulin sensitivity. The effects of GH deficiency on WAT are depot-specific, with increased size of adipocytes and reduced fibrosis in subcutaneous but not perigonadal WAT. Glucose tolerance in GH-/- mice is reduced despite their extreme insulin sensitivity. This is associated with reduced size of pancreatic islets and almost certainly represents reduced ability to produce a surge of insulin secretion in response to a rapid increase in blood glucose levels. In other words, the dissociation of changes in insulin and glucose tolerance in these animals presumably reflects reduced insulin secretory reserve. In GH-deficient $Prop1^{df}$ (Ames dwarf) mice, insulin sensitivity is markedly increased as determined by the ratio of circulating insulin and glucose levels (homeostatic model assessment, HOMA), insulin tolerance, and results of clamp studies [41-43]. However, improvements in glucose tolerance are less consistent [41-43]. This has been related to reduced area and volume of the islets of Langerhans in these animals [44] and to reduced insulin secretory response to exogenous glucose [41] or refeeding after a fast (Bartke, unpublished). Clamp studies showed greater regulation of glucose metabolism in the liver in these dwarf animals with enhanced glucose clearance through glucose uptake by skeletal muscle and white adipose tissue [45]. Insulin is reduced also in Ghr-/- mice, consistent with the role of GH and IGF-I in the development and function of pancreatic beta cells [46,47].

Acute lipolytic effects of GH were recently studied by Høyer et al [48] in human subjects treated with GH, in novel FaGHRKO mice mentioned earlier in this section, and in 3T3-L1 adipocytes. The results indicated that GH stimulates lipolysis in a GHR-dependent manner, and that this action of GH involves suppression of antilipolytic signals at gene expression level. Antilipolytic signals suppressed by GH included PDE3b, GOS2, and RASD, which are upregulated by insulin or are insulin dependent. Moreover, GH upregulated PTEN, a suppressor of insulin signaling [48]. These findings expand the present understanding of lipolytic and antiinsulinemic actions of GH, which are importantly associated with the phenotypic characteristics of animals in which the rate of growth, development, and aging are altered by suppression or enhancement of GH signaling.

Long-lived mice with mutations disrupting GH signaling have increased amount and activity of BAT, increased oxygen consumption (VO_2), and reduced respiratory quotient (RQ, equivalent to respiratory exchange ratio, RER), a marker of increased oxidation of free fatty acids [36]. We hypothesized that these changes in energy metabolism represent enhanced thermogenic response to the standard animal room temperature likely due to increased body surface to body mass ratio in these diminutive animals. In support of this hypothesis, we have recently shown that housing Ames dwarf mice at increased environmental temperature (approximately 30°C, considered thermoneutral for mice) normalizes these markers of energy metabolism leading to disappearance of differences between VO_2 and RQ values measured in dwarf and normal mice [49]. Importantly, normalization of VO_2 and RQ values in Ames dwarfs was associated with impairment (that is, partial normalization) of glucose homeostasis. This indicates that the exquisite insulin sensitivity characterizing these long-lived mutants is due, in part, to increased thermogenesis and thus adds to the evidence that mitochondrial uncoupling in BAT and beige adipose tissue is beneficial for health and longevity [50,51]. Recent analysis of metabolome and lipidome in BAT and WAT of Ames dwarfs and their normal siblings revealed features consistent with increased thermogenesis and enhanced insulin sensitivity, including an increase in cardiolipin and a decrease in ceramide [52]. Of particular interest was increase in 5-hydroxyeicosapentaenoic acid (5-HEPE) in BAT and blood serum of Ames dwarf mice. Increased 5-HEPE is a marker of BAT activation and, in humans, 5-HEPE levels are negatively correlated with body weight, insulin resistance, and blood levels of triglycerides [51,52].

In addition to influencing the accumulation, distribution, and function of WAT and BAT, GH also plays a role in the induction of thermogenic functions in WAT, the so-called WAT "beiging." In a recent study, formation of beige fat *in vivo* was shown to depend on activation of STAT5 by GH [53]. This action of GH sensitizes WAT to adrenergic input and thus likely contributes to anti-obesity effects. Other studies showed that lack of GH signaling in GHR-/- and Ames dwarf mice alters the function of adipose tissue. Surgical removal visceral fat in improved insulin sensitivity and glucose tolerance in normal animals, while the same procedure produced no metabolic benefits or had detrimental effects in long-living dwarfs [35,42].

INVOLVEMENT OF THE SOMATOTROPIC AXIS IN SEXUALLY DIMORPHIC EFFECTS OF ANTI-AGING INTERVENTIONS

Several of the drugs which were shown to significantly extend longevity of laboratory mice have much stronger beneficial effects in one sex or are effective only in one sex [54,55]. We suspected involvement of the somatotropic axis in these sex differences because the secretory pattern of GH is strongly sexually dimorphic (with different frequency of GH peaks in the plasma) and sex differences in various characteristics, including hepatic transcriptional profile and expression of enzymes involved in drug metabolism, are due to the differences between the sexes in the pattern of GH release [56-58]. Treatment of mice with Estradiol 17 alpha (17αE2; a weakly estrogenic compound, distinct from the main female sex hormone, estradiol 17 beta) produces health benefits such as improved insulin sensitivity and extends longevity in males but not in females [59]. We found that treatment with 17αE2 increased hepatic IGF-I production exclusively in males [60]. Surprisingly, this effect did not involve modifications of the pattern of GH release or "feminization" of the hepatic transcriptional profile. However, this effect of 17αE2 on IGF-I production was GH-dependent since it was not elicited in GH-resistant Ghr-/- mice [60]. Apparently, anti-aging effects of 17αE2 in male mice are GH-dependent and involve alterations in IGF-I, but not GH dynamics. Studies of the effects of 17αE2 on the ovaries of normal mice and GHR-/- mice in which ovarian as well as somatic aging are delayed, revealed that in the absence of GH signals, 17αE2 decreased the number of primordial follicles, an index of ovarian aging [61]. These studies indicate that the complex interplay of sex steroids and the somatotropic axis includes regulation of gonadal aging as well as somatic aging and longevity.

