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Non-pituitary GH regulation of the tissue microenvironment

Vera Chesnokova,

Shlomo Melmed

Pituitary Center, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Abstract

Non-pituitary GH (npGH) expression is well established in extrapituitary tissues, but understanding of the physiological role of npGH remains rather limited. Pro-tumorigenic npGH impacting the tumor microenvironment has been reviewed (Basu and Kopchick 2019; Basu, *et al.* 2017; Brittain, *et al.* 2017; Chesnokova and Melmed 2019; Kopchick, *et al.* 2022; Perry, *et al.* 2017), and we focus here on autocrine/paracrine npGH effects in non-tumorous tissues and discuss its mechanisms of action in the normal tissue microenvironment. We address tissue-specific effects of npGH in regulating stem, endothelial, immune, and epithelial cells and highlight the related role of npGH-associated changes in tissue aging.

Keywords

non-pituitary growth hormone; non-tumorous tissue microenvironment; aging

Introduction

Pituitary growth hormone (GH) secretion is highly regulated physiologically, and declines with age (Hartman, *et al.* 1993; Ho and Hoffman 1993). The contribution of non-pituitary GH (npGH) to the circulation is considered to be negligible (Harvey and Hull 1997),, but is expressed in multiple tissues (Devesa, *et al.* 2016a; Harvey, *et al.* 2000a; Harvey, *et al.* 2015; Hattori 2009) and may exhibit autocrine/paracrine actions that affect the tissue microenvironment. Many effects of pituitary GH are mediated by insulin-like growth factor 1 (IGF1), and the GH/IGF1 axis plays an important role in skeletal growth and lipid and carbohydrate metabolism (Isaksson, *et al.* 1988; Moller and Jorgensen 2009). The membrane GH receptor (GHR) dimer signals through JAK2/STAT (Waters, *et al.* 2006), as well as through Src/ERK (Ling, *et al.* 2003; Rowlinson, *et al.* 2008). GHR is also translocated to the nuclei of proliferating cells, for example in hepatocytes during tissue regeneration (Conway-Campbell, *et al.* 2007) and in several cancers where nuclear GHR enhances proliferation (Brooks, *et al.* 2008). During pregnancy, pituitary GH (GH-N) is suppressed while placental GH (GH-V) is induced. As GH mRNA and protein are also expressed in extrapituitary tissues [for reviews see (Chesnokova and Melmed 2019; Harvey and Hull 1997; Harvey, *et*

Corresponding author: Shlomo Melmed, MB ChB, Cedars-Sinai Medical Center, 8700 Beverly Blvd., NT 2015, Los Angeles, CA 90048, Tel: (310) 423 4691, melmed@csmc.edu.

Declaration of Interests

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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al. 2000a; Kyle, *et al.* 1981; Perez-Ibave, *et al.* 2014)], ubiquitous GHR expression facilitates autocrine or paracrine npGH acting on tissue physiology *in situ.*

GH exerts multiple actions favoring cell survival (Sanders, *et al.* 2010) and tissue development (Baudet, *et al.* 2009; Nguyen, *et al.* 1996; Sanders and Harvey 2004). Extrapituitary GH mRNA transcripts are identical to those expressed in the anterior pituitary, and share similar endonuclease restriction sites. Indeed, the GH cDNA nucleotide sequence in human mammary cells (Raccurt, *et al.* 2002) and in human and rat lymphocytes is homologous with pituitary GH cDNA (Lin, *et al.* 1993; Liu, *et al.* 1997; Rohn and Weigent 1995), as is GH cDNA isolated from chicken immune (Render, *et al.* 1995a) and neural (Render, *et al.* 1995b) tissues. Although extrapituitary GH is produced in brain, liver, kidney, bone cartilage, heart, colon, and retina [(Daude, *et al.* 2016; Sundler, *et al.* 1979) and reviewed in (Harvey, *et al.* 2000b; Perez-Ibave, *et al.* 2014)], understanding physiological npGH actions remains largely unexplored.

The question arises as to how npGH is regulated in peripheral tissue. While pituitary GH transcription is regulated by the Pit1 transcription factor, extrapituitary GH may be Pit1–independent and regulated by other transcription factors (Harvey, *et al.* 2000b), such as, for example, FOXF1, as shown for hGH-V (Lomenick, *et al.* 2006). Pit1 is not ubiquitously expressed, and even when present, may be unrelated to GH gene expression (Harvey, *et al.* 2000b). For example, npGH is expressed in bone marrow of Pit1-deficient Snell dwarf mice (Harvey, *et al.* 2000b; Kooijman, *et al.* 1997a), and placental hGH-V is expressed in Pit1-deficient patients unable to express pituitary GH (Melen, *et al.* 1997). We found that colon cell npGH expression does not require Pit1 (unpublished data), and showed that GH can be transcriptionally induced by p53 in both pituitary and non-pituitary cells (Chesnokova, *et al.* 2013).

