The somatotropic axis and longevity in mice

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Brown-Borg HM. The somatotropic axis and longevity in mice. Am J Physiol Endocrinol Metab 309: E503–E510, 2015. First published July 28, 2015; doi:10.1152/ajpendo.00262.2015.—The somatotropic signaling pathway has been implicated in aging and longevity studies in mice and other species. The physiology and lifespans of a variety of mutant mice, both spontaneous and genetically engineered, have contributed to our current understanding of the role of growth hormone and insulin-like growth factor I on aging-related processes. Several other mice discovered to live longer than their wild-type control counterparts also exhibit differences in growth factor levels; however, the complex nature of the phenotypic changes in these animals may also impact lifespan. The somatotropic axis impacts several pathways that dictate insulin sensitivity, nutrient sensing, mitochondrial function, and stress resistance as well as others that are thought to be involved in lifespan regulation.

growth hormone; insulin-like growth factor; aging; lifespan regulation

THE SOMATOTROPIC AXIS HAS GARNERED GREAT ATTENTION in aging research over the last two decades. Once thought to primarily direct proliferation, growth, and the counterregulatory effects on glucose metabolism, a multitude of evidence indicates that this endocrine pathway affects several factors that impact aging-related processes, age-related disease, and ultimately longevity.

Fifty years ago, Everitt and Cavanagh (36) demonstrated that hypophysectomy (surgical removal of the pituitary gland) in rats resulted in fewer age-related changes in collagen fibers of tail tendons and delayed the onset of proteinuria compared with intact animals. For the next 20 years pituitary factors were further implicated in the delayed onset of several age-related pathologies and in lifespan extension. The results of these studies have been confirmed more recently using hypophysectomized adult mice (87). The role of pituitary hormones in aging processes was also suggested by early food restriction studies (35, 37, 80). Plasma pituitary hormones were observed to be lower in animals subjected to dietary restriction, and thus several years ago, dietary restriction (DR) was termed a “functional hypophysectomy” (see Refs. 26, 41, 52, and 80; also see Interventions That Alter GH or IGF-I).

Independent of the mammalian pituitary work, evidence in invertebrates suggested that mutations inactivating pathways that promoted growth also extended life. Downregulation or disruption of glucose and amino acid signaling in yeast or insulin/IGF-I signaling in nematodes and flies significantly impacted longevity (27, 38, 40, 60, 61, 104). The evolutionary significance of these studies in insulin/IGF-I signaling and the mammalian evidence that the growth hormone pathway influences lifespan regulation are enormous.

The large body of work on pituitary factors and longevity was linked to the invertebrate work by the observation that the Ames dwarf mouse was shown to have an extraordinarily long lifespan (Table 1) (23). These diminutive mice (one-third the size of normal) result from a point mutation in a gene that encodes a protein (Prop1) necessary for PIT-1 expression (94). PIT-1 drives differentiation of the anterior pituitary gland. These mice are devoid of somatotroph, lactotroph, and thyrotrhop cells and thus are deficient in circulating growth hormone (GH), prolactin (PRL), and thyrotropin, respectively. Although they lack three hormones, studies demonstrate that the GH deficiency is the primary driver of the differences in lifespan in these mice (85). Phenotypically similar Snell dwarf mice also lack plasma GH, PRL, and TSH, owing to a mutation in PIT-1, hence the close similarity with the Ames mice, including the extended longevities (Table 1) (39). Flurkey et al. (39) replaced PRL in Snell dwarf mutants and showed that the PRL deficiency had no impact on lifespan. The administration of thyroxine to Ames dwarf mice for 6 wk had no bearing on longevity of males or females with thyroxine-treated mice living as long as saline-treated mice (85). However, lifelong treatment of Snell dwarf mice with thyroxine shortened lifespan such that treated mice lived 83% of the untreated-dwarf lifespan (110). A more recent report indicated that Ames mice treated with GH and thyroxine between the ages of 2 and 8 wk did not reduce lifespan to match wild-type controls yet increased body weights of the dwarf mice to that of untreated wild-type mice (~18 g) (31). Mutations that impact GH status, both spontaneous and engineered, strongly support a major role for GH in lifespan regulation. Further examples of these mutants will be described in the context of their relationship to GH and longevity.

