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Covert actions of growth hormone: fibrosis, cardiovascular diseases and cancer

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Abstract

Since its discovery nearly a century ago, over 100,000 studies of growth hormone (GH) have investigated its structure, how it interacts with the GH receptor and its multiple actions. These include effects on growth, substrate metabolism, body composition, bone mineral density, the cardiovascular system and brain function, among many others. Recombinant human GH is approved for use to promote growth in children with GH deficiency (GHD), along with several additional clinical indications. Studies of humans and animals with altered levels of GH, from complete or partial GHD to GH excess, have revealed several covert or hidden actions of GH, such as effects on fibrosis, cardiovascular function and cancer. In this Review, we do not concentrate on the classic and controversial indications for GH therapy, nor do we cover all covert actions of GH. Instead, we stress the importance of the relationship between GH and fibrosis, and how fibrosis (or lack thereof) might be an emerging factor in both cardiovascular and cancer pathologies. We highlight clinical data from patients with acromegaly or GHD, alongside data from cellular and animal studies, to reveal novel phenotypes and molecular pathways responsible for these actions of GH in fibrosis, cardiovascular function and cancer.

Recombinant human growth hormone (hGH) is used primarily to treat children with short stature due to GH deficiency (GHD). In addition, hGH is approved for use in children

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born small for gestational age, as well as children with idiopathic short stature, Turner syndrome, Noonan syndrome, Prader–Willi syndrome, short stature homeobox-containing gene deficiency and chronic renal insufficiency, and in adults with GH deficiency. Despite this success, controversial issues remain, and not all indications are approved in all countries[1,2].

The Argentine clinician Bernardo Houssay discovered an adverse effect of GH nearly 90 years ago; namely its ability to inhibit insulin action, which is now known as its diabetogenic effect[3]. Since that time and despite the astonishing success of hGH, several puzzling actions of GH have been and continue to be described. Here, we review three interrelated covert actions reported in adult mice and humans: fibrosis, cardiovascular disease and cancer. Many have joked that ‘too much of a good thing is bad’, which in this context is too much GH. Interestingly, the absence of GH action in animals and humans, despite short stature, results in resistance to type 2 diabetes mellitus (T2DM) and cancer, and improvements in other indicators of healthspan[4]. With regard to longevity, mice with a reduction or absence in GH action have a robust and reproducible increase in lifespan[5]. Although data from humans is insufficient to draw firm conclusions, some cohorts of individuals with isolated GHD (for example, in the Brazilian Itabaianinha cohort) have attained extreme longevity despite representing a fairly small proportion of the population. Such observations suggest that the findings in rodents are relevant to humans[5]. The effects of the GH–insulin-like growth factor 1 (IGF1) axis on human ageing, how GH levels change during ageing and the relationship to age-related diseases are discussed in detail elsewhere[6].

In this Review, we explore the possibility that too much, too little or inappropriately expressed GH might provoke covert physiological actions related to fibrosis, cardiovascular function and cancer development.

GH and fibrosis

Fibrosis is characterized by excessive accumulation of the extracellular matrix (ECM) within tissues. Although fibrosis is initially a protective and adaptive response to wound healing and tissue repair, it can become uncontrolled and lead to tissue dysfunction and pathology. Almost every tissue type can be affected by pathological fibrosis; however, heart, adipose tissue, liver, kidney, intestine and skin are among the best studied. Tissue fibrosis is thought to be a major underlying cause of death in humans, with some studies estimating that it is associated with as much as 45% of all-cause mortality in industrialized nations[7]. As GH has an important role in growth and collagen turnover, it is a likely factor in ECM remodelling and fibrosis formation.

Influence of GH on collagens

A compelling reason for a GH–fibrosis link is the close correlation between GH exposure and collagen production. For example, in vitro studies of GH treatment of cells indicate increases in *Colla1*, *Col3a1* and *Col6a1* expression in differentiated adipocyte-like 3T3-L1 cells (a mouse cell line)[8] and type I collagen mRNA and protein in rodent intestinal primary myofibroblasts[9]. Animal studies have shown a similar positive correlation between collagen and GH. For example, GH treatment increases collagen IV protein in mouse neural tissue

damaged by stroke[10], and type I collagen RNA and protein in the jejunum of GH-treated rats[9]. Chronic exposure to excess GH in rodent models also increases collagen expression in other tissues such as kidneys and tendons[11,12].