npGH may act by inducing IGF1 or may elicit direct IGF1-independent effects in peripheral tissues. While the liver is the main production source of circulating IGF1, this protein can also be produced locally. Thus, GH is expressed in human cartilage (Kyle, *et al.* 1981), and its growth-promoting effects in bone may be mediated by stimulating local IGF1 production (Schlechter, *et al.* 1986). Both GH and IGF1 are synthesized in CNS during development, but exhibit distinct overlapping roles in CNS function. Thus, despite stimulation of cellular PI3 kinase (PI3K) activity by each hormone, IGF1-stimulated (but not GH-stimulated) PI3K is predominantly associated with insulin receptor substrate (IRS1), while GH stimulation (but not IGF1 stimulation) of PI3K activity is maintained in IRS1-null cells. Further, while IRS1 is required for GH-stimulated STAT5-mediated transcription, IGF1 stimulates neither phosphorylation nor transactivation through STAT5 (Lobie, *et al.* 2000). npGH is produced in the liver of hypophysectomized rats subjected to partial hepatectomy, and directly induces hepatocyte growth factor (Devesa, *et al.* 2016b; Ekberg, *et al.* 1992). We showed that GH induced in colon cells in response to DNA damage and p53 upregulation and suppresses DNA damage repair independent of IGF1 (Chesnokova, *et al.* 2019a). Thus, whether acting through IGF1, or directly, npGH effects appear to be tissue- and cell-type specific.

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npGH in the Non-Tumorous Tissue Microenvironment

The tissue microenvironment is composed tissue-specific epithelial cell types and tissue-resident cell types including immune, mesenchymal, and endothelial cells and stem cells. These cells maintain tissue homeostasis, which may also be disrupted with a propensity for age-related or neoplastic changes. Knowledge of the microenvironment complexity and adaptability in response to external or internal insults is limited, especially for non-tumorous tissue. npGH is expressed in all cell types comprising the tissue microenvironment (Harvey and Hull 1997; Harvey, *et al.* 2000a; Hattori 2009; Kyle, *et al.* 1981; Perez-Ibave, *et al.* 2014), and autocrine/paracrine npGH effects are likely tissue-specific.

npGH Effects on Stem/Progenitor Cells—npGH expression in fetal and adult brain enables a favorable milieu for developing neurons (Donahue, *et al.* 2002; Harvey, *et al.* 2003; Laron and Galatzer 1985; Sun, *et al.* 2005a). GH is expressed in brain regions where neurogenesis occurs, including the hippocampal dentate gyrus. npGH emanating from mature neurons and glia provides a favorable microenvironment for neuronal stem cell proliferation, differentiation, migration, and survival (Donahue, *et al.* 2006; Pathipati, *et al.* 2011; Sun, *et al.* 2005a), while blocking GHR impedes neuronal precursor survival (Devesa, *et al.* 2011). GH effects on proliferation could be mediated by IGF1, as IGF1 administration also induced proliferation of rat neural progenitors (Aberg, *et al.* 2000). GH-induced neuroprotection mediated by PI3K and MAPK, exerting pro-survival functions by inhibiting pro-apoptotic caspases 3 and 9, as well as GSK3β (Herrington and Carter-Su 2001). Abundant rat hippocampal GH is induced by 17β-estradiol (Donahue, *et al.* 2006) and also by injury (Parent 2003) and npGH was suggested to promote neuron generation (Blackmore, *et al.* 2009; Parent 2003). Homozygous Ames Prop1 knockout mice deficient in pituitary GH, prolactin, and thyrotrophin paradoxically exhibit increased hippocampal GH with increased numbers of hippocampal neurons(Sun, *et al.* 2005b).

Mesenchymal stem cells or multipotent mesenchymal stromal cells (MSCs) constitute a reserve to replace damaged and aged cells (Caplan 2005; da Silva Meirelles, *et al.* 2006), and may differentiate into chondrocytes, myocytes, osteoblasts, and adipocytes (Pittenger, *et al.* 2019). Activated npGH can affect MSC proliferation by triggering GHR internalization and nuclear translocation via STAT5 phosphorylation and initiation of cyclinD1 and cyclinD1/CDK4 to phosphorylate Rb and release E2F1, which, in turn, promotes MSCs proliferation (Zheng, *et al.* 2022). npGH can also suppress differentiation toward adipocytes in MSCs derived from human trabecular bone (Bolamperti, *et al.* 2019)

