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Mini-Review

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GH and Senescence: A New Understanding of Adult GH Action

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Abbreviations: ATM, ataxia telangiectasia mutated; DDR, DNA damage response; GH, growth hormone; GHR, growth hormone receptor; GHRH, growth hormone–releasing hormone; IGF, insulin-like growth factor; IL, interleukin; SA-β-gal, senescence-associated β-galactosidase; SASP, senescence-associated secretory phenotype; TRIM29, tripartite motif-containing 29.

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Abstract

Replicative senescence occurs due to an inability to repair DNA damage and activation of p53/p21 and p16INK4 pathways. It is considered a preventive mechanism for arresting proliferation of DNA-damaged cells. Stably senescent cells are characterized by a senescence-associated secretory phenotype (SASP), which produces and secretes cytokines, chemokines, and/or matrix metalloproteinases depending on the cell type. SASP proteins may increase cell proliferation, facilitating conversion of premalignant to malignant tumor cells, triggering DNA damage, and altering the tissue microenvironment. Further, senescent cells accumulate with age, thereby aggravating age-related tissue damage. Here, we review a heretofore unappreciated role for growth hormone (GH) as a SASP component, acting in an autocrine and paracrine fashion. In senescent cells, GH is activated by DNA-damage-induced p53 and inhibits phosphorylation of DNA repair proteins ATM, Chk2, p53, and H2AX. Somatotroph adenomas containing abundant intracellular GH exhibit increased somatic copy number alterations, indicative of DNA damage, and are associated with induced p53/p21. As this pathway restrains proliferation of DNA-damaged cells, these mechanisms may underlie the senescent phenotype and benign nature of slowly proliferating pituitary somatotroph adenomas. In highly proliferative cells, such as colon epithelial cells, GH induced in response to DNA damage suppresses p53, thereby triggering senescent cell proliferation. As senescent cells harbor unrepaired DNA damage, GH may enable senescent cells to evade senescence and reenter the cell cycle, resulting in acquisition of harmful mutations. These mechanisms, at least in part, may underlie pro-aging effects of GH observed in animal models and in patients with chronically elevated GH levels.

Key Words: growth hormone, senescence, DNA damage, DNA repair, aging

Aging is characterized by accumulated cellular damage resulting in functional and structural loss of tissue integrity, frailty, and multiple comorbidities resulting from chronic illnesses [1, 2]. Mechanisms contributing to the aging processes have been

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extensively reviewed [3-5], and several hallmarks of the aging cell identified. These include genomic instability, cellular senescence, telomere attrition, epigenetic alteration, mitochondrial dysfunction, stem cell exhaustion, loss of proteostasis, deregulated nutrient sensing, and altered intercellular communication [5]. These processes may occur distinctively, but most are interrelated, and delineating the contributions of each respective mechanism to the aging process remains challenging. Changes in growth hormone (GH)/insulin-like growth factor 1 (IGF1) axis signaling with age are well recognized [2], and increasing evidence supports a role in cellular senescence. This review focuses on mechanistic relationships between GH and senescence, highlighting how senescence appears to underlie age-associated processes and diseases [6].

Search Strategy and Selection Criteria

References for this mini-review were identified through searches of PubMed for articles published from database inception until October 15, 2021, using the terms *growth hormone*, *insulin-like growth factor*, and *somatotroph* in combination with the terms *senescence*, *aging*, *DNA damage*, and *DNA repair*. English-language articles resulting from these searches and relevant references cited in those articles were reviewed. Relevant articles were also identified through searching authors' personal files. Greater emphasis was placed on articles published in higher impact journals, although formal systematic review and grading of evidence was not undertaken.

Cellular Senescence

Senescence was originally identified by Hayflick [7], describing what is now known as replicative senescence in human fibroblasts after prolonged cell passaging in culture. Later studies showed senescence is characterized by p16INK4 accumulation, which sustains stable proliferative arrest; p16INK4 expression correlates with chronological age in multiple tissues [8] and the INK4/ARF locus is strongly linked to age-association pathologies [8-10]. Senescence-associated cell cycle arrest protects genomic integrity in response to genotoxic stress, cytokines, reactive oxygen species, mitochondrial dysfunction, and oncogene activation. Most senescence types are caused by DNA damage triggered by replicative errors, telomere shortening, and oxidative damage, although it may also be caused by environmental insults including UV light or chemotherapeutic drugs. When the cell cannot repair DNA damage, it is either destined to die from apoptosis or becomes senescent and exits the cell cycle. DNA-damage-induced senescence is initiated by activation of the p53/p21 pathway, which triggers cell cycle arrest (reviewed in (11-13)).