The data in adult humans are similar. Both acute and chronic GH treatment in older men increases collagen expression in tendon and muscle[13]. Furthermore, the same study failed to detect an effect of GH on muscle fibre synthesis[13]. Acromegaly is a rare disease usually caused by a benign GH-producing pituitary tumour and elevated serum levels of IGF1 (REF.[14]). Adult patients with acromegaly have increased collagen turnover and serum levels of type I collagen and procollagen III amino-terminal propeptide (PIIINP)[15], which decline with remission of the disease[16,17]. The close association among GH, collagen synthesis and turnover, and fibrosis in clinical populations is further illustrated by several examples, including the use of validated tests to detect GH doping in sport that are based on elevated serum levels of IGF1 and PIIINP levels[18]. Moreover, a marker of growth plate activity and overall rate of linear bone growth (the intact trimeric non-collagenous domain of type X collagen) shows promise for reflecting GH action in children and adults with GHD[19]. Finally, hGH is used in a combination therapy to treat osteogenesis imperfecta, an inherited connective tissue disorder characterized by a quantitative or qualitative defect in collagen synthesis[20].

GH and other fibrosis-promoting factors

GH influences many factors besides collagens that contribute to fibrosis, including ECM-modifying proteins, several proteins and pathways implicated in fibrosis (for example, the transforming growth factor-β (TGFβ) pathway and mitogen-activated protein kinase (MAPK) pathways), senescence, immune cell function, and fibroblast activation or plasticity. In general, fibrosis is also often preceded by and closely associated with inflammation[7]. These fibrotic effects of GH are frequently context-specific and tissue-specific and not always in a direction that favours fibrosis. For example, an ECM-degrading endopeptidase, matrix metalloproteinase 2 (MMP2), is decreased after GH treatment of individuals with GHD[21], but increased in patients with active acromegaly[22]. Likewise, TGFβ, a master regulator and promoter of fibrosis in multiple tissues, is regulated distinctly by GH in a tissue-specific manner. For example, TGFβ expression is decreased by GH in primary cardiac fibroblasts[23]. Furthermore, TGFβ expression is increased in the glomeruli of bovine *GH* (bGH) transgenic mice, a model of GH overexpression[11]. Interestingly, GH action itself might also be influenced by ECM-modifying proteins. Tissue inhibitor of metalloproteinase 3 (TIMP3) is unique among the TIMP family because it alone has a high affinity for ECM proteoglycans and possesses the broadest range of substrates. TIMP3 modulates GH receptor (GHR) abundance on the cell surface in human cell lines that stably express GHR and JAK2, and dampens the GH-induced intracellular signalling cascade, revealing an interesting interplay between GH and the ECM[24].

Senescence.—Cellular senescence is characterized by irreversible cell cycle arrest and a senescence-associated secretory phenotype (SASP). The SASP is the main feature of senescent cells and includes pro-inflammatory cytokines and chemokines, growth factors and proteases, which contribute to a harmful tissue microenvironment. However, whether

senescence is beneficial or detrimental for the development of fibrosis remains debated. For example, senescence might be beneficial by preventing fibroblast differentiation and the ability of these fibroblasts to contribute to liver fibrosis, based on studies using senolytic chimeric antigen receptor T cells that efficiently target and ablate senescent cells in mice[25]. However, senescent cells could be detrimental, as removal of senescent cells in rodents either pharmacologically or genetically can reverse fibrosis at least in some tissues such as lung[26], and can extend median lifespan[27]. Of note, GH and/or IGF1 levels are positively correlated with senescence and SASP in white adipose tissue in mice[28], as well as in cardiomyocytes and skin fibroblasts from patients with acromegaly[29], and in human primary fibroblasts and mouse embryonic fibroblasts[30]. In fact, GH can also be secreted by senescent cells, thus constituting a component of the SASP[31]. By contrast, however, GH treatment attenuated senescence of primary human endothelial progenitor cells[32], and IGF1 overexpression in rats improved stress-induced senescence in the liver[33].

Fibroblasts.—Dysregulation of fibroblasts has long been considered a root cause of fibrosis. Data from the past 5 years show marked heterogeneity in fibroblast subtypes, which localize to unique anatomical sites and have distinct physiological functions[34]. Many studies have shown that GH and/or IGF1 influence the differentiation and proliferation of fibroblasts[35,36]. This association has been best studied in wound healing. For example, GH was identified as an inhibitor of TGFβ-induced myofibroblast differentiation in the skin of bGH transgenic mice[37]. A 2020 study showed that fibroblast activation protein (FAP) has been linked to GH action in humans[16]. FAP is a cell surface protease that has an important role in the degradation of ECM and with known substrates that include type I and III collagens[38]. FAP expression is limited after birth except in activated fibroblasts and in conditions associated with notable ECM remodelling, such as liver fibrosis[39]. Interestingly, serum levels of FAP are elevated in patients with untreated acromegaly and become considerably reduced after disease management, which closely correlates with reductions in markers of collagen turnover[16]. Additional studies are needed to determine if GH directly influences FAP abundance and action to influence ECM remodelling, as well as the ability of FAP to serve as a biomarker for GH-induced fibrosis.