NOVEL FINDINGS IN INDIVIDUALS WITH GROWTH HORMONE DEFICIENCY OR GROWTH HORMONE RESISTANCE

Adult GH deficiency can lead to unfavorable changes in body composition and to reduced quality of life and constitutes an approved indication for GH replacement therapy [62,63]. Congenital GH deficiency has been associated with increased risk of cardiovascular disease and, in one study, reduced life expectancy [64]. In contrast to these reports, long term follow-up of large homogenous cohorts of individuals with hereditary IGHD or severe GH resistance (Laron syndrome) provided evidence for normal lifespan, protection from chronic age-related disease, and various indications of healthy aging and extension in healthspan [23,31,65]. Since our review of findings concerning aging of individuals with these endocrine syndromes published in this journal in 2019 [1], additional data concerning impact of IGHD and GH resistance on health and aging became available.

Marinho et al [66] reported that subjects with IGHD from the Itabaianinha cohort (*i.e.*, subjects with the Itabaianinha syndrome) are not fully protected from cancer. Four cases of skin cancers (three epidermoid cancers and one fibroepithelial polyp) were detected, one of which was fatal. In addition, one subject who had GH replacement therapy earlier in her life, developed an ependymoma and appears to be tumor-free after surgical treatment. It was also shown that subjects with this syndrome have a reduction in sleep quality with no subjective consequences on the quality of life [67], deeper periodontal pockets with locally increased levels of several immune mediators [68], as well as higher prevalence of modest vestibular impairment and abnormal vestibular ocular reflex, likely related to the reported dizziness but without negative effects on postural balance or fall risk [69]. Furthermore, IGHD subjects had improved insulin sensitivity (ower homeostatic model assessment for insulin resistance [HOMA-IR], reduced creatine phosphokinase [CPK], higher C-reactive protein [CRP], lower sweating, normal vitamin D levels, and normal phosphorus: calcium homeostasis [70]. No detrimental changes were detected in muscular function [71] or in cerebral vasoreactivity, a surrogate marker of cerebrovascular disease [72]. The changes in GLP-1 secretion and postprandial ghrelin levels detected in IGHD subjects from this cohort were viewed as favorable [73]. Interestingly, macrophages from subjects with the Itabaianinha syndrome were less prone to infection by *Leishmania amazonensis* [74]. This appears to be related to reduced circulating IGF-I levels in these individuals, because adding IGF-I to the medium increased the infection rate [74]. The picture that emerges from these and previous studies by the group of Prof. Aguiar-Oliveira is that severe (but not

complete) suppression of GH secretion in these subjects leads to multiple functional changes, some of which are beneficial and some detrimental, with the beneficial effects prevailing in terms of the apparent extension of health span and reduced risk of age-related chronic disease [31,65,75].

Individuals with congenital GH resistance (GH receptor deficiency, GHRD, Laron syndrome) from the large and genetically uniform Ecuadorian cohort are remarkably protected from diabetes and cancer [23]. Although their average longevity does not significantly differ from their unaffected relatives or the general population, their cognitive performance is better and structural features of their brains resemble those found in younger adults [76]. In a recent study, Guevara-Aguirre et al [77] examined correlations of various parameters of carbohydrate metabolism and brain characteristics. Results confirmed the association of enhanced insulin sensitivity with brain structure and function and uncovered a unique relationship of the levels of free IGF-binding protein 1 (IGFBP1) to the main elements of carbohydrate metabolism in individuals with GHRD which was not present in their unaffected relatives. The authors interpreted their findings as suggestive of a direct relationship between an efficient insulin sensitivity and healthy brain [77]. Since IGF-I, the key mediator of some of the GH actions, is known to be neurostimulatory and neuroprotective, the evidence for improved brain structure and function in individuals with GHRD and severely reduced circulating IGF-I levels would appear counterintuitive. Improved insulin sensitivity, reported by Guevara-Aguirre et al [77], provides a plausible explanation of this paradox. It should also be mentioned that IGF-I expression in the brain may not be GH-dependent [78,79].

CAN GROWTH HORMONE REVERSE AGING?