In transgenic GH-overexpressing mice (bGH-Tg), expression of adipogenic C/EBPα and adiponectin as well as lipogenic lipoprotein lipase and acetyl-CoA carboxylase are reduced, whereas osteogenic factors are increased. Adipose tissue derived from these GH-overexpressing animals exhibit less lipid accumulation and lower levels of adipogenesis-related genes than do both wild type and GHR knockout (GHRKO) mice (Olarescu, *et al.* 2015). Wnt signaling plays a key role in MSC commitment by favoring osteogenesis at the expense of adipogenesis (Prestwich and Macdougald 2007; Ross, *et al.* 2000). As transcription of AXIN2, a target of Wnt/β-catenin signaling, is increased in bGH-Tg mice, GH could modulate MSC fate toward osteogenesis (Olarescu, *et al.* 2015). npGH may also

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synergize with BMP9, an osteogenesis activator, which directly stimulates GH transcription, suggesting an autocrine/paracrine activity for npGH. In an ectopic bone formation model, BMP9 and GH co-stimulation of MSCs induces more bone formation than does BMP9 alone, an effect inhibited by silencing GH or by JAK/STAT signaling pathway inhibitors (Huang, *et al.* 2012).

Growth and regeneration of intestinal mucosa are dependent on crypt intestinal stem cells (ISCs), which produce transit-amplifying cells that migrate and differentiate into Paneth cells, absorptive enterocytes, goblet cells, and enteroendocrine lineages (Barker 2014). Lgr5, Bmi (Sangiorgi and Capecchi 2008), Msi1 (Potten, *et al.* 2003), and EphB3 (Holmberg, *et al.* 2006), are ISC stemness markers. GH induces Lgr5 in murine 3-dimensional intestinal organoids, and *in vivo* GH increased Lgr5, Msi1, and EphB3 and increased crypt Ki67, a marker of proliferation (Chen, *et al.* 2018). As npGH is markedly induced in colonocytes and in intestinal stroma cells in response to DNA damage (Chesnokova, *et al.* 2021), it is plausible that local GH accelerates intestinal crypt stem cell proliferation, differentiation, and turnover. These npGH properties may protect intestinal mucosa during inflammation.

C2C12 myoblasts express npGH and GHR (Ogilvie, *et al.* 2000; Sadowski, *et al.* 2001), and autocrine GH/IGF1, but not exogenous GH, inhibits apoptosis, increases DNA synthesis, and retards myotube differentiation by suppressing AKT, required for myogenic conversion (Jiang, *et al.* 1999), as well as α actin (Shimokawa, *et al.* 1998) and troponin T (Meriane, *et al.* 2000), both molecular markers for myogenic differentiation, (Segard, *et al.* 2003).

Breast epithelium cells that express stem/progenitor cell markers express GHR. npGH secreted locally by normal human mammary epithelial cells upon progesterone stimulation increases stem- and early progenitor-cell proliferation. Expanded GHR-positive cell population occurs in ductal carcinoma *in situ* lesions (Lombardi, *et al.* 2014).

Overall, available evidence suggests that npGH induces stem cell/progenitor proliferation with tissue-specific effects on cell differentiation.

npGH and the Vascular System—GH contributes to diabetic retinopathy, the most frequent cause of adult blindness, characterized by increased vascular permeability and often by growth of new retinal and vitreous blood vessels (Antonetti, *et al.* 2012). npGH is synthesized and secreted in retinal ganglion cells and stimulates endothelial cell proliferation (Rymaszewski, *et al.* 1991; Sanders, *et al.* 2009; Struman, *et al.* 1999). Within retinal ganglion cells (RGCs), GH has also been shown to promote cell survival by acting as an antiapoptotic factor by inducing STAT 5 phosphorylation and increased BCL2 production. In post-mortem study of humans with eye disease, most of the RGC positive for GH were negative for apoptotic markers, while RGC negative for GH were all positive for TUNEL labeling (Sanders, *et al.* 2009). GHRs are detected in blood vessels and in endothelial cells (Clapp, *et al.* 2009). In the microvascular endothelial-like cell line HMEC-1, autocrine/paracrine npGH promotes capillary-like tube formation as a consequence of VEGF-A expression. Blocking HMEC-1–derived npGH reduced cell survival, proliferation, migration/invasion, and tube formation (Brunet-Dunand, *et al.* 2009). npGH may induce retinal blood vessels via IGF1, which is also expressed in retinal cells

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and is altered in response to hyperglycemia and hypoxia. Vitreous IGF1 is increased with diabetic retinopathy, and may induce proliferation by stimulating Akt (Xu, *et al.* 2012; Zheng and Quirion 2006), NFκB/AP1 (Chetty, *et al.* 2006), and HIF1α/PI3K to induce VEGF (Akagi, *et al.* 1998; Fukuda, *et al.* 2002). Trials of GHR antagonists and antisense oligonucleotides, somatostatin analogues, and IGF1R neutralizing antibodies aim to impair retinal neovascularization(Wilkinson-Berka, *et al.* 2006) and a microenvironment favoring vascularization and aberrant cell growth.