Senescent cells are flattened, increased in size, and vacuolated, and generally express senescence-associated β-galactosidase (SA-β-gal). Senescent human cells also exhibit senescence-associated chromatin foci, and these, along with SA-β-gal, thus serve as senescence markers [14-16]. A distinctive feature of stably senescent cells is that they express and secrete multiple proteins as part of the senescence-associated secretary phenotype (SASP), including matrix metalloproteinases, IGF binding proteins, the immunomodulators and chemokines interleukin-1 (IL-1), IL-6, and IL-8, as well as vascular endothelial growth factor A, all of which act in an autocrine and/or paracrine fashion. The SASP configuration depends on senescence-triggering stimuli and is usually cell-type specific [17, 18]. Importantly, while SASP may be beneficial in activating immune responses to eliminate tissue senescent cells [10], pathophysiological effects of senescent cells are also mediated by SASP. Thus, SASP may reinforce senescence in an autocrine manner, or induce senescence through paracrine action on neighboring cells, altering tissue homeostasis [19]. SASP also induces bystander DNA damage and activates p16 and p21 along with chemokines and interleukins [20]. Furthermore, SASP factors may facilitate conversion of premalignant to malignant cells and enhance tumor progression by sustaining chronic inflammation [13, 21]. Such effects of stromal senescence were evident on established cancers that become more invasive and metastasize more readily when surrounded by an aged microenvironment with increased numbers of senescent cells [22, 23]. In elderly patients undergoing surgery, a panel of 7 SASP proteins positively correlated with age, patient fragility, and adverse postsurgery outcomes [24].

As DNA repair mechanisms are suboptimal in senescent cells, these cells usually harbor damaged DNA. Senescent cells accumulate with age in human [25, 26] and murine [27, 28] tissue, potentially aggravating age-related tissue damage, and, via paracrine SASP activity, alter the tissue microenvironment, triggering changes in neighboring cells.

In light of the adverse effects of SASP on tissue homeostasis, attempts have been made to eliminate senescent cells. A pioneer study showed that clearance of p16INK4-positive senescence cells by inducible apoptosis extended healthy lifespan in genetically altered mice, providing evidence that senescence may underlie certain aging phenotypes [29]. Small molecule senolytics selectively induce apoptosis in senescent but not in proliferating cells, resulting in fewer senescent cells [30]. Additionally, senomorphics, which attenuate expression of SASP cytokines such as IL-6, are currently undergoing clinical trials for treating a variety of age-related pathologies [31].

Thus, cellular senescence may exemplify an "antagonistic pleiotropy" [32] that evolved as a beneficial protective

mechanism restraining proliferation of DNA-damaged cells, thereby preventing acquisition of harmful mutations, while accumulation of senescent cells may negatively affect tissue homeostasis and facilitate development of cellular aging features.

GH in Aging and Senescence

Endocrine GH is mainly secreted by pituitary somatotrophs, while peripheral tissues, including colon, breast, and lymphocytes, locally express nonpituitary GH recognized by the same GH receptor (GHR). Regardless of the source of the GH ligand, activation of the surface GHR leads to multiple intracellular metabolic and proliferative signals, including those regulating the cell cycle [33, 34].

Many growth-promoting effects of GH are mediated by IGF1, which has also been implicated in the aging process. Specific roles for IGF1 and IGF1 receptor in human aging and in experimental models have been extensively discussed [35-37], with specific observations describing the role of the IGF1 system in cellular senescence [38-41]. In this review, we mostly focus on direct and indirect effects of GH.

GH contribution to the aging process has been reviewed in detail [42-45]. Briefly, aging in humans is associated with somatopause, a spontaneous decline in GH secretion by approximately 15% for every decade of adult life as well as a reduction in IGF1 [46, 47]. Similar declines were observed across mammalian species due to decreased hypothalamic growth hormone–releasing hormone (GHRH) secretion [48, 49]. It has been suggested that suppression of the GH/IGF1 axis is a component of a conserved pathway that shifts energy usage away from growth and proliferation in aging organisms [2]. These findings have prompted a hypothesis postulating that GH signaling decline is associated with organismal aging.