Effects of GH therapy in a group of elderly men reported by Rudman et al in 1990 [37], suggested that GH can reverse an increase in adiposity, a decline in muscle mass, as well as other symptoms of aging. This led to a surge of interest in the potential benefits of GH therapy and to aggressive promotion of GH, as well as nutritional supplements intended to stimulate endogenous GH secretion, as anti-aging agents. The notion of GH being an "elixir of youth" was largely discredited in subsequent studies which show that GH treatment of adults without established GH deficiency produces no clear benefits except for a modest improvement in body composition, and that these benefits are outweighed by undesirable side effects [80]. Moreover, studies in many laboratories indicated that in experimental animals, physiological as well as excessive GH levels act to promote, rather than to prevent, aging [1,31]. However, the relationship of GH actions at various stages of life history to aging and longevity remains to be fully explored and the controversies concerning species differences and dose-response relationships remain to be resolved. These issues are further complicated by the fact that IGF-I, the key mediator of GH actions on somatic growth, impacts metabolism and body composition very differently from GH. Moreover, IGF-I has divergent effects on different accompaniments of aging. It has well-documented neuroprotective and neurostimulatory actions, and it is also positively related to the incidence and progression of cancers.

A very interesting recent study addressed the issue of potential utility of GH for rejuvenation, that is reversal of the process of aging. In this study, ten healthy men, ranging in age from 51 to 65 years, were treated for one year with a combination of GH, metformin, and dehydroepiandrosterone [81]. The treatment was designed to promote restitution of thymic function and it did produce beneficial changes in several immunological parameters. Moreover, it reduced the biological age of the subjects as assessed by measurements of DNA methylation (the "methylation clock"). Report of these findings was followed by publication of a commentary on the likely utility of this therapeutic approach for protection from Covid-19 infection and Covid-19-induced pathology and complications [82]. These findings are not likely to end the controversy concerning GH as an anti-aging agent. The authors focus on evidence that GH can improve various facets of immune system maintenance and its responses to infection and cite important supporting evidence. However, GH was also reported to have pro-inflammatory effects by promoting cell senescence and secretion of pro-inflammatory cytokines while reducing the secretion of anti-inflammatory adiponectin [26-28,83]. IGHD was reported to protect from Leishmania infection [74]. Apparently, GH has divergent effects on different aspects of immune function, inflammation, and responses to infection. Different, and in many cases opposite,

changes in different markers of immune function were reported in acromegalic patients [84,85], as well as in long-lived GH-resistant Ghr-/- mice [33,86].

GH receptors are widely expressed in the central nervous system (CNS) [87], suggesting that GH may affect development and maintenance of brain tissue and regulate cognitive health during aging. Studies shows that IGF-I is an important factor for neuronal cell survival and repair and that it plays major role in neurogenesis, synaptogenesis, and cerebrovascular integrity [88]. Balasubramanian et al [89] argued that age-dependent IGF-I decline or IGF-I deficiency may also impact aging through modulation of autonomic nervous system. Interestingly, intranasal delivery of IGF-I in old mice showed improvement in learning and memory [90]. However, there is currently no evidence to support safe use of GH for cognitive impairment therapy in humans [91].

NOVEL MECHANISMS LINKING GROWTH HORMONE AND AGING

Studies in mice with genetic disruption of somatotrope differentiation, GH secretion, or GH receptors identified multiple candidate mechanisms of slower and/or delayed aging of these animals. Although positive identification of the underpinning cause-effect relationships will require further work, the available data indicate that a complex network of interacting mechanisms is responsible for the observed extension of healthspan and lifespan in mice with absence or severe suppression of GH signals [1,31]. Several recent studies identified additional characteristics of hypopituitary, GH deficient, or GH resistant mice that likely represent mechanisms of their remarkable longevity. Jensen et al [92] compared gut microbiomes in adult GH-deficient GH-/- mice and in transgenic mice expressing high levels of bovine GH. The results revealed alterations in the abundance of different types of bacteria, with changes in the GH-deficient mice being generally opposite to changes detected in animals with GH excess. These studies also suggested GH promotes maturity of the microbiome. In the same year, Wiesenborn et al [93] described differences in gut microbiota between juvenile Ames dwarf mice and their normal siblings. In this study, the impact of a life extending *Prop1* gene mutation on the microbiome was more pronounced than the impact of six months of calorie restriction. Rapidly accumulating evidence for a major role of gut microbiome in the control of metabolism and risk for various diseases suggests that changes detected in long-lived mutants are very likely representing a novel mechanistic link between GH and aging.

Recent studies of Saccon et al [94] and her colleagues were aimed at identifying mechanisms of delayed ovarian aging in Ames dwarf mice. The results indicated that the slower rate of primordial follicle activation (increased ovarian reserve) in these animals is associated with reduced accumulation of DNA damage in the oocytes and reduced macrophage infiltration of the ovaries. These studies add to the evidence for association of reduced gonadal aging with slower somatic aging in these mutants [95], and identify likely mechanisms of this association.

Royce et al [96] discussed the importance of necroptosis (programmed necrosis triggered by noxious factors) of cells known to increase inflammation in the control of aging and chronic age-associated disease and pointed out that necroptosis is reduced in Ames dwarf mice and in calorie restricted mice in which lifespan is extended, and increased in Sod1-/- mice in which disruption of a superoxide dismutase gene impairs antioxidant defense and reduces longevity. Importantly, changes in the markers of inflammation in these animals corresponded to the changes in necroptosis. These findings suggest that reduced inflammaging (one of key mechanisms of aging) in hypopituitary mice lacking GH [32,33] may be due, in part, to a decrease in necroptosis.