There are two long-living mutant mice with genetic perturbations upstream of GH, the Little (lit/lit) and the GH-releasing hormone-knockout (GHRH-KO) mice. The Little mice have a mutation in the GHRH receptor and exhibit GH deficiency (34,
43). These animals are 50% smaller and live 23–25% longer than normal wild-type mice (male and females, respectively; Table 1) (39). The Little mice also exhibit an upregulation of xenobiotic metabolism. Elegant work by Sun et al. (100) reported on the generation of mice with isolated GH deficiency due to a targeted disruption of the GHRH gene. The GHRH-KO animals live 43–51% longer than wild-type females and exhibits enhanced insulin sensitivity and measures of stress resistance (xenobiotic metabolism is increased). These animals are not confounded by other hormone deficiencies, clearly supporting GH as a key component of aging processes and lifespan regulation.

The GH receptor-knockout (GHRKO) mouse lives significantly longer than wild-type controls while exhibiting GH resistance (30). Disruption of the GH receptor/binding protein gene generated mice that are about one-half the size of wild-type mice with high plasma GH levels and low circulating IGF-I levels. There have been several tissue-specific GHRKO mice generated to determine the effects of tissue-specific actions of GH signaling, but no lifespan data are available at this time (99). Another mouse of interest is the fibroblast growth factor 21 (FGF21) mouse. FGF21 is a hormone secreted by the liver during nutrient deprivation. FGF21-transgenic mice are GH resistant and remarkably similar to the long-living Ames dwarf and GHRKO mice in terms of lifespan extension, insulin sensitivity, circulating IGF-I, and adiponectin levels (118).

Heterozygous expression of IGF1R (+/-) in mice results in partial GH resistance. These animals were first reported to live 33% longer (females only); however, the wild-type controls lived to only 19 mo of age, suggesting that the mutant allele was rescuing a defect in the background strain (54). These researchers also reported that lifespan was increased with heterozygous expression of IGF-I receptor (IGF-IR) on a different strain. When Bokov et al. (14) repeated the lifespan studies in another IGF-IR line (+/-), they observed a 5% extension in females only. A brain-specific IGF1R knockout is GH and IGF-I resistant and lives 9% longer than wild-type controls (58), implicating the neural system as a potential regulator.

The effects of IGF-IR mutations on longevity have been debated, with some suggesting that the underlying background strain may modulate the degree of life extension. Yuan et al. (117) evaluated plasma IGF-I levels in several mouse strains and reported an inverse relationship between IGF-I levels and lifespan. Plasma IGF-I levels between the 129S1 and B6 strains in females were similar (260 vs. 248 ng/ml, respectively). In males there was a greater difference [129S1 (320 ng/ml) vs. C57Bl/6 (256 ng/ml)], although it was not significantly between strains. Thus, strains with high IGF-I lived shorter than strains with low IGF-I. The increase in the lifespan of heterozygous IGF1R +/- mutants is GH and IGF-I resistant and lives 9% longer than wild-type controls (58), implicating the neural system as a potential regulator.