Whether attenuated GH levels and GHR signaling are beneficial to optimizing human lifespan and thus, in turn, attenuate deleterious impacts of age-associated diseases including atherosclerosis, stroke, diabetes, and cancer, has been the subject of intense study. Age-associated GH decline may indeed be beneficial as human subjects with GH receptor mutations and disrupted GHR signaling display markedly reduced pro-aging features, including lower rates of cancer development and diabetes [50, 51]. Animal models with GH signaling deficiency exhibit extended lifespan, with decreased incidence of cancer, age-associated metabolic abnormalities, and decreased cognitive decline, as extensively reviewed [37, 43, 52]. *GHR* gene mutations occur in bats, known for their unusual longevity compared to similar sized mammals, exhibiting transcriptomic changes that resemble those observed in *GHR* knockout mice [53, 54]. By contrast, GH excess both in human patients with acromegaly and in murine transgenic models results in shorter lifespan. Patients with acromegaly develop cardiovascular, cerebrovascular, and respiratory comorbidities and show an increased cancer risk [55]. Transgenic mice overexpressing heterologous GH have significantly decreased lifespan (~50%) with symptoms of accelerated aging, including early development of mammary tumors in females, increased astrogliosis, shortened reproductive lifespan, and early onset of age-related changes in cognitive function, hypothalamic neurotransmitter turnover, and plasma corticosterone levels as well as an increased inflammatory state with adverse lipid profile [56-59]. Similarly, a negative association between somatic growth and longevity was demonstrated in mice [56, 60] and in dogs [61]. By contrast, murine models with GH deficiency or GH resistance have extended lifespan due to reduced activity of TORC1 kinase complex, resistance to neoplastic growth, favorable metabolic profile, and other anti-aging features [42, 43, 52, 62]. In human cohorts enriched for offspring of centenarians with familial longevity, entropic GH secretion is reduced and tightly controlled [63]. These results underscore a significant role for GH as an *adverse* determinant of the aging phenotype.

Cellular senescence is an important element of the aging process, and evidence supports involvement of GH in signaling pathways underlying the senescence phenotype. Pituitary tumor transforming gene (Pttg) is the index mammalian securin responsible for faithful sister chromatid separation during mitosis [64-66]. *Pttg* overexpression resulted in pituitary tumor development in *Pttg* transgenic mice [67], while *Pttg*$^{-/-}$ mice exhibit pituitary hypoplasia [68]. However, due to distorted securin function, both *Pttg* overexpression and *Pttg* deletion result in pituitary aneuploidy and chromosomal instability with increased DNA damage. Pituitary glands in *Pttg*$^{-/-}$ mice exhibit a senescent phenotype with increased SA-β-gal activity and induced senescence-associated p53/p21 pathway, resulting in decreased pituitary cell proliferation and decreased organ size [69]. To identify mechanisms underlying these specific effects, we tested the DNA damage signaling pathway and found increased ataxia telangiectasia mutated (ATM), Mlh1, and Mlh3 kinase expression, indicative of DNA damage, while p21 mRNA and protein expression was also induced, protecting DNA-damaged pituitary cells from further proliferation. We also found that, in *Pttg*$^{-/-}$ mice, GH closely associated with a senescent phenotype, and higher p21 expression and more abundant SA-β-gal activity was observed in pituitary somatotrophs compared with other pituitary cell types. Human GH-secreting pituitary adenomas also exhibit significantly increased p21, p53, and SA-β-gal expression compared with other pituitary tumor

types [70]. Similar results were obtained with whole-exome sequencing of 159 prospectively resected pituitary adenomas, which showed that somatic copy number alteration (SCNA), indicative of chromosomal instability, is highest for both p53 and p21 expression in GH-secreting tumors as compared with nonfunctioning adenomas. GH secretion depends on cAMP activation and GHRH stimulation, and treatment with forskolin, an activator of cAMP, and with a GHRH analogue induced GH production as well as DNA damage accumulation [71]. Thus, by inducing DNA damage, GH may establish senescence in pituitary adenoma somatotrophs.

Association of GH with senescence was confirmed in both pituitary and nonpituitary cells. Nutlin3 (nutlin) is a small molecule that activates DNA damage pathway by protecting p53 from degradation [72], and treatment with nutlin induces a strong senescence phenotype. Rat pituitary GC cells and primary pituitary cells treated with nutlin showed induced GH mRNA and protein expression. Similar results were obtained in human MCF7 breast and HCT116 colon adenocarcinoma cells. We also found that p53, a senescence activator, binds the GH promoter and induces both GH promoter activity and GH mRNA transcription. Importantly, GH is not only induced but is also secreted from senescent cells, thus constituting a SASP component. In human pituitary GH-secreting adenomas, GH expression closely correlates with SA-β-gal expression, and treatment of primary pituitary adenoma cells with nutlin in vitro also resulted in significantly increased secreted GH in culture medium. In vivo experiments confirmed this observation, as mice injected with nutlin and exhibiting high tissue p53 also demonstrate increased pituitary, lung, and liver local GH mRNA levels [73]. Thus, in senescent cells, GH expression is triggered by p53.