npGH and the Immune System—Immune-cell microenvironment components express GHR and npGH (Weigent, *et al.* 1988). npGH is expressed in leukocytes and bone marrow-derived granulocytes (Hattori 2009), and npGH is secreted from human peripheral blood mononuclear cells (Hattori, *et al.* 1990; Melen, *et al.* 1997; Varma, *et al.* 1993), neutrophils (Hattori, *et al.* 1999; Kooijman, *et al.* 1997b), and T- and B- lymphocytes(Kao, *et al.* 1992). As immune cells also produce GH releasing hormone (Varma, *et al.* 1993) and somatostatin (Lygren, *et al.* 1984), npGH production and secretion from peripheral blood cells may be regulated (Hattori, *et al.* 1994; Poppi, *et al.* 2002). Unlike in the anterior pituitary, immune cells do not store GH in secretory granules and instead immediately release the hormone upon production. Moreover, secreted npGH enhances further lymphocyte npGH secretion (Hattori, *et al.* 1993). Potential mechanisms of immune cell-derived npGH secretion affecting the microenvironment include phosphorylation of JAK/STAT3 and p125FAK, thus enforcing neutrophil adhesion to tissue inflammation sites (Ryu, *et al.* 2000). Additionally, npGH, acting through PI3K/MAPK, acts as a monocyte hemoattractant to repair tissue damage (Kahler, *et al.* 2001). Autocrine/paracrine GH induces release of IFN-γ (Ivashkiv and Donlin 2014) from mononuclear cells (Malarkey, *et al.* 2002). Furthermore, intrathymic GH injection modulates T-cell migration (Dardenne, *et al.* 2009). npGH secreted from T-lymphocytes, even without stimulation, may participate in intrathymic T-cell differentiation and thymocyte migration (Savino and Dardenne 2010). Indeed, GH increases T-cell proliferation 2.5-fold in rat splenic cells (Postel-Vinay, *et al.* 1997) and GH treatment reversed thymic atrophy in HIV-1 infected adults (Napolitano, *et al.* 2008). T-cell lymphoma npGH overexpression reduced expression of pro-apoptotic BAD as well as caspases 3, 8 and 9, while anti-apoptotic BCL2 was induced. Inhibition of endogenous GH in lymphoma cells enhanced lymphoma apoptosis (Arnold and Weigent 2004).

GH modulates inflammatory responses (Huang, *et al.* 2020), although reports are inconsistent. Acromegaly patients have increased proinflammatory cytokines including TNFα, IL1β, and IL6 (Arikan, *et al.* 2009; Huang, *et al.* 2022; Longobardi, *et al.* 1998), with similar changes in healthy volunteers injected with GH (Andreassen, *et al.* 2012), although the inflammatory marker CRP is decreased (Verhelst, *et al.* 2013). Similarly, GH-transgenic animal models exhibit increased levels of circulating proinflammatory cytokines (Friedbichler, *et al.* 2012). Inconsistent with proinflammatory GH effects, however, patients with adult GH deficiency exhibit increased inflammatory cytokines and CRP, and GH replacement yields anti-inflammatory effects (Huang, *et al.* 2020). Further complicating interpretation of these observations, older pituitary-deficient Snell dwarf mice and GHRKO mice have reduced tissue inflammation (Li, *et al.* 2020; Young, *et al.* 2020) GH treatment of aging animals reduces hepatic, pancreatic, and thymic inflammatory markers, and reduced

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NFκB activation occurs in aging WT animals (Cuesta, *et al.* 2011; de Mello-Coelho, *et al.* 2017; Kireev, *et al.* 2010).

npGH action in the colon microenvironment is more consistent in its anti-inflammatory role. npGH expression is markedly induced in colon plasma cells from patients with inflammatory bowel disease (IBD) (Chesnokova, *et al.* 2016). In experimental models of colitis (Soendergaard, *et al.* 2017), GH/STAT5 signaling promotes mucosal wound healing and improves barrier function during inflammation (Gilbert, *et al.* 2012; Han, *et al.* 2009), likely by inducing proliferation and suppressing apoptosis. GH, by inhibiting NFκB transcription factor, also suppresses TNFα (Han, *et al.* 2007), thus interrupting proinflammatory cytokine effects on colon mucosa, an effect likely underlying anti-inflammatory GH actions in IBD patients (Slonim, *et al.* 2000). We found GH signaling deficiency also results in severe colon inflammation and morbidity of GHRKO mice with acute colitis induced by dextran sodium sulfate (DSS) (unpublished data). Discordant pituitary and npGH action may be explained by direct GH effects versus those mediated through IGF1, insulin, glucose, or free fatty acids, which are normally induced with GH increase (Huang, *et al.* 2022). Thus, high IGF1, but not GH, may activate cytokine production (Wolters, *et al.* 2019). It is plausible that effects of GH/IGF1 on inflammation differ from direct GH effects when IGF1 is not expressed or not locally regulated by GH.