EVIDENCE THAT SUPPRESSION OF GROWTH HORMONE SIGNALING HAS DETRIMENTAL AS WELL AS BENEFICIAL EFFECTS

Studies conducted during the last 25 years clearly established that suppression of GH production or action in laboratory mice results in beneficial changes in metabolism, protection from age-related pathology, extension of healthspan, and a substantial increase in longevity. Interestingly, cognitive function (assessed by testing for spatial learning and memory retention) was also improved in transgenic GHA mice expressing an antagonistic analog of GH in which GH signaling is inhibited but longevity is not significantly extended [97]. Not surprisingly, loss of physiological actions of the

somatotropic axis also produces detrimental effects: reduced growth, delayed puberty, reduced fecundity, and also in some of these animals reduced glucose tolerance, despite greatly enhanced insulin sensitivity. Recent studies identified other detrimental consequences of GH deficiency or resistance. Leone et al [98] reported decreased cognitive performance (measured in Morris water maze and eight arm radial maze tests) in GH deficient GHRHKO mice. However age-related decline in cognitive function appeared to have been delayed in these animals. Other studies by the same group of authors revealed that GHRHKO mice are more sensitive to thermal pain and to inflammatory stimuli [99], and have exaggerated carcinogenic responses to pharmacologic induction of colon inflammation [100].

Schneider et al [101] examined effects of GH on bone marrow-derived macrophages and presented evidence for a role of GH in priming and maturation of these cells. Results of this study suggest that age-related decline in circulating GH levels may play a role in the reduction of antimicrobial capacity and antigen presentation in older animals. Study of various parameters of mitochondrial function in osteocytes isolated from cortical bone of Ghr-/- mice reveled impairments, including increased cytoplasmic reactive oxygen species (ROS) levels and reduced glutathione [102]. The results were interpreted as additional evidence for decreased skeletal healthspan in these animals. Wasinski et al [103] used several animal models including animals with deletion of GH receptors in neurons expressing leptin receptor or agouti-related peptide to examine effects of GH on hypothalamic innervation involved in the control of appetite and metabolism. The results showed that GHR deletion reduces density of axonal projections from the arcuate nucleus to other regions of the hypothalamus, indicating existence of direct trophic effects of GH on development of hypothalamic neurocircuits.

Novel findings described in this section add to the evidence for the existence of both beneficial and detrimental effects of suppression of GH actions. These findings also support the notion that various trade-offs are involved in the impact of somatotropic signaling on the life history, including the trajectory of aging [31,104]. Coexistence of beneficial and detrimental effects of a particular factor (in this case, GH) on different facets or different mechanisms of the same process (in this case, aging) would seem to fit a novel concept of "antagonistic heterogeneity." Antagonistic heterogeneity refers to coexistence of positive and negative correlation of the same genetic variant with traits that are directly correlated with each other [105].

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Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: AB. Data curation: AB. Formal analysis: AB. Funding acquisition: AB, KH, EH. Project administration: AB. Supervision: AB. Writing – original draft: AB, MMM, KH, EH. Writing – review & editing: AB, MMM, KH, EH.

REFERENCES

1. Bartke A. Growth hormone and aging: updated review. World J Mens Health 2019;37:19-30.
2. Vijg J, Suh Y. Genome instability and aging. Annu Rev Physiol 2013;75:645-68.
3. Niedernhofer LJ, Gurkar AU, Wang Y, Vijg J, Hoeijmakers JHJ, Robbins PD. Nuclear genomic instability and aging. Annu Rev Biochem 2018;87:295-322.
4. Chesnokova V, Melmed S. Growth hormone in the tumor microenvironment. Arch Endocrinol Metab 2019;63:568-75.
5. Anisimov VN, Bartke A. The key role of growth hormone-insulin-IGF-1 signaling in aging and cancer. Crit Rev Oncol Hematol 2013;87:201-23.
6. Basu R, Kopchick JJ. The effects of growth hormone on therapy resistance in cancer. Cancer Drug Resist 2019;2:827-46.
7. Benyi E, Linder M, Adami J, Kieler H, Palme M, Sävendahl L. Adult height is associated with risk of cancer and mortality in 5.5 million Swedish women and men. J Epidemiol Community Health 2019;73:730-6.
8. Jiang Y, Marshall RJ, Walpole SC, Prieto-Merino D, Liu DX, Perry JK. An international ecological study of adult height in relation to cancer incidence for 24 anatomical sites. Cancer