p53 displays a positive-negative feedback regulation with GH. p53 induces GH, while GH, in turn, significantly suppresses p53 in vitro and in vivo [74]. Thus, mice bearing xenografts expressing high circulating GH exhibit decreased colon and liver p53 expression. Consistent with these findings, when patients with acromegaly were treated with the GHR antagonist pegvisomant, colon mucosal p53 was markedly induced, indicative of the antiproliferative impact of attenuating GH signaling clinically [74, 75]. GH-induced p53 suppression appears to be mediated by activation of E3 ligase tripartite motif-containing 29 (TRIM29) [54], which binds p53, rendering p53 susceptible to ubiquitination [76]. GH markedly upregulates both TRIM29 and ubiquitin E3 ligase Pirh2, likely responsible for rapid p53 degradation after GH treatment [74]. In human colon, age-associated DNA damage induces GH, and GH suppressive action on DNA damage response (DDR) and DNA repair pathways results in further DNA damage accumulation, a hallmark of an aging microenvironment (Chesnokova et al, *Cell Reports*, in press).

GH Effects in Senescent Cells

GH may exert autonomous and nonautonomous effects in senescent cells. As p53 plays an important role in establishing senescence, induced GH may suppress p53, changing the senescent cell profile; it can also affect p53 expression in neighboring nonsenescent cells via paracrine actions. p53 suppression is often associated with increased proliferation, and when suppressed, senescent cells, usually harboring unrepaired damaged DNA, may reenter the cell cycle, while in neighboring nonsenescent cells, proliferation potential may also increase.

DNA damage accumulates with age and is considered both a marker of and a cause of aging [2, 5, 75, 77]. As unrepaired DNA damage often renders the cell prematurely senescent, mechanisms regulating DDR play an important role in senescence development. ATM is a key component of signaling pathways activated by DNA damage [34]. Activation of ATM by autophosphorylation at Ser1981 phosphorylates checkpoint kinase 2 (Chk2) to arrest cell proliferation [35], and phosphorylates p53 at Ser15, resulting in its activation and stabilization [36]. In turn, phosphorylated p53 promotes cell cycle arrest and activates DNA repair proteins [37]. ATM also phosphorylates γ-histone 2A variant (γH2AX) which marks DNA-damaged sites to assemble DNA repair protein [33, 38, 39]. In both normal colon cells and in human 3-dimensional intestinal organoids, GH, activated in response to DNA damage-induced p53, decreases ATM kinase activity and suppresses ATM autophosphorylation, resulting in decreased H2AX and p53 phosphorylation. In both in vitro and in vivo models, high levels of GH were shown to induce TRIM29 and suppress the tat interacting protein 60 kDa (Tip60), leading to ATM deactivation [42]. Furthermore, by suppressing DDR activity, GH increases unrepaired DNA both in vivo and in vitro, as evidenced by suppression of nonhomologous end-joining and homologous recombination, and also increased DNA damage detected by Comet assay [78, 79]. Thus, GH induced in damaged senescent cells results in accumulated DNA damage in neighboring cells to alter the tissue microenvironment.

In the pituitary, these mechanisms underlying GH action could explain the unique properties of senescent GH-secreting pituitary adenoma cells, potentially linking hormone hypersecretion to genome instability [71], and also providing an explanation for why pituitary adenomas are almost invariably benign. GH is also associated with

senescence in other tissues, likely through signaling pathways described above. For example, skin fibroblasts derived from patients with acromegaly exhibit shortened telomeres and cellular senescence [80], senescence is induced in adipose tissue derived from 10-month-old GH-transgenic females, and the number of SA-β-gal positive cells is increased in GH-injected 19-month-old female mice as compared with age-matched saline-injected controls [81, 82].