Fibrosis and GH: the yin and the yang

As outlined above, GH has a complex relationship with many factors that contribute to fibrosis and ECM remodelling. Whether GH promotes or reduces pathological tissue fibrosis depends on the experimental conditions, the tissues analysed and the degree of GH signalling.

The yin: acromegaly and GH-transgenic mice.—Acromegaly is accompanied by soft-tissue enlargement and increases in ECM constituents; for example, glycosaminoglycan deposits that contribute to generalized oedema are apparent in the skin of patients with acromegaly[40]. Both early autopsy studies done in the 1980s[41] as well as in vivo studies from 2015 using cardiac MRI have revealed myocardial fibrosis in adult patients with acromegaly[42]. Furthermore, increased hepatic fibrosis has also been shown in subpopulations of adult patients with acromegaly, particularly those that are already at genetic risk of developing hepatic steatosis[43]. Finally, hard thyroid nodules are common in

patients with acromegaly and are also thought to be caused by increased nodular fibrosis[44]. However, overdiagnosis due to surveillance bias is inherent with regard to thyroid nodules, and further studies are needed[45].

Data derived from mice are more definitive of the actions of excess GH and IGF1 in inducing fibrosis and organ dysfunction. In fact, most tissues assessed for fibrosis in bGH mice show some increase in fibrosis at older ages (FIG. 1) compared with wild-type mice, which might reflect an unexplored benefit of somatopause (the gradual decline in GH secretion that occurs with ageing). The older bGH mice have an enlarged heart with impaired function and marked distinct perivascular and interstitial fibrosis[46,47]. These older transgenic mice also have renal damage with increased fibrosis and glomerular lesions[47]. Marked fibrosis is also apparent in their adipose tissue, more prominently in subcutaneous depots[8], as well as in the intestines[48]. Severe skin fibrosis has also been found in bGH mice, which is more prominent in males than females[37]. Overall, increased fibrosis has been observed in many tissues assessed in bGH mice relative to controls, with males often exhibiting a more robust phenotype. By contrast, several mouse lines with decreased GH action (such as GHR antagonist mice[8], mice with GHR disruption in adipocytes[49] or mice deficient in GH[50]) have decreased fibrosis, at least in adipose tissue. Collectively, these data in humans with acromegaly and GH transgenic mice provide strong support of fibrosis being an underlying component of the organ dysfunction that is common with pathological increases in GH and/or IGF1 action.

The yang: therapeutic potential of GH.—The benefits of GH in promoting collagen deposition are best illustrated by its effect on promoting longitudinal growth and bone acquisition[51]. However, GH might also have therapeutic potential for selected fibrotic diseases. These benefits might relate to restored GH levels in deficient states or to indirect influences on other disease pathologies or severe conditions. For example, studies have suggested that the dysregulation of the GH–IGF1 axis in patients with morbid obesity or in adult patients with hypopituitarism and GHD might contribute to the severity of hepatic fibrosis[52,53]. Furthermore, in at least one small study of adult patients with GHD, GH replacement therapy improved hepatic fibrosis[54]. Another example of GH action to attenuate fibrosis was provided by a rat model of intestinal inflammation, in which GH improved rather than exacerbated intestinal fibrosis[55], Moreover, in a randomized controlled trial, GH therapy was beneficial in the treatment of severely burned children, in whom it promoted healing without the development of hypertrophic scarring caused by tissue fibrosis[56]. Initial small, randomized studies in patients with large burns treated with GH have shown promising clinical benefit. However, treatment with GH also induces hyperglycaemia in adults with severe burns, which raises questions for its utility in clinical practice in the treatment of large burns[57].

Importantly, several limitations exist for the use of GH therapy for fibrotic disease. First, in most studies that showed some benefit of GH therapy on fibrosis, GH was restored to normal levels in patients with GHD. Second, many studies assessed acute or short-term GH therapy without evaluating the long-term cardiometabolic effects. Third, attenuation of fibrosis, treatment of burns and improvement in obesity and its complications are non-approved uses of GH.