Causes Control 2015;26:493-9.
9. Ong JS, An J, Law MH, Whiteman DC, Neale RE, Gharahkhani P, et al. Height and overall cancer risk and mortality: evidence from a Mendelian randomisation study on 310,000 UK Biobank participants. Br J Cancer 2018;118:1262-7.
10. Wu XY, Chen C, Yao XQ, Cao QH, Xu Z, Li WS, et al. Growth hormone protects colorectal cancer cells from radiation by improving the ability of DNA damage repair. Mol Med Rep 2014;10:486-90.
11. Madrid O, Varea S, Sanchez-Perez I, Gomez-Garcia L, De Miguel E, Gomez De Segura IA, et al. Growth hormone protects against radiotherapy-induced cell death. Eur J Endocrinol 2002;147:535-41.
12. Gentilin E, Minoia M, Bondanelli M, Tagliati F, Degli Uberti EC, Zatelli MC. Growth hormone differentially modulates chemoresistance in human endometrial adenocarcinoma cell lines. Endocrine 2017;56:621-32.
13. Ikeno Y, Bronson RT, Hubbard GB, Lee S, Bartke A. Delayed occurrence of fatal neoplastic diseases in ames dwarf mice: correlation to extended longevity. J Gerontol A Biol Sci Med Sci 2003;58:291-6.
14. Vergara M, Smith-Wheelock M, Harper JM, Sigler R, Miller RA. Hormone-treated snell dwarf mice regain fertility but remain long lived and disease resistant. J Gerontol A Biol Sci Med Sci 2004;59:1244-50.
15. Boguszewski CL, Boguszewski MC, Kopchick JJ. Growth hormone, insulin-like growth factor system and carcinogenesis. Endokrynol Pol 2016;67:414-26.
16. Podlutsky A, Valcarcel-Ares MN, Yancey K, Podlutskaya V, Nagykaldi E, Gautam T, et al. The GH/IGF-1 axis in a critical period early in life determines cellular DNA repair capacity by altering transcriptional regulation of DNA repair-related genes: implications for the developmental origins of cancer. Geroscience 2017;39:147-60.
17. Fantini C, Sgrò P, Pittaluga M, de Perini A, Dimauro I, Sartorio A, et al. Short-term, supra-physiological rhGH administration induces transient DNA damage in peripheral lymphocytes of healthy women. J Endocrinol Invest 2017;40:645-52.
18. Morante J, Vallejo-Cremades MT, Gómez-García L, Vázquez I, Gómez-de-Segura IA, Sanchez M, et al. Differential action of growth hormone in irradiated tumoral and nontumoral intestinal tissue. Dig Dis Sci 2003;48:2159-66.
19. Chesnokova V, Zonis S, Barrett RJ, Gleeson JP, Melmed S. Growth hormone induces colon DNA damage independent of IGF-1. Endocrinology 2019;160:1439-47.
20. Dominick G, Bowman J, Li X, Miller RA, Garcia GG. mTOR regulates the expression of DNA damage response enzymes in long-lived Snell dwarf, GHRKO, and PAPPA-KO mice. Aging Cell 2017;16:52-60.
21. Bayram F, Bitgen N, Donmez-Altuntas H, Cakir I, Hamurcu Z, Sahin F, et al. Increased genome instability and oxidative DNA damage and their association with IGF-1 levels in patients with active acromegaly. Growth Horm IGF Res 2014;24:29-34.
22. Elbialy A, Asakawa S, Watabe S, Kinoshita S. A zebrafish acromegaly model elevates DNA damage and impairs DNA repair pathways. Biology (Basel) 2018;7:47.
23. Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M, Wei M, Madia F, Cheng CW, et al. 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.
24. Jiang S, Guo Y. Epigenetic clock: DNA methylation in aging. Stem Cells Int 2020;2020:1047896.
25. Unnikrishnan A, Freeman WM, Jackson J, Wren JD, Porter H, Richardson A. The role of DNA methylation in epigenetics of aging. Pharmacol Ther 2019;195:172-85.
26. Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nat Rev Genet 2018;19:371-84.
27. Bell CG, Lowe R, Adams PD, Baccarelli AA, Beck S, Bell JT, et al. DNA methylation aging clocks: challenges and recommendations. Genome Biol 2019;20:249.
28. Wang T, Tsui B, Kreisberg JF, Robertson NA, Gross AM, Yu MK, et al. Epigenetic aging signatures in mice livers are slowed by dwarfism, calorie restriction and rapamycin treatment. Genome Biol 2017;18:57.
29. Horvath S, Erhart W, Brosch M, Ammerpohl O, von Schönfels W, Ahrens M, et al. Obesity accelerates epigenetic aging of human liver. Proc Natl Acad Sci U S A 2014;111:15538-43.
30. Sandoval-Sierra JV, Helbing AHB, Williams EG, Ashbrook DG, Roy S, Williams RW, et al. Body weight and high-fat diet are associated with epigenetic aging in female members of the BXD murine family. Aging Cell 2020;19:e13207.
31. Aguiar-Oliveira MH, Bartke A. Growth hormone deficiency: health and longevity. Endocr Rev 2019;40:575-601.
32. Wang Z, Al-Regaiey KA, Masternak MM, Bartke A. Adipocytokines and lipid levels in ames dwarf and calorie-restricted mice. J Gerontol A Biol Sci Med Sci 2006;61:323-31.
33. Hascup ER, Wang F, Kopchick JJ, Bartke A. Inflammatory and glutamatergic homeostasis are involved in successful aging. J Gerontol A Biol Sci Med Sci 2016;71:281-9.
34. Berryman DE, List EO, Coschigano KT, Behar K, Kim JK, Kopchick JJ. Comparing adiposity profiles in three mouse models with altered GH signaling. Growth Horm IGF Res 2004;14:309-18.