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**Table 1. Characteristics and lifespan of GH/IGF-I mutant mice**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Endocrine Effect</th>
<th>Lifespan Extension</th>
<th>Plasma GH</th>
<th>Stress Resistance</th>
<th>Insulin Sensitivity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHR/IGF-I deficient</td>
<td>GH deficient</td>
<td>23–25% ND</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
<td>Flurkey et al. (39)</td>
</tr>
<tr>
<td>GHRBP/IGF-II deficient</td>
<td>GH resistant</td>
<td>18% ND</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>Bonkowski et al. (17)</td>
</tr>
<tr>
<td>FGFR-Tg</td>
<td>GH resistant</td>
<td>36% ND</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Holzenberger et al. (54)</td>
</tr>
<tr>
<td>IGF-IR +/-</td>
<td>Partial GH resistance</td>
<td>33%* ND</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Bokov et al. (14)</td>
</tr>
<tr>
<td>Li-Igf1 +/-</td>
<td>Reduced IGF-I</td>
<td>16%* ND</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Yamasaki et al. (102)</td>
</tr>
<tr>
<td>LiID</td>
<td>Reduced IGF-I</td>
<td>↑</td>
<td>ND</td>
<td>↑</td>
<td>↑</td>
<td>Gong et al. (44)</td>
</tr>
<tr>
<td>Klotho Tg</td>
<td>RGF-I-resistant</td>
<td>18–30% ND</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Kurosu et al. (65)</td>
</tr>
<tr>
<td>Irs1 +/-</td>
<td>Insulin resistant</td>
<td>18%* ND</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Selman et al. (92)</td>
</tr>
<tr>
<td>Ins2 +/-, Ins2 +/-</td>
<td>Insulin sensitive</td>
<td>18%, 14% ND</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Taguchi et al. (103)</td>
</tr>
<tr>
<td>FIKKO</td>
<td>Reduced insulin signaling</td>
<td>18% ND</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Blüher et al. (12a)</td>
</tr>
<tr>
<td>α-MUPA</td>
<td>Reduced IGF-I</td>
<td>20% ND</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Miskin and Masos (78)</td>
</tr>
<tr>
<td>IGF-I hypomorph</td>
<td>Reduced IGF-I</td>
<td>18%* ND</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Lorentzini et al. (68)</td>
</tr>
<tr>
<td>Papp-A -/-</td>
<td>Reduced local free IGF-I</td>
<td>38%</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Conover and Bale (28)</td>
</tr>
<tr>
<td>MYC +/-</td>
<td>Reduced IGF-I</td>
<td>10–20% ND</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Hofmann et al. (53)</td>
</tr>
</tbody>
</table>

GH, growth hormone; GHRHR, growth hormone-releasing hormone receptor; Tg, transgenic; IGF-IR, IGF-I receptor; ND, not determined; GHRKO, GH receptor knockout; FGF21, fibroblast growth factor 21; LID, liver IGF-I ablated; iLID, inducible liver-specific IGF-I knockout; FIKKO, fat insulin receptor knockout; α-MUPA, α-mouse urokinase-type plasminogen activator; Papp-A, pregnancy-associated plasma protein-A. *Females only; ‡wild-type LS (18 mo); †males decreased. ↑ Increases, ↓ decreases, and ±no change; comparisons with control mice.
leads to speculation that the sexual dimorphism observed in many longevity studies may be related to underlying growth factor levels. Reduced plasma IGF-I as well as IGF-I resistance has been found to enhance longevity in several other lines of mutant mice. Liver-specific IGF-I-knockout (−/−; Li-Igf1) females live 16% longer than wild-type mice (102), whereas a different liver IGF-I-ablated (LID) mouse generated several years earlier showed no increase in lifespan in females and a slight decrease in males (116). High levels of GH due to the lack of negative feedback inhibition as well as hyperinsulinemia and insulin resistance in the LID mouse were thought to counter the potential positive effects of the low IGF-I concentrations. A recent report by Gong et al. (44) compared the LID mice to inducible LID animals and found that reductions in IGF-I, along with corresponding high plasma GH following the first year of life, impaired healthspan. However, no lifespan studies were performed. These studies support a role for GH deficiency in delaying aging and extending life.