Conclusions

The role of GH in the development and maintenance of senescence is complex. Persistently elevated circulating or intracellular GH abundance may induce DNA damage, evoking senescence in highly differentiated and minimally proliferating cells such as aging dermal fibroblasts [83], adipocytes [84], and pituitary somatotrophs [85]. By contrast, in highly proliferative cells such as colon cells, senescence and p53 upregulation induces endogenous GH, which, in turn, suppresses p53, predisposing senescent cells for cell cycle reentry and potentially for neoplastic transformation. GH, as a component of SASP, may enhance the proliferative potential of neighboring cells via paracrine action, and, by suppressing DNA damage repair, may also increase DNA damage accumulation in bystander cells. Furthermore, depending on tissue type and proliferative properties, several lines of evidence derived from cell, animal, and human observations suggest that GH may induce a senescence-enhancing aging phenotype or may enable DNA-damaged cells to proliferate and acquire harmful mutations, also a hallmark of aging [5]. These mechanisms, at least in part, may underlie the pro-aging effects of GH observed in animal models and in patients with chronically elevated GH levels.

Given the evidence supporting a prosenescent function of GHR signaling in cell, animal, and human models, the inappropriate administration of GH as an "anti-aging" or "anti-frailty" agent should be viewed with caution. Importantly, adult GH replacement is only approved for patients with proven GH deficiency, or for those with AIDS-associated muscle wasting [86, 87]. The benefits of unapproved GH abuse by athletes, or by those seeking an anti-aging elixir, have not been substantiated in rigorously controlled trials, and the safety and ethical use of GH has not been justified [34].

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Additional Information

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References

1. Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. From discoveries in ageing research to therapeutics for healthy ageing. *Nature*. 2019;**571**(7764):183-192.
2. Schumacher B, Garinis GA, Hoeijmakers JH. Age to survive: DNA damage and aging. *Trends Genet*. 2008;**24**(2):77-85.
3. Khan SS, Singer BD, Vaughan DE. Molecular and physiological manifestations and measurement of aging in humans. *Aging Cell*. 2017;**16**(4):624-633.
4. McHugh D, Gil J. Senescence and aging: Causes, consequences, and therapeutic avenues. *J Cell Biol*. 2018;**217**(1):65-77.
5. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;**153**(6):1194-1217.
6. Khosla S, Farr JN, Tchkonia T, Kirkland JL. The role of cellular senescence in ageing and endocrine disease. *Nat Rev Endocrinol*. 2020;**16**(5):263-275.
7. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. *Exp Cell Res*. 1961;**25**:585-621.
8. Krishnamurthy J, Torrice C, Ramsey MR, et al. Ink4a/Arf expression is a biomarker of aging. *J Clin Invest*. 2004;**114**(9):1299-1307.
9. Jeck WR, Siebold AP, Sharpless NE. Review: a meta-analysis of GWAS and age-associated diseases. *Aging Cell*. 2012;**11**(5):727-731.
10. Krizhanovsky V, Xue W, Zender L, Yon M, Hernando E, Lowe SW. Implications of cellular senescence in tissue damage response, tumor suppression, and stem cell biology. *Cold Spring Harb Symp Quant Biol*. 2008;**73**:513-522.
11. Gorgoulis V, Adams PD, Alimonti A, et al. Cellular Senescence: Defining a Path Forward. *Cell*. 2019;**179**(4):813-827.
12. Sharpless NE, Sherr CJ. Forging a signature of in vivo senescence. *Nat Rev Cancer*. 2015;**15**(7):397-408.
13. Lee S, Schmitt CA. The dynamic nature of senescence in cancer. *Nat Cell Biol*. 2019;**21**(1):94-101.
14. Kuilman T, Peeper DS. Senescence-messaging secretome: SMS-ing cellular stress. *Nat Rev Cancer*. 2009;**9**(2):81-94.
15. Rodier F, Campisi J. Four faces of cellular senescence. *J Cell Biol*. 2011;**192**(4):547-556.
16. Campisi J. Aging, cellular senescence, and cancer. *Annu Rev Physiol*. 2013;**75**:685-705.
17. Childs BG, Durik M, Baker DJ, van Deursen JM. Cellular senescence in aging and age-related disease: from mechanisms to therapy. *Nat Med*. 2015;**21**(12):1424-1435.
18. Basisty N, Kale A, Jeon OH, et al. A proteomic atlas of senescence-associated secretomes for aging biomarker development. *Plos Biol*. 2020;**18**(1):e3000599.
19. Hoare M, Narita M. Transmitting senescence to the cell neighbourhood. *Nat Cell Biol*. 2013;**15**(8):887-889.