35. Masternak MM, Bartke A, Wang F, Spong A, Gesing A, Fang Y, et al. Metabolic effects of intra-abdominal fat in GHRKO mice. Aging Cell 2012;11:73-81.
36. Darcy J, Bartke A. Functionally enhanced brown adipose tissue in ames dwarf mice. Adipocyte 2017;6:62-7.
37. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, et al. Effects of human growth hormone in men over 60 years old. N Engl J Med 1990;323:1-6.
38. Householder LA, Comisford R, Duran-Ortiz S, Lee K, Troike K, Wilson C, et al. Increased fibrosis: a novel means by which GH influences white adipose tissue function. Growth Horm IGF Res 2018;39:45-53.
39. List EO, Berryman DE, Buchman M, Parker C, Funk K, Bell S, et al. Adipocyte-specific GH receptor-null (AdGHRKO) mice have enhanced insulin sensitivity with reduced liver triglycerides. Endocrinology 2019;160:68-80.
40. List EO, Berryman DE, Buchman M, Jensen EA, Funk K, Duran-Ortiz S, et al. GH knockout mice have increased subcutaneous adipose tissue with decreased fibrosis and enhanced insulin sensitivity. Endocrinology 2019;160:1743-56.
41. Dominici FP, Hauck S, Argentino DP, Bartke A, Turyn D. Increased insulin sensitivity and upregulation of insulin receptor, insulin receptor substrate (IRS)-1 and IRS-2 in liver of ames dwarf mice. J Endocrinol 2002;173:81-94.
42. Menon V, Zhi X, Hossain T, Bartke A, Spong A, Gesing A, et al. The contribution of visceral fat to improved insulin signaling in ames dwarf mice. Aging Cell 2014;13:497-506.
43. Wiesenborn DS, Ayala JE, King E, Masternak MM. Insulin sensitivity in long-living ames dwarf mice. Age (Dordr) 2014;36:9709.
44. Parsons JA, Bartke A, Sorenson RL. Number and size of islets of Langerhans in pregnant, human growth hormone-expressing transgenic, and pituitary dwarf mice: effect of lactogenic hormones. Endocrinology 1995;136:2013-21.
45. Wiesenborn DS, Menon V, Zhi X, Do A, Gesing A, Wang Z, et al. The effect of calorie restriction on insulin signaling in skeletal muscle and adipose tissue of ames dwarf mice. Aging (Albany NY) 2014;6:900-12.
46. Zhou Y, Xu BC, Maheshwari HG, He L, Reed M, Lozykowski M, et al. A mammalian model for Laron syndrome produced by targeted disruption of the mouse growth hormone receptor/binding protein gene (the Laron mouse). Proc Natl Acad Sci U S A 1997;94:13215-20.
47. Liu JL, Coschigano KT, Robertson K, Lipsett M, Guo Y, Kopchick JJ, et al. Disruption of growth hormone receptor gene causes diminished pancreatic islet size and increased insulin sensitivity in mice. Am J Physiol Endocrinol Metab 2004;287:E405-13.
48. Høyer KL, Høgild ML, List EO, Lee KY, Kissinger E, Sharma R, et al. The acute effects of growth hormone in adipose tissue is associated with suppression of antilipolytic signals. Physiol Rep 2020;8:e14373.
49. Darcy J, McFadden S, Fang Y, Berryman DE, List EO, Milcik N, et al. Increased environmental temperature normalizes energy metabolism outputs between normal and ames dwarf mice. Aging (Albany NY) 2018;10:2709-22.
50. Darcy J, Bartke A. From white to brown - adipose tissue is critical to the extended lifespan and healthspan of growth hormone mutant mice. Adv Exp Med Biol 2019;1178:207-25.
51. Darcy J, Tseng YH. ComBATing aging-does increased brown adipose tissue activity confer longevity? Geroscience 2019;41:285-96.
52. Darcy J, Fang Y, McFadden S, Lynes MD, Leiria LO, Dreyfuss JM, et al. Integrated metabolomics reveals altered lipid metabolism in adipose tissue in a model of extreme longevity. Geroscience 2020;42:1527-46.
53. Nelson CN, List EO, Ieremia M, Constantin L, Chhabra Y, Kopchick JJ, et al. Growth hormone activated STAT5 is required for induction of beige fat in vivo. Growth Horm IGF Res 2018;42-43:40-51.
54. Strong R, Miller RA, Bogue M, Fernandez E, Javors MA, Libert S, et al. Rapamycin-mediated mouse lifespan extension: late-life dosage regimes with sex-specific effects. Aging Cell 2020;19:e13269.
55. Sadagurski M, Cady G, Miller RA. Anti-aging drugs reduce hypothalamic inflammation in a sex-specific manner. Aging Cell 2017;16:652-60.
56. MacLeod JN, Pampori NA, Shapiro BH. Sex differences in the ultradian pattern of plasma growth hormone concentrations in mice. J Endocrinol 1991;131:395-9.
57. Hao P, Waxman DJ. Functional roles of sex-biased, growth hormone-regulated microRNAs miR-1948 and miR-802 in young adult mouse liver. Endocrinology 2018;159:1377-92.
58. Jansson JO, Edén S, Isaksson O. Sexual dimorphism in the control of growth hormone secretion. Endocr Rev 1985;6:128-50.
59. Harrison DE, Strong R, Allison DB, Ames BN, Astle CM, Atamna H, et al. Acarbose, 17-α-estradiol, and nordihydroguaiaretic acid extend mouse lifespan preferentially in males. Aging Cell 2014;13:273-82.
60. Sidhom S, Schneider A, Fang Y, McFadden S, Darcy J, Sathiaseelan R, et al. 17α-Estradiol modulates IGF1 and hepatic gene expression in a sex-specific manner. J Gerontol A Biol Sci Med Sci 2020. doi: 10.1093/gerona/glaa215 [Epub].
61. Isola JVV, Zanini BM, Sidhom S, Kopchick JJ, Bartke A, Masternak MM, et al. 17α-Estradiol promotes ovarian aging