Animals with altered IGF-I due to other mutations also exhibit differences in longevity. α-MUPA mice overexpress a protease in the brain, urokinase-type plasminogen activator, and exhibit reduced plasma IGF-I while living 20% longer than nontransgenic mice (Table 1) (78). When the zinc metalloprotease gene pregnancy-associated plasma protein-A (Papp-A) is knocked out, a significant reduction in local free IGF-I occurs at the tissue level, and the mice live 38% longer than wild types (28). Reduced circulating IGF-I has also been demonstrated in an IGF-I hypomorph mouse that exhibits an 18% increase in lifespan (females only) over wild-type mice (68). These animals are distinguished from the other lines by the reduction of IGF-I in all tissues vs. specific ablation of liver IGF-I or IGF-I signaling via reduced expression of the IGF-I receptor. A recent mutant heterozygous for Myc (+/−) expression was found to have low plasma IGF-I levels and an increase in lifespan of 15% (53). The lifespan extension observed in these lines of mice confirms that decreased IGF-I signaling is associated with longevity compared with hormone-sufficient controls. Furthermore, wild caught mice exhibit reduced plasma IGF-I levels as well as live longer than standard laboratory-adapted mice (48, 75). In fact, IGF-I levels at 6 mo of age served as a significant predictor of lifespan in different populations of F2 hybrid (wild-derived × laboratory) mice. Harper et al. (47) also reported that IGF-I levels in mice at 15 mo correlated with longevity.

A few mouse lines have also been shown to live longer than wild-type controls when the related insulin pathway is altered. The Irs1−/−, Irs2+/−, Irs2−/−, and brain-specific Irs2+/− and Irs2−/− lines of mice exhibit 14–18% extensions in lifespan (92, 103). Klotho is a peptide hormone that suppresses insulin/IGF-I signaling by attenuating phosphorylation of insulin and IGF receptors, rendering the transgenic animals insulin and IGF-I resistant. Klotho-transgenic mice have lifespans of 18–30% longer than controls, whereas the Klotho-knockout mouse lives for only ~2 mo (64, 65). The altered longevity of insulin mutants also implicates this related hormone in aging processes.

One phenotype common to several of the longest-living mutant mice is increased insulin sensitivity. The Ames and Snell dwarf mice exhibit enhanced insulin sensitivity with low circulating glucose and insulin levels (32, 55, 71). The Little, GHRKO, GHRH-KO, and FGF21-transgenic mice are also insulin sensitive compared with wild-type mice of the same strain (30, 39, 100, 118). Each of these mouse mutants is either GH deficient or resistant. However, when GH signaling is not compromised, animals exhibit either insulin resistance or no difference in insulin sensitivity from wild-type control mice (IGFR+/−, Li-IGF1+/−, LID, Klotho Tg, Irs1−/−, Irs2+/−, Irs2−/−, Papp-A, and IGF-I-deficient hypomorphic mouse). Thus, the relationship between insulin sensitivity and longevity is unclear when IGF-I has been targeted directly.

Arum et al. (4) tested the hypothesis that the enhanced insulin sensitivity in the GHRKO mice was important for their improved healthspan. They increased insulin production in GHRKO mice to normalize insulin sensitivity transgenically by promoting ectopic IGF-I production in pancreatic β-cells. They found that the increased circulating insulin concentrations normalized blood glucose regulatory control, respiratory quotient, lipid, and cognitive parameters. These results suggest that the enhanced sensitivity to insulin is necessary for the slow aging of the GHRKO mice, as few other characteristics measured differed from the GHRKO. Concomitantly, mice raised in crowded litters (12–15 pups) are long-lived and exhibit lower plasma IGF-I and enhanced insulin sensitivity, glucose tolerance, and xenobiotic metabolism compared with mice in normal-size (8 pups) litters (89, 98).

Interventions That Alter GH or IGF-I

In addition to the variety of genetic mutants discussed above, interventions that alter GH or IGF-I also influence lifespan. One of the proposed mechanisms by which DR extends lifespan is via reductions in somatotropic signaling (9). Several mammalian studies have linked the observed differences in lifespan following DR to plasma GH, IGF-I, and insulin levels. DR was shown to increase lifespan in rodents more than eight decades ago (73, 113). Thousands of studies have been conducted since that time exploring aging, longevity, and the possible mechanisms responsible for these observations in many different species. Whereas serum GH increases during fasting and chronic DR, plasma IGF-I levels decrease (25, 45, 106, 107, 112). Moreover, DR was shown to increase the clearance and degradation of IGF-I. The lower IGF-I is also thought to contribute to reduced tumor incidence and progression in DR (33, 114). In rodents, chronic DR delays many age-related diseases in terms of onset and incidence and appears to slow several aspects of aging (70).