npGH is expressed in macrophages (Hattori 2009; Huang, *et al.* 2020), and autocrine/paracrine npGH in tissue microenvironment may modulate the macrophage gene signature (Lawrence and Natoli 2011; Soler Palacios, *et al.* 2020). GH enriches anti-inflammatory gene expression, while proinflammatory genes are suppressed in monocyte-derived human macrophages and in macrophages from bGH-Tg mice with acute DSS-induced colitis. Yet multiple *in vitro* studies show both pro- and anti-inflammatory action of GH treatment in macrophages (Huang, *et al.* 2022). An attractive hypothesis (Huang, *et al.* 2022) postulates that in quiescent macrophages, GH and IGF1 polarize cells toward a proinflammatory phenotype. They promote anti-infection function through activation of STAT5 and MAPK/ERK, which regulate production of TNFα and IL1β, whereas JAK/JNK triggers production of TNFα, IFNγ, and IL-12, mediating proinflammatory macrophage responses to GH (Tripathi and Sodhi 2009). Thereafter, GH and IGF1 autocrine-paracrine action may limit pro-inflammatory responses through PI3K-mediated downregulation of activin A and upregulation of MAFB, supporting anti-inflammatory macrophages (Soler Palacios, *et al.* 2020). In macrophage-specific GHRKO mice, increased NFκB activity and proinflammatory marker expression with an increased ratio of pro-/anti-inflammatory macrophages in adipose tissue occurred under high fat diet (Lu, *et al.* 2013). This effect could be mediated by decreased autocrine IGF1 macrophage production, as deletion of the IGF1 receptor led to reduced anti-inflammatory–related gene expression (Huang, *et al.* 2022; Spadaro, *et al.* 2017). Thus, paracrine npGH may attenuate macrophage microenvironment anti-inflammatory responses.

npGH in Epithelial Cells and Stroma: Implications for Aging and the Preneoplastic Environment—Although aging-associated physiological and pathological changes leading to tissue fragility and neoplasia have been well studied (Martincorena, *et al.* 2015), little is known about early microenvironmental steps underlying these changes.

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Cancer may arise from a “cancerized condition” (Curtius, *et al.* 2018), with cancerization of the microenvironmental field mostly referring to development of pro-tumorigenic genetic mutations (Braakhuis, *et al.* 2003; Curtius, *et al.* 2018; Rubin 2011; Slaughter, *et al.* 1953). It is, however, now apparent that progression of preneoplastic and neoplastic cells depends on surrounding microenvironmental changes (Marongiu, *et al.* 2016); driver mutations alone may not be sufficient to induce aging or tumorigenesis, as they, too, require a permissive microenvironment of cellular promoting factors (Balmain 2020). Thus, based on more recent advances, we propose a broader understanding of field cancerization that encompasses both cells with an age-associated phenotype potentiating benign tissue growth that may progress to malignancy, as well as stromal processes enabling these early changes. Such phenotypic changes could include increased proliferation, decreased apoptosis, increased unrepaired DNA damage accumulation, chromosomal instability, and immune landscape changes. While the GH role in the cancer microenvironment and in cancer therapy resistance has been observed (Basu and Kopchick 2019; Boguszewski and Boguszewski 2019; Brittain, *et al.* 2017; Chesnokova and Melmed 2019; Chhabra, *et al.* 2011; Kopchick, *et al.* 2022; Perry, *et al.* 2017), it could be equally important to understand npGH action as contributing to an aging tissue milieu that may support development of benign or malignant tumors.

Although GH is an important determinant of aging, its role remains enigmatic (Aguiar-Oliveira and Bartke 2019; Anisimov and Bartke 2013; Bartke 2008, 2021; Colon, *et al.* 2019; Corpas, *et al.* 1993). The GH/IGF1 system plays a key role during the lifespan, and pituitary GH secretion declines with age (Ho and Hoffman 1993), concomitant with age-related decreased protein synthesis, bone mass, and changes in body composition, all of which are classically attributed to GH decline. However, decreased GH/IGF1 signaling also has been shown to extend lifespan and reduce age-associated pathologies in experimental models (Anisimov and Bartke 2013; Bartke 2021; Basu, *et al.* 2018; Qian, *et al.* 2022), as well as increase insulin sensitivity and cancer prevention in human subjects (Aguiar-Oliveira and Bartke 2019). In contrast to decreased circulating GH, npGH expression remains abundant with aging in both non-tumorous human epithelial cells and in stromal fibroblasts but is low in colon samples derived from young individuals (Chesnokova, *et al.* 2021). These intracellular changes could be explained by increased npGH in response to age-associated DNA damage accumulation (Chesnokova, *et al.* 2021). DNA damage is associated with upregulation of p53, which induces npGH transcription (Chesnokova, *et al.* 2013). Thus, it is likely that aging colon GH induction is p53-dependent. Indeed, npGH is induced in both epithelial and stromal cells after DNA-damaging radio- and chemotherapy, and is also secreted from DNA-damaged normal human colon cells and intestinal organoids (Chesnokova, *et al.* 2019a; Chesnokova, *et al.* 2021).