in growth hormone receptor knockout mice, but not wild-type littermates. Exp Gerontol 2020;129:110769.
62. Ahmad AM, Hopkins MT, Thomas J, Ibrahim H, Fraser WD, Vora JP. Body composition and quality of life in adults with growth hormone deficiency; effects of low-dose growth hormone replacement. Clin Endocrinol (Oxf) 2001;54:709-17.
63. Gupta V. Adult growth hormone deficiency. Indian J Endocrinol Metab 2011;15 Suppl 3:S197-202.
64. Besson A, Salemi S, Gallati S, Jenal A, Horn R, Mullis PS, et al. Reduced longevity in untreated patients with isolated growth hormone deficiency. J Clin Endocrinol Metab 2003;88:3664-7.
65. Aguiar-Oliveira MH, Souza AHO, Oliveira CRP, Campos VC, Oliveira-Neto LA, Salvatori R. Mechanisms in endocrinology: the multiple facets of GHRH/GH/IGF-I axis: lessons from lifetime, untreated, isolated GH deficiency due to a GHRH receptor gene mutation. Eur J Endocrinol 2017;177:R85-97.
66. Marinho CG, Mermejo LM, Salvatori R, Assirati JA Junior, Oliveira CRP, Santos EG, et al. Occurrence of neoplasms in individuals with congenital, severe GH deficiency from the Itabaianinha kindred. Growth Horm IGF Res 2018;41:71-4.
67. Oliveira FT, Salvatori R, Marcondes J, Macena LB, Oliveira-Santos AA, Faro ACN, et al. Altered sleep patterns in patients with non-functional GHRH receptor. Eur J Endocrinol 2017;177:51-7.
68. Araújo IMP, Albuquerque-Souza E, Aguiar-Oliveira MH, Holzhausen M, Oliveira-Neto LA, Salvatori R, et al. Immunological and microbiological periodontal profiles in isolated growth hormone deficiency. J Periodontol 2018;89:1351-61.
69. Santana-Ribeiro AA, Moreira-Brasileiro GA, Aguiar-Oliveira MH, Salvatori R, Carvalho VO, Alvim-Pereira CK, et al. Walking and postural balance in adults with severe short stature due to isolated GH deficiency. Endocr Connect 2019;8:416-24.
70. Barros-Oliveira CS, Salvatori R, Dos Santos JSS, Santos PFC, Oliveira-Santos AA, Marinho CG, et al. Sweat and vitamin D status in congenital, lifetime, untreated GH deficiency. Endocrine 2019;65:710-3.
71. Andrade-Guimarães AL, Aguiar-Oliveira MH, Salvatori R, Carvalho VO, Alvim-Pereira F, Daniel CRA, et al. Adult individuals with congenital, untreated, severe isolated growth hormone deficiency have satisfactory muscular function. Endocrine 2019;63:112-9.
72. Marinho CG, Melo HA, Salvatori R, Nunes MAP, Oliveira CRP, Campos VC, et al. Cerebral vasoreactivity, a surrogate marker of cerebrovascular disease, is not impaired in subjects with lifetime, untreated, congenital isolated GH deficiency. Endocrine 2020;70:388-95.
73. Oliveira-Santos AA, Salvatori R, Nogueira MC, Bueno AC, Barros-Oliveira CS, Leal ÂCGB, et al. Enteroendocrine connections in congenital isolated GH deficiency due to a GHRH receptor gene mutation. J Clin Endocrinol Metab 2019;104:2777-84.
74. Barrios MR, Campos VC, Peres NTA, de Oliveira LL, Cazzaniga RA, Santos MB, et al. Macrophages from subjects with isolated GH/IGF-I deficiency due to a GHRH receptor gene mutation are less prone to infection by *Leishmania amazonensis*. Front Cell Infect Microbiol 2019;9:311.
75. Aguiar-Oliveira MH, Salvatori R. Disruption of the GHRH receptor and its impact on children and adults: the Itabaianinha syndrome. Rev Endocr Metab Disord 2020. doi: 10.1007/s11154-020-09591-4 [Epub].
76. Nashiro K, Guevara-Aguirre J, Braskie MN, Hafzalla GW, Velasco R, Balasubramanian P, et al. Brain structure and function associated with younger adults in growth hormone receptor-deficient humans. J Neurosci 2017;37:1696-707.
77. Guevara-Aguirre J, Teran E, Lescano D, Guevara A, Guevara C, Longo V, et al. Growth hormone receptor deficiency in humans associates to obesity, increased body fat percentage, a healthy brain and a coordinated insulin sensitivity. Growth Horm IGF Res 2020;51:58-64.
78. Lupu F, Terwilliger JD, Lee K, Segre GV, Efstratiadis A. Roles of growth hormone and insulin-like growth factor 1 in mouse postnatal growth. Dev Biol 2001;229:141-62.
79. Sun LY. Hippocampal IGF-1 expression, neurogenesis and slowed aging: clues to longevity from mutant mice. Age (Dordr) 2006;28:181-9.
80. Liu H, Bravata DM, Olkin I, Nayak S, Roberts B, Garber AM, et al. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. Ann Intern Med 2007;146:104-15.
81. Fahy GM, Brooke RT, Watson JP, Good Z, Vasanawala SS, Maecker H, et al. Reversal of epigenetic aging and immunosenescent trends in humans. Aging Cell 2019;18:e13028.
82. Brooke RT, Fahy GM. Reversing immunosenescence for prevention of COVID-19. Aging (Albany NY) 2020;12:11161-2.
83. Stout MB, Tchkonia T, Pirtskhalava T, Palmer AK, List EO, Berryman DE, et al. Growth hormone action predicts age-related white adipose tissue dysfunction and senescent cell burden in mice. Aging (Albany NY) 2014;6:575-86.
84. Wolters TLC, van der Heijden CDCC, van Leeuwen N, Hijmans-Kersten BTP, Netea MG, Smit JWA, et al. Persistent inflammation and endothelial dysfunction in patients with treated acromegaly. Endocr Connect 2019;8:1553-67.
85. Ozkan C, Altinova AE, Cerit ET, Yayla C, Sahinarslan A, Sahin D, et al. Markers of early atherosclerosis, oxidative stress