20. Acosta JC, Banito A, Wuestefeld T, et al. A complex secretory program orchestrated by the inflammasome controls paracrine senescence. *Nat Cell Biol*. 2013;**15**(8):978-990.
21. Schmitt CA. The persistent dynamic secrets of senescence. *Nat Cell Biol*. 2016;**18**(9):913-915.
22. Kaur A, Webster MR, Marchbank K, et al. Corrigendum: sFRP2 in the aged microenvironment drives melanoma metastasis and therapy resistance. *Nature*. 2016;**537**(7619):254. doi:10.1038/nature18939
23. Hoare M, Narita M. Notch and senescence. *Adv Exp Med Biol*. 2018;**1066**:299-318.
24. Schafer MJ, Zhang X, Kumar A, et al. The senescence-associated secretome as an indicator of age and medical risk. *JCI Insight*. 2020;**5**(12):e133668. doi:10.1172/jci.insight.133668
25. Chkhotua AB, Gabusi E, Altimari A, et al. Increased expression of p16(INK4a) and p27(Kip1) cyclin-dependent kinase inhibitor genes in aging human kidney and chronic allograft nephropathy. *Am J Kidney Dis*. 2003;**41**(6):1303-1313.
26. Dimri GP, Lee X, Basile G, et al. A biomarker that identifies senescent human cells in culture and in aging skin in vivo. *Proc Natl Acad Sci U S A*. 1995;**92**(20):9363-9367.
27. Wang C, Jurk D, Maddick M, Nelson G, Martin-Ruiz C, von Zglinicki T. DNA damage response and cellular senescence in tissues of aging mice. *Aging Cell*. 2009;**8**(3):311-323.
28. Yousefzadeh MJ, Zhao J, Bukata C, et al. Tissue specificity of senescent cell accumulation during physiologic and accelerated aging of mice. *Aging Cell*. 2020;**19**(3):e13094.
29. Baker DJ, Wijshake T, Tchkonia T, et al. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature*. 2011;**479**(7372):232-236.
30. Kirkland JL, Tchkonia T. Cellular senescence: a translational perspective. *Ebiomedicine*. 2017;**21**:21-28.
31. Thoppil H, Riabowol K. Senolytics: a translational bridge between cellular senescence and organismal aging. *Front Cell Dev Biol*. 2019;**7**:367. doi:10.3389/fcell.2019.00367
32. Giaimo S, d'Adda di Fagagna F. Is cellular senescence an example of antagonistic pleiotropy? *Aging Cell*. 2012;**11**(3):378-383.
33. Waters MJ, Conway-Campbell BL. The oncogenic potential of autocrine human growth hormone in breast cancer. *Proc Natl Acad Sci U S A*. 2004;**101**(42):14992-14993.
34. Melmed S. Pathogenesis and Diagnosis of Growth Hormone Deficiency in Adults. *N Engl J Med*. 2019;**380**(26):2551-2562.
35. Vitale G, Pellegrino G, Vollery M, Hofland LJ. Role of IGF-1 system in the modulation of longevity: controversies and new insights from a centenarians' perspective. *Front Endocrinol (Lausanne)*. 2019;**10**:27. doi:10.3389/fendo.2019.00027
36. Mao K, Quipildor GF, Tabrizian T, et al. Late-life targeting of the IGF-1 receptor improves healthspan and lifespan in female mice. *Nat Commun*. 2018;**9**(1):2394. doi:10.1038/s41467-018-04805-5
37. Junnila RK, List EO, Berryman DE, Murrey JW, Kopchick JJ. The GH/IGF-1 axis in ageing and longevity. *Nat Rev Endocrinol*. 2013;**9**(6):366-376.
38. Tran D, Bergholz J, Zhang H, et al. Insulin-like growth factor-1 regulates the SIRT1-p53 pathway in cellular senescence. *Aging Cell*. 2014;**13**(4):669-678.