Aging is associated with senescent cell accumulation due to telomere shortening followed by DNA damage induction. Radiation, oxidative stress, and activated oncogenes induce DNA damage and trigger senescence when DNA is not repaired, and unrepaired DNA damage, in turn, is linked to chromosomal instability and malignant transformation (O’Driscoll 2012; Schumacher, *et al.* 2008). Senescence is a protective mechanism for arresting uncontrolled proliferation of potentially tumorigenic cells and also results in depletion of viable cells (Di Micco, *et al.* 2021; Gorgoulis, *et al.* 2019; McHugh and Gil 2018; Sharpless and Sherr 2015). DNA damage and senescence are both hallmarks of aging (Lopez-Otin, *et al.*

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2023), and we found that npGH is induced and secreted from DNA-damaged senescent cells (Chesnokova, *et al.* 2013). This may explain increased npGH expression in aging colon tissue concomitant with DNA damage accrual (Chesnokova, *et al.* 2021), potentially resulting in chromosomal instability, as demonstrated for GH-secreting pituitary tumors (Ben-Shlomo, *et al.* 2020).

Although acutely protective, stably senescent cells contribute to a pro-neoplastic environment by a senescence-associated secretory phenotype (SASP) comprising metalloproteases, IGF binding proteins, cytokines, chemokines, and growth factors (Coppe, *et al.* 2010; Kuilman and Peeper 2009). While SASP may be beneficial in activating immune responses to eliminate senescent cells (Krizhanovsky, *et al.* 2008), it also may have pathological effects. Thus, SASP may induce senescence through paracrine action on neighboring cells, altering tissue homeostasis (Hoare and Narita 2013). Furthermore, SASP factors may alter the microenvironment by promoting low-grade inflammation, enhancing proliferation of neighboring cells and facilitating conversion of premalignant to malignant cells (Lee and Schmitt 2019). We found that npGH induced in senescent cells is a SASP component acting in an autocrine/paracrine manner (Chesnokova and Melmed 2022). npGH, induced and secreted in non-tumorous colon cells either as a result of acute DNA damage, or as a result of senescence, may suppress p53 in neighboring cells (Chesnokova, *et al.* 2019b), triggering senescence evasion with proliferation of post-senescent cells.

A complex network of DNA repair mechanisms minimizes damage and maintains cellular homeostasis. However, these mechanisms become less efficient with age (Feng, *et al.* 2007; Gutierrez-Martinez, *et al.* 2018; Stead and Bjedov 2021; Vijg and Dong 2020) and accumulation of genomic damage enhances susceptibility to cancer and other age-related diseases. Ineffective DNA repair accelerates tissue aging and underlies several progeroid syndromes that may also predispose to cancers. Thus, genomic instability is proposed to be a “meta-hallmark” of both aging and cancer. (Lopez-Otin, *et al.* 2023).

npGH constrains the DNA damage pathway by inhibiting phosphorylation of DNA repair proteins including ATM, Chk2, and H2AX in neighboring cells, which, in turn, reduces DNA repair by both homologous and non-homologous end-joining, promoting DNA damage accumulation (Chesnokova, *et al.* 2019b; Chesnokova, *et al.* 2021) and creating a pro-neoplastic environment in aging tissue. These observations may, to some extent, resolve the uncertainty surrounding the role of GH in aging. In addition to low IGF1, improved insulin sensitivity, and increased mitochondrial biogenesis [for review see (Bartke, *et al.* 2016; Basu, *et al.* 2018)], animal models with GH deficiency lacking not only circulating GH but also *local* GH signaling exhibit enhanced tissue DNA repair efficiency (Chesnokova and Melmed 2020) and may be resistant to age-associated microenvironment changes leading to neoplastic growth. Thus, GHRKO mice exhibit remarkably low cancer incidence (Basu, *et al.* 2018; Junnila, *et al.* 2013; Zhou, *et al.* 1997) similar to Laron syndrome patients harboring inactivating GHR mutations (Bartke, *et al.* 2016; Guevara-Aguirre, *et al.* 2011; Laron 2015), while in acromegaly, unrepaired lymphocyte DNA damage (Bayram, *et al.* 2014), high rates of colon polyps, enhanced soft tissue growth, and probably colon adenocarcinomas (Melmed 2009) occur, and bGH-Tg mice also develop tumors at early age (Kopchick, *et al.* 2014). These results provide potential mechanisms for observed decreased