A further extension of life (mean, median, and maximum) is observed in Ames dwarf mice subjected to DR, suggesting that additional but overlapping mechanisms are at play (9, 10). Restricting a single amino acid such as methionine also increases longevity in normal rats and mice (74, 83, 119) yet does not impact lifespan in GH signaling mutants (Ames dwarf, GHRKO) (20). Thus intact signaling of the somatotropic pathway appears to be necessary for amino acid sensing in terms of metabolism and lifespan regulation (19). We also know that GH treatment abolishes the DR lifespan benefits in dwarf mice (30% DR started at 5 mo of age; GH administration started 2 wk after DR at 4 mg·g body wt−1·day−1) (42).
Physiological Characteristics of Long-Living Mice

Several key physiological mechanisms appear to play roles in the delay of aging-related processes and longevity via reduced somatotropic signaling. Bartke's laboratory has focused on insulin signaling and shown that increased insulin sensitivity is one of the primary markers predicting long life (7). Ames mice are extremely insulin sensitive (low glucose, low insulin), and DR further enhances this sensitivity. However, GHRKO mice are also extremely insulin sensitive, and yet DR does not further increase insulin sensitivity, nor does this nutritional intervention extend longevity further than ad libitum-fed knockout mice (17), again suggesting that nutritional interventions require intact GH signaling for efficacy in lifespan regulation.

Many studies have shown that reduced GH signaling is associated directly with enhanced cellular defense and stress resistance. Our own work in Ames dwarf mice demonstrated enhanced expression and activities of many proteins involved in antioxidative defense, detoxification, and redox reactions such as catalase, glutathione peroxidase, superoxide dismutase, glutathione S-transferases, glutathione, thioredoxin, and glutaredoxin (21, 85, 88). Expression of each of these factors is suppressed following the administration of GH in vitro, in vivo, and also in animals that overexpress GH. Others have also found enhanced stress resistance in each of the GH mutants, including Ames dwarf, Snell dwarf, GHRKO, GHRH-KO, and Little mice as well as some of the IGF-IR mutants (IGF-IR<sup>+/−</sup>) or mice in which IGF-I signaling is altered (2, 3, 13, 14, 39, 49, 51, 54, 57, 65, 82, 90, 100, 101, 115). The upregulated mechanisms of cellular stress resistance are limited not to reactive oxygen species defense but many different types of stressors, including heavy metals, UV radiation, paraquat, and heat as well as others. The results of these studies suggest that cellular stress resistance may underlie late-life disease resistance in these animals.

Overall, xenobiotic metabolism, including phase I and II enzymes, appears to be at least in part under the direct control of GH or by downstream effectors of this pathway. Several pathways impacted by GH are involved in the control of cellular stress resistance and include Nrf, forkhead box O (FOXO), mammalian target of rapamycin, p38 MAPK, peroxisome proliferator-activated receptor (PPAR), PPARγ coactivator-1α, sirtuin, ERK, and heat shock proteins, among others (6, 18, 22, 29, 57, 69, 85, 93, 95, 98, 111). A number of reports support the role for the somatotropic axis in cellular defense mechanisms that in turn contribute to aging and longevity in mice.

The missing conversation in many of the IGF-I and longevity discussions regards plasma GH status. The episodic nature of GH release from the pituitary makes accurate measurement challenging, and thus GH levels are rarely reported. However, it is clear that mice with GH deficiency or GH resistance live much longer than wild-type controls, whereas in mice with IGF-I resistance or isolated IGF-I deficiency, the longevity effect is only modest. These differences are likely due to the higher GH levels due to the lack of negative feedback and that intact GH signaling imparts metabolic effects that counter the effects of low IGF-I in many of the mutants.