39. Panganiban RA, Day RM. Inhibition of IGF-1R prevents ionizing radiation-induced primary endothelial cell senescence. *Plos One*. 2013;**8**(10):e78589.
40. Sanada F, Taniyama Y, Muratsu J, et al. IGF binding protein-5 induces cell senescence. *Front Endocrinol (Lausanne)*. 2018;**9**:53. doi:10.3389/fendo.2018.00053
41. Takahashi Y. The role of growth hormone and insulin-like growth factor-I in the liver. *Int J Mol Sci*. 2017;**18**(7):1447. doi:10.3390/ijms18071447
42. Bartke A. Growth hormone and aging. *Rev Endocr Metab Disord*. 2021;**22**(1):71-80.
43. Bartke A, List EO, Kopchick JJ. The somatotropic axis and aging: Benefits of endocrine defects. *Growth Horm IGF Res*. 2016;**27**:41-45.
44. Bartke A. Somatic growth, aging, and longevity. *NPJ Aging Mech Dis*. 2017;**3**:14. doi:10.1038/s41514-017-0014-y
45. Bartke A, Hascup E, Hascup K, Masternak MM. Growth Hormone and Aging: New Findings. *World J Mens Health*. 2021;**39**(3):454-465.
46. Iranmanesh A, Lizarralde G, Veldhuis JD. Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half-life of endogenous GH in healthy men. *J Clin Endocrinol Metab*. 1991;**73**(5):1081-1088.
47. Hersch EC, Merriam GR. Growth hormone (GH)-releasing hormone and GH secretagogues in normal aging: fountain of youth or pool of tantalus? *Clin Interv Aging*. 2008;**3**(1):121-129.
48. Sonntag WE, Steger RW, Forman LJ, Meites J. Decreased pulsatile release of growth hormone in old male rats. *Endocrinology*. 1980;**107**(6):1875-1879.
49. Kuwahara S, Kesuma Sari D, Tsukamoto Y, Tanaka S, Sasaki F. Age-related changes in growth hormone (GH)-releasing hormone and somatostatin neurons in the hypothalamus and in GH cells in the anterior pituitary of female mice. *Brain Res*. 2004;**1025**(1-2):113-122.
50. Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M, 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**(70):70ra13.
51. Werner H, Lapkina-Gendler L, Achlaug L, et al. Genome-wide profiling of laron syndrome patients identifies novel cancer protection pathways. *Cells*. 2019;**8**(6):596. doi:10.3390/cells8060596
52. List EO, Basu R, Duran-Ortiz S, Krejsa J, Jensen EA. Mouse models of growth hormone deficiency. *Rev Endocr Metab Disord*. 2021;**22**(1):3-16.
53. Seim I, Fang X, Xiong Z, et al. Genome analysis reveals insights into physiology and longevity of the Brandt's bat Myotis brandtii. *Nat Commun*. 2013;**4**:2212.
54. Gorbunova V, Seluanov A, Kennedy BK. The world goes bats: living longer and tolerating viruses. *Cell Metab*. 2020;**32**(1):31-43.
55. Melmed S. Acromegaly pathogenesis and treatment. *J Clin Invest*. 2009;**119**(11):3189-3202.
56. Bartke A. Can growth hormone (GH) accelerate aging? evidence from GH-transgenic mice. *Neuroendocrinology*. 2003;**78**(4):210-216.
57. Ding J, Berryman DE, Kopchick JJ. Plasma proteomic profiles of bovine growth hormone transgenic mice as they age. *Transgenic Res*. 2011;**20**(6):1305-1320.
58. Knapp JR, Chen WY, Turner ND, Byers FM, Kopchick JJ. Growth patterns and body composition of transgenic mice