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cancer development, as we observed that fibroblasts derived from Laron patients exhibit increased p53 expression and decreased proliferation (Chesnokova, *et al.* 2016),while 24-month-old GHRKO mice also exhibit induced colon p53 associated with reduced unrepaired DNA damage (Chesnokova, *et al.* 2021). When DNA damage persists, the cell may become senescent. In fact, GH-deficient and -resistant mice exhibited a lower senescent adipocyte burden. Conversely, concordant with deficient DNA damage repair caused by GH, GH-overexpressing and GH-treated mice accumulated more senescent adipose cells similar to observations in chronologically aged mice (Stout, *et al.* 2015; Stout, *et al.* 2014)

The ultimate effects of npGH may also depend on intermediate interacting factors. Thus, in addition to antiapoptotic and pro-proliferative effects of npGH via p53 suppression as well as attenuation of DNA damage repair, the colon microenvironment could be primed by suppressing tumor suppressors APC and PTEN in non-tumorous human colon cells and 3-D intestinal organoids (Chesnokova, *et al.* 2016). APC is regulated by CDX2 (Olsen, *et al.* 2013), and GH, by inducing ERK phosphorylation (Hodge, *et al.* 1998; Ji, *et al.* 2002), in turn, suppresses CDX2, resulting in decreased APC (Chesnokova, *et al.* 2016). Low APC expression leads to β-catenin nuclear accumulation and increased Wnt signaling with activation of pro-proliferative genes (Clevers and Nusse 2012). In human non-tumorous colon cells, GH induced β-catenin nuclear translocation, with subsequent activation of β-catenin–mediated transcriptional activity (Chesnokova, *et al.* 2016). As PTEN blocks mTOR signaling (Carracedo and Pandolfi 2008), restraining cell proliferation, p53, APC, and PTEN suppression may underlie pro-growth potentials of GH. By suppressing both p53 and PTEN, GH also abrogated apoptosis, thereby favoring cell survival (Zoncu, *et al.* 2011).

Stromal reprogramming may also determine the age-associated microenvironment, and aberrant stroma and immune cell population composition occurs in pre-malignant disease (Curtius, *et al.* 2018). npGH is expressed in colon epithelial and stromal cells (Chesnokova, *et al.* 2016; Chesnokova, *et al.* 2021), and we found that co-culture of normal human colon fibroblasts secreting GH results in suppressed p53/p21 and increased proliferation of neighboring human normal colon epithelial cells growing on a Colon Intestine-Chip microfluidic device. Paracrine npGH also leads to epithelial cell DNA damage (Chesnokova, *et al.* 2016; Chesnokova, *et al.* 2021).

Thus, npGH emanating from senescent epithelial cells, or from stromal cells as observed in IBD colon (Chesnokova 2016), may have similar detrimental effects on the tissue microenvironment, promoting genomic instability and ultimately neoplasia.

Microenvironmental npGH may also trigger malignant transformation of preneoplastic or existing benign lesions. Sustained activation of both S6 kinase and AKT could trigger progression of benign to rapidly growing malignant lesions. (Stemmer, *et al.* 2009), and we showed increased phosphorylation of S6 kinase in GH-treated cells followed by increased proliferation (Chesnokova, *et al.* 2016). BMP family members expressed by stromal cells are important for cancer development risk (Tomlinson, *et al.* 2011), and stromal GH induces BMP2/4 in human dental fibroblasts (Li, *et al.* 1998). Similar to effects of npGH on neuronal precursors, it also increases stem and early progenitor cell proliferation in normal breast epithelium (Lombardi, *et al.* 2014).

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npGH also enables progression of normal mammary human tissue to benign lesion to premetastatic stage (fibroadenoma) to metastatic cancer (Raccurt, *et al.* 2002). GH was detected in epithelial cells and also in cells of the reactive stroma, including myofibroblastic and myoepithelial cells, inflammatory lymphocytes, and endothelial cells in areas of neovascularization, and in both the epithelial and stromal compartments, expression was always stronger compared with that in adjacent normal tissue. hGH was also more abundant in proliferative disorders of the mammary gland compared with extracts derived from normal mammary gland, suggesting a role for autocrine hGH in neoplastic mammary progression. npGH, acting through STAT5, induced DNA-damage inducible transcript 3 (CHOP), which enhances GH protection against apoptosis in a p38 MAPK-dependent manner (Mertani, *et al.* 2001), and also induced anti-apoptotic p53-regulated placental PTGH-β (Graichen, *et al.* 2002), suppressing apoptosis and inducing mammary cancer cell progression. Autocrine GH also increases telomerase activity in mammary carcinoma by upregulating αCP1 and αCP2, which stabilize TERT mRNA (Emerald, *et al.* 2007), likely ensuring enhanced tumor cell proliferation. Moreover, autocrine GH induces trefoil factors that promote cell survival, motility, anchorage-independent growth, and cell transformation (Perry, *et al.* 2008). Fibroblast-derived npGH triggered transformation of an already cancerized lineage, as we showed increased migration and anchorage independent growth of human colon adenocarcinoma HCT116 cells co-cultured with normal colon fibroblasts expressing npGH, likely by inducing early-stage EMT transcription factors Snai1 and Twist2 (Chesnokova, *et al.* 2016) and permitting a permissive microenvironment toward a mesenchymal phenotype. By contrast, disrupted GH signaling attenuates progression from initiated prostate cells to intraepithelial neoplasia in T-antigen transgenic mice (Wang, *et al.* 2005). Thus, induced npGH contributes to a microenvironment favoring age-associated tissue changes that may potentially support neoplastic development.