The evidence that somatotropic signaling is a key regulator of aging and aging processes is supported by hormone replacement studies. GH treatment counters not only the enhanced stress resistance exhibited in long-living mice but also the longevity benefits afforded by many of the mutations listed elsewhere in this report. Ames mice treated with GH do not live as long as those not receiving GH treatment (72, 85). Moreover, GH administration abolishes the DR benefits in Ames mice (42). This evidence is supported by the lack of a DR effect in GHRKO mice (17). When DR is applied to the GHRKO, no additional insulin sensitivity is observed, nor is there an extension of lifespan in contrast to the Ames dwarf. However, when GH is combined with thyroxine treatment for 6 wk in juvenile Ames mice, no effect on longevity is observed (31). Treatment with growth hormone in vitro and in vivo decreases antioxidative enzyme activities and glutathione and methionine metabolism in Ames mice (21, 59). In agreement, short-living GH transgenic mice exhibit insulin resistance, increased tumor incidence, suppressed antioxidative enzymes, reduced immune function, and cellular stress resistance (8, 24, 50, 86). Many of these detrimental health issues are also observed in humans with high GH levels (56).

The relationships of GH, IGF-I, and downstream factors to human longevity have been explored in several populations, with most reports focused on IGF-I and IGF-I receptors. A homozygous mutation in the PRO1 gene in humans was discovered in a small group exhibiting dwarfism that resides on the Island of Krk (Croatia). These individuals are deficient in GH, TSH, and prolactin, similar to the Ames and Snell mice, but also lack luteinizing hormone as well as follicle-stimulating hormone. They live as long as the normal population in the area, with several living between 80 and 90 yr of age (62, 63). There are also several cohorts of individuals with GH deficiencies (GH or GHR receptor mutations) or GH resistance (GH receptor mutations) that report shortened or normal longevity but significantly lower diabetes and cancer incidence despite obesity (1, 11, 46, 91, 96). In mammals, including humans, there is a progressive decline in plasma GH levels postpuber tally (109). Although no differences in GH levels have been observed in healthy centenarians, differences in IGF-I have been identified (5). Individuals that carry a specific allele of the IGF-I receptor have low plasma levels of IGF-I and have an increased representation among long-lived people (15, 16). Another study showed that low IGF-I levels were predictive of survival in humans and those with a history of cancer, suggesting that low GH/IGF-I may extend longevity (77). Suh et al. (97) reported that reduced human IGF-I receptor activity is overrepresented in human centenarians. This diminished IGF-I signaling was due to a functional mutation in the IGF-I receptor, resulting in high IGF-I levels and IGF-I resistance. Two specific heterozygous IGF-IR gene mutations were found to be more frequent in this population of Ashkenazi Jewish centenarians than in individuals from the same population lacking the exceptional longevity history (105). Leduc et al. (66) found a quantitative trait loci that colocalized with the IGF-I gene, emphasizing the role of genetic background in longevity determination. Low GH/IGF-I signaling has also been linked to lower incidence of aging-related diseases such as cancer and diabetes, yet the role of these growth factors in human aging remains controversial. The FOXO transcription factors are downstream of the growth factor pathways. FOXO3 appears to be involved in a wide variety of processes that are involved in healthy aging with polymorphisms in FOXO3a, showing con-
sistent associations with longevity in several populations of humans (79). The evidence to date suggests that reduced somatotropic signaling may potentially be linked to human longevity via a reduction in age-related disease.

There has been a considerable effort to explore the relationships between the somatotropic axis and longevity and aging processes. GH deficiencies clearly extend longevity in mice with multiple downstream effector contributions. The role of IGF-I in rodent aging is less clear, as this hormone is mostly responsible for the somatic actions of GH, whereas GH itself exhibits many IGF-I-independent metabolic activities, each of which may be tissue specific. The invertebrate studies support the overall role of the growth factor axis in aging and longevity. Consistent with this concept, the natural physiological decline of GH in humans and mammals in general may be a protective mechanism that reduces the incidence of age-related diseases such as diabetes and cancer. There have been many detrimental effects of GH overexpression and systemic GH administration that have been observed in animal and human studies. Great care should be taken when considering growth factor treatment of aging-related symptoms in humans (12, 56, 84, 108).

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AUTHOR CONTRIBUTIONS
H.B.-B. conception and design of research; H.B.-B. performed experiments; H.B.-B. drafted manuscript; H.B.-B. edited and revised manuscript; H.B.-B. approved final version of manuscript.

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