expressing mutated bovine somatotropin genes. *J Anim Sci*. 1994;**72**(11):2812-2819.
59. Kaps M, Moura AS, Safranski TJ, Lamberson WR. Components of growth in mice hemizygous for a MT/bGH transgene. *J Anim Sci*. 1999;**77**(5):1148-1154.
60. Miller RA, Harper JM, Galecki A, Burke DT. Big mice die young: early life body weight predicts longevity in genetically heterogeneous mice. *Aging Cell*. 2002;**1**(1):22-29.
61. Greer KA, Canterberry SC, Murphy KE. Statistical analysis regarding the effects of height and weight on life span of the domestic dog. *Res Vet Sci*. 2007;**82**(2):208-214.
62. Basu R, Qian Y, Kopchick JJ. MECHANISMS IN ENDOCRINOLOGY: Lessons from growth hormone receptor gene-disrupted mice: are there benefits of endocrine defects? *Eur J Endocrinol*. 2018;**178**(5):R155-R181.
63. van der Spoel E, Jansen SW, Akintola AA, et al. Growth hormone secretion is diminished and tightly controlled in humans enriched for familial longevity. *Aging Cell*. 2016;**15**(6):1126-1131.
64. Zhang X, Horwitz GA, Heaney AP, et al. Pituitary tumor transforming gene (PTTG) expression in pituitary adenomas. *J Clin Endocrinol Metab*. 1999;**84**(2):761-767.
65. Zhang X, Horwitz GA, Prezant TR, et al. Structure, expression, and function of human pituitary tumor-transforming gene (PTTG). *Mol Endocrinol*. 1999;**13**(1):156-166.
66. Melmed S. Mechanisms for pituitary tumorigenesis: the plastic pituitary. *J Clin Invest*. 2003;**112**(11):1603-1618.
67. Abbud RA, Takumi I, Barker EM, et al. Early multipotential pituitary focal hyperplasia in the alpha-subunit of glycoprotein hormone-driven pituitary tumor-transforming gene transgenic mice. *Mol Endocrinol*. 2005;**19**(5):1383-1391.
68. Wang Z, Moro E, Kovacs K, Yu R, Melmed S. Pituitary tumor transforming gene-null male mice exhibit impaired pancreatic beta cell proliferation and diabetes. *Proc Natl Acad Sci U S A*. 2003;**100**(6):3428-3432.
69. Chesnokova V, Kovacs K, Castro AV, Zonis S, Melmed S. Pituitary hypoplasia in Pttg-/- mice is protective for Rb+/- pituitary tumorigenesis. *Mol Endocrinol*. 2005;**19**(9):2371-2379.
70. Chesnokova V, Zonis S, Kovacs K, et al. p21(Cip1) restrains pituitary tumor growth. *Proc Natl Acad Sci U S A*. 2008;**105**(45):17498-17503.
71. Ben-Shlomo A, Deng N, Ding E, et al. DNA damage and growth hormone hypersecretion in pituitary somatotroph adenomas. *J Clin Invest*. 2020;**130**(11):5738-5755.
72. Vassilev LT, Vu BT, Graves B, et al. In vivo activation of the p53 pathway by small-molecule antagonists of MDM2. *Science*. 2004;**303**(5659):844-848.
73. Chesnokova V, Zhou C, Ben-Shlomo A, et al. Growth hormone is a cellular senescence target in pituitary and nonpituitary cells. *Proc Natl Acad Sci U S A*. 2013;**110**(35):E3331-E3339.
74. Chesnokova V, Zonis S, Zhou C, et al. Growth hormone is permissive for neoplastic colon growth. *Proc Natl Acad Sci U S A*. 2016;**113**(23):E3250-E3259.
75. Ou HL, Schumacher B. DNA damage responses and p53 in the aging process. *Blood*. 2018;**131**(5):488-495.
76. Yuan Z, Villagra A, Peng L, et al. The ATDC (TRIM29) protein binds p53 and antagonizes p53-mediated functions. *Mol Cell Biol*. 2010;**30**(12):3004-3015.
77. Monnat RJ Jr. From broken to old: DNA damage, IGF1 endocrine suppression and aging. *DNA Repair (Amst)*. 2007;**6**(9):1386-1390.
78. Chesnokova V, Zonis S, Barrett R, et al. Excess growth hormone suppresses DNA damage repair in epithelial cells. *JCI Insight*. 2019;**4**(3):e125762. doi:10.1172/jci.insight.125762
79. Chesnokova V, Zonis S, Barrett RJ, Gleeson JP, Melmed S. Growth Hormone Induces Colon DNA Damage Independent of IGF-1. *Endocrinology*. 2019;**160**(6):1439-1447.
80. Matsumoto R, Fukuoka H, Iguchi G, et al. Accelerated telomere shortening in acromegaly; IGF-I induces telomere shortening and cellular senescence. *Plos One*. 2015;**10**(10):e0140189.
81. Stout MB, Tchkonia T, Pirtskhalava T, et al. Growth hormone action predicts age-related white adipose tissue dysfunction and senescent cell burden in mice. *Aging (Albany NY)*. 2014;**6**(7):575-586.
82. Poudel SB, Dixit M, Neginskaya M, et al. Effects of GH/IGF on the aging mitochondria. *Cells*. 2020;**9**(6).
83. Hiraoka C, Toki F, Shiraishi K, et al. Two clonal types of human skin fibroblasts with different potentials for proliferation and tissue remodeling ability. *J Dermatol Sci*. 2016;**82**(2):84-94.
84. Spalding KL, Arner E, Westermark PO, et al. Dynamics of fat cell turnover in humans. *Nature*. 2008;**453**(7196):783-787.
85. Knosp E, Kitz K, Perneczky A. Proliferation activity in pituitary adenomas: measurement by monoclonal antibody Ki-67. *Neurosurgery*. 1989;**25**(6):927-930.
86. Clemmons DR, Molitch M, Hoffman AR, et al. Growth hormone should be used only for approved indications. *J Clin Endocrinol Metab*. 2014;**99**(2):409-411.
87. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML; Endocrine Society. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;**96**(6):1587-1609.