Conclusions

Our understanding of GH action has changed with time. More than simply a pituitary growth factor acting mostly by inducing IGF1, we now recognize GH as a multifunctional hormone involved in complex tissue- and cell-specific actions shaping the tissue microenvironment. From an evolutionary point of view the fact that the GH gene evolved from a common GH-PRL gene by multiple duplications and conversion may allow other actions reflecting changes in GH functions in addition to its basic growth-promoting effects (Devesa and Devesa 2023; Wallis 1997).

Several in vivo examples underscore the significance of npGH effects. Thus, in homozygous Prop1 knockout (Ames) mice hippocampal GH compensates for the absence of pituitary GH activating neurogenesis (Sun, *et al.* 2005b). npGH is expressed in bone marrow of Pit1-deficient Snell mice lacking pituitary GH, promoting hematopoiesis (Harvey, *et al.* 2000b; Kooijman, *et al.* 1997a). In a patient with Pit1 deficiency, placental hGH-V is expressed (Melen, *et al.* 1997) contributing to fetal health during pregnancy. In all these cases, npGH appeared to serve as a back-up for pituitary GH failure. However, in other instances, npGH manifests its own specific role in the tissue microenvironment.

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GH appears to act by antagonistic pleiotropy, supporting growth and development at an early age, while facilitating the aging phenotype later in life as it is secreted from senescent cells, suppressing p53 and DNA repair and triggering genomic instability, all hallmarks of aging. Thus, the “somatopause” described with declining circulating GH appears to be protective as it restrains adverse GH actions. However, local intracellular npGH, induced with age by environmental insults, ionizing radiation, chemotherapy, or oncogenes may reverse this protection, enabling a tissue microenvironment primed for age-associated pre-neoplastic changes.

npGH acts on stem/progenitor cells, affecting processes of cell differentiation and tissue repair, induces vascularization, and interacts with local immune cells. The conflicting results of npGH effects in the immune system may depend on the *in vivo* microenvironment, which is difficult to reproduce *in vitro* (Huang, *et al.* 2022).

Unresolved issues and controversies precluding better understanding of npGH actions in the aging microenvironment include effects on fibrosis [recently reviewed for circulating GH in (Kopchick, *et al.* 2022)]. Little is known about which pathways — other than DNA damage — are involved in npGH induction in normal, non-tumorous tissues. It is not clear what mechanisms underlie tissue-specificity of npGH effects. For example, npGH triggers proliferation and differentiation of neuronal stem cells, not creating tumors, but enhancing cognition in Ames mice (Sun, *et al.* 2005a). At the same time, increased proliferation of mammary stem cells by npGH may be associated with creating pre-neoplastic and neoplastic lesions (Mertani, *et al.* 2001; Raccurt, *et al.* 2002). In some tissues, action of exogenous GH differs from npGH action, as demonstrated in C2C12 stem cells (Segard, *et al.* 2003), suggesting that this phenomenon may also be applicable for paracrine vs autocrine npGH effects. In this regard it is important to note that post-translation modification of npGH protein could also be tissue specific. Post-translationally modified forms of hGH include N-acylated, deamidated, and O-glycosylated forms of monomeric GH, as well as non-covalent and disulfide-linked oligomers up to pentameric GH (Baumann 1991). For example, in immune cells, higher molecular weight (100–35 kDa) oligomer GH isoforms appear in response to oxidative stress, with specific nuclear 65 kDa and 48 kDa detected (Weigent 2011). Thus, oligomeric isoforms may exert biological activity distinct from monomeric pituitary 22 kDa. Furthermore, npGH actions in each tissue and cell type may depend on its ability to induce local IGF1, which may have independent tissue microenvironment actions. Although, in contrast to GH, blocking IGF1/IGF1R increased DNA damage repair, these experiments were performed mostly in tumorous cell lines (Chesnokova and Melmed 2020). In non-tumorous colon cells, blocking colon IGF1R did not disrupt suppressive effects of GH on DNA damage (Chesnokova, *et al.* 2019a).

Notwithstanding the apparent inconsistencies, elucidating available information on npGH action in the normal and diseased microenvironment have enhanced knowledge and added new perspectives to our understanding of mechanisms underlying normal tissue homeostasis and aging processes engendered by GHR signaling.

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