Summary

Overall, the available data suggest an intricate balance between having sufficient GH action to promote favourable ECM remodelling and avoiding excess GH action that promotes ECM deposition and scarring, thereby resembling a ‘Goldilocks effect’. Although the focus of this Review is GH, disentangling the direct effects of GH versus indirect effects exerted via IGF1 is difficult in vivo. Endocrine and paracrine IGF1 also has an important role in fibrosis development. For example, local IGF1 administration stimulates in vivo tendon collagen synthesis in healthy, sedentary humans[13]. In addition, overexpression of IGF1 receptor (IGF1R) in human primary dermal fibroblasts suggests a role for IGF1 signalling in the development of keloid and hypertrophic scarring[58]. However, excess levels of GH, but not IGF1, have been shown to promote kidney glomerulosclerosis[59]. Together, these findings illustrate the need for additional studies or experimental systems that can help delineate the contributions of each individual hormone to fibrosis in specific tissues. In addition, further studies are needed to evaluate whether GH and IGF1 are primary drivers of fibrosis or if fibrosis occurs secondary to organ dysfunction.

GH and cardiovascular disease

GH hypersecretion: acromegaly

The onset of acromegaly is gradual, with a diagnostic delay of 5–10 years in most patients, which has negative therapeutic and prognostic implications. Patients with acromegaly are exposed to long-standing GH and IGF1 excess and have increased cardiovascular mortality[60] that is associated with hypertension and heart failure[14,61]. Interestingly, atherosclerosis is not always present in acromegaly despite the presence of classic risk factors such as hypertension, insulin resistance and T2DM[62]. By contrast, typical cardiomyopathy present in active acromegaly is cardiomegaly and, in particular, hypertrophy of the left ventricle[14,62]. Histopathology of cardiac tissue from patients with acromegaly reveals pronounced interstitial fibrosis (FIGS. 1,2), myocardial hypertrophy and evidence of myocarditis with infiltration of inflammatory cells[41]. Importantly, 85% of patients with acromegaly have been observed to have interstitial fibrosis[41]. In addition, regurgitation of the aortic and mitral valves, as well as diastolic dysfunction, are described in acromegaly, whereas systolic dysfunction is a rare and late-onset occurrence[14,62].

Due to the gradual onset of the disease and the paucity of long-term prospective studies, the pathogenesis of the cardiovascular complications of overt acromegaly remains elusive. Individual and combined effects can also be exerted by GH and IGF1, further complicating the picture. However, short-term experimental studies in humans could provide clues. For example, 1 week of supra-physiological GH administration in healthy men aged ~30 years substantially increased fractional shortening of the left ventricle, which was mainly attributed to a reduced end-systolic diameter[63]. In concomitance with a significant 15% increase in resting heart rate, cardiac output increased by ~13% without a change in mean arterial blood pressure[63,64], which suggests a simultaneous reduction in peripheral vascular resistance. Increased blood flow and reduced vascular resistance via a nitric oxide-dependent mechanism are also observed after short-term, high-dose GH infusion into the brachial artery of healthy individuals[65]. In addition, the GH–IGF1 axis is well recognized to acutely

induce fluid and sodium retention[66] and increases heart rate without a change in blood pressure[67]. Similar findings of increased myocardial contractility and cardiac output are also encountered in patients with active acromegaly[68] together with sodium and fluid retention[69]. Taken together, sustained fluid and sodium retention, in combination with direct inotropic effects of GH–IGF1, are hypothesized to promote hyperperfusion, cardiac hypertrophy and ultimately systemic hypertension in acromegaly[66]. In combination with other risk factors such as insulin resistance[70], T2DM and obstructive sleep apnoea, these effects might eventually cause cardiomyopathy and heart failure in the absence of coronary atherosclerosis (FIG. 2).

Treatment of acromegaly that achieves biochemical remission[71], translates into a life expectancy that is close to that in the general population[61]. Regarding cardiovascular function, successful surgical resection of the GH-producing adenoma improves diastolic function and reduces left ventricular mass, together with reductions in heart rate and blood pressure[72]. Similar beneficial effects have been reported after disease control obtained by pharmacological treatment with a somatostatin analogue alone[73] as well as with a GHR antagonist (pegvisomant)[14]. In addition, disease control in acromegaly improves certain risk factors for cardiovascular disease, such as insulin resistance and obstructive sleep apnoea; however, body composition changes towards increased adipose mass and reduced lean body mass[14].