and inflammation in patients with acromegaly. Pituitary 2015;18:621-9.
86. 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 U S A 2001;98:6736-41.
87. Lobie PE, García-Aragón J, Lincoln DT, Barnard R, Wilcox JN, Waters MJ. Localization and ontogeny of growth hormone receptor gene expression in the central nervous system. Brain Res Dev Brain Res 1993;74:225-33.
88. Logan S, Pharaoh GA, Marlin MC, Masser DR, Matsuzaki S, Wronowski B, et al. Insulin-like growth factor receptor signaling regulates working memory, mitochondrial metabolism, and amyloid-β uptake in astrocytes. Mol Metab 2018;9:141-55.
89. Balasubramanian P, Hall D, Subramanian M. Sympathetic nervous system as a target for aging and obesity-related cardiovascular diseases. Geroscience 2019;41:13-24.
90. Farias Quipildor GE, Mao K, Hu Z, Novaj A, Cui MH, Gulinello M, et al. Central IGF-1 protects against features of cognitive and sensorimotor decline with aging in male mice. Geroscience 2019;41:185-208.
91. Colon G, Saccon T, Schneider A, Cavalcante MB, Huffman DM, Berryman D, et al. The enigmatic role of growth hormone in age-related diseases, cognition, and longevity. Geroscience 2019;41:759-74.
92. Jensen EA, Young JA, Jackson Z, Busken J, List EO, Carroll RK, et al. Growth hormone deficiency and excess alter the gut microbiome in adult male mice. Endocrinology 2020;161:bqaa026.
93. Wiesenborn DS, Gálvez EJC, Spinel L, Victoria B, Allen B, Schneider A, et al. The role of ames dwarfism and calorie restriction on gut microbiota. J Gerontol A Biol Sci Med Sci 2020;75:e1-8.
94. Saccon TD, Rovani MT, Garcia DN, Mondadori RG, Cruz LAX, Barros CC, et al. Primordial follicle reserve, DNA damage and macrophage infiltration in the ovaries of the long-living ames dwarf mice. Exp Gerontol 2020;132:110851.
95. Schneider A, Saccon TD, Garcia DN, Zanini BM, Isola JVV, Hense JD, et al. The interconnections between somatic and ovarian aging in murine models. J Gerontol A Biol Sci Med Sci 2020. doi: 10.1093/gerona/glaa258 [Epub].
96. Royce GH, Brown-Borg HM, Deepa SS. The potential role of necroptosis in inflammaging and aging. Geroscience 2019;41:795-811.
97. Basu A, McFarlane HG, Kopchick JJ. Spatial learning and memory in male mice with altered growth hormone action. Horm Behav 2017;93:18-30.
98. Leone S, Recinella L, Chiavaroli A, Ferrante C, Orlando G, Vacca M, et al. Behavioural phenotyping, learning and memory in young and aged growth hormone-releasing hormone-knockout mice. Endocr Connect 2018;7:924-31.
99. Leone S, Chiavaroli A, Recinella L, Orlando G, Ferrante C, Marconi GD, et al. Increased pain and inflammatory sensitivity in growth hormone-releasing hormone (GHRH) knockout mice. Prostaglandins Other Lipid Mediat 2019;144:106362.
100. Leone S, Chiavaroli A, Recinella L, Di Valerio V, Veschi S, Gasparo I, et al. Growth hormone-releasing hormone (GHRH) deficiency promotes inflammation-associated carcinogenesis. Pharmacol Res 2020;152:104614.
101. Schneider A, Wood HN, Geden S, Greene CJ, Yates RM, Masternak MM, et al. Growth hormone-mediated reprogramming of macrophage transcriptome and effector functions. Sci Rep 2019;9:19348.
102. Liu Z, Solesio ME, Schaffler MB, Frikha-Benayed D, Rosen CJ, Werner H, et al. Mitochondrial function is compromised in cortical bone osteocytes of long-lived growth hormone receptor null mice. J Bone Miner Res 2019;34:106-22.
103. Wasinski F, Furigo IC, Teixeira PDS, Ramos-Lobo AM, Peroni CN, Bartolini P, et al. Growth hormone receptor deletion reduces the density of axonal projections from hypothalamic arcuate nucleus neurons. Neuroscience 2020;434:136-47.
104. Bartke A, Sun LY, Longo V. Somatotropic signaling: trade-offs between growth, reproductive development, and longevity. Physiol Rev 2013;93:571-98.
105. Kulminski AM, Loika Y, Nazarian A, Culminskaya I. Quantitative and qualitative role of antagonistic heterogeneity in genetics of blood lipids. J Gerontol A Biol Sci Med Sci 2020;75:1811-9.