GH deficiency

GHD in adults is caused by diseases affecting the hypothalamic–pituitary region, the most common being benign tumours. The diagnosis of GHD in adults must be made in the correct clinical context (that is, in patients with a well-defined hypothalamic–pituitary disorder) using a validated GH stimulation test, unless four or more anterior pituitary hormone deficiencies exist together with a low serum concentration of IGF1 (REF.[74]). GHD in adults can occur in isolation but is commonly associated with other pituitary hormone deficiencies. These deficiencies can also affect patient outcomes; for example, inadequate or untreated sex steroid deficiencies in women with hypopituitarism can affect their GHD outcome, inadequate treatment of central hypothyroidism might have negative effects on many metabolic processes and inadequate treatment of adrenal insufficiency has negative effects on metabolism as well as on risk of premature mortality[75–77]. Cardiovascular disease is a complication in adults with GHD; adults with GHD have increased blood pressure, a phenotype resembling the metabolic syndrome[78] and increased cardiovascular mortality[79]. Several cardiovascular risk factors are increased in adults with GHD, which can be explained by many of the effects of GH and IGF1 on the cardiovascular system (which expresses both GHR and IGF1R[80]), as well as effects on lipid and lipoprotein metabolism and systemic inflammation[81].

Adults with GHD often have overweight or obesity, with accumulation of visceral adipose tissue[82,83]. Studies on their body composition show that their total body adipose mass is increased (predominantly abdominal), muscle mass is reduced and extracellular fluid is reduced. GH antagonizes the effects of insulin in several important tissues such as liver, muscle and adipose tissue[83,84]. Studies in children and young adults with GHD have

clearly shown that these individuals have increased insulin sensitivity, and young children in particular might even experience hypoglycaemia[85]. Surprisingly, adults with long-standing untreated GHD deficiency showed markedly reduced insulin sensitivity, measured using the hyperinsulinaemic glucose clamp technique[86,87]. Their abdominal adiposity together with reduced muscle mass, reduced serum concentration of IGF1 and physical inactivity due to reduced exercise capacity might help explain this finding[83,86,88]. Abdominal adiposity and associated insulin resistance are therefore important mediators of premature atherosclerosis and increased risk of cardiovascular disease seen in adults with GHD.

Adults with GHD have reduced nitric oxide urinary excretion, increased peripheral vascular resistance[89], increased sympathetic nervous system activity[90] and increased systemic inflammation[81] (FIG. 2). A consistent finding is that the extracellular fluid volume and plasma volume are decreased in GHD[91]. Untreated acromegaly is associated with hypertension, therefore blood pressure would be expected to increase with GH replacement in adults with GHD. However, the initial placebo-controlled trials with adult GH replacement showed that diastolic blood pressure decreases[92] despite a sustained increase in extracellular fluid and plasma volume[91]. The mechanisms for reduced diastolic blood pressure seem to be nitric oxide-mediated vasodilation and reduced peripheral resistance[89,93], reduced sympathetic nervous system activity[93] and improved endothelial function[94]. Also, MMP and vascular endothelial growth factors, which are markers of endothelial function, are increased in adults with GHD and decline with GH replacement[21]. Of note, individuals with isolated GHD that is caused by an inactivating mutation of the GH-releasing hormone RH receptor (GHRHR) have obesity, elevated levels of LDL cholesterol, C-reactive protein (CRP) and mild systolic hypertension, but an absence of atherosclerosis or heart failure[95].

Long-term GH replacement therapy in patients with GHD induces sustained sodium and water retention[96,97]. This effect is due to increased sodium and water reabsorption from the distal renal tubuli, mediated by the direct actions of GH and IGF1, but also indirectly through stimulation of the renin–angiotensin–aldosterone system[96–98]. This sustained increase in extracellular water is in contrast to the effects of mineralocorticoids, which after administration increase the extracellular volume for days, where after renal sodium escape occurs, extracellular volume returns to baseline levels[99]. A probable explanation for the sustained sodium and water retention induced by GH is the reduction of natriuretic peptides induced by GH treatment, which mitigates renal sodium escape[96,100], together with increased glycosaminoglycan deposition in peripheral tissues[40].

Reduced exercise capacity has consistently been shown in adults with GHD, which improves with GH replacement[101,102]. The mechanism responsible could be related to effects on the heart and cardiovascular system, but also due to effects on muscle size and muscle function[103]. GHD is associated with reduced left ventricular mass index, reduced cardiac output with both impaired diastolic and systolic left ventricular function and reduced fractional shortening[104]. With GH replacement, an increase occurs in the left ventricular mass index as well as improvements in systolic and diastolic function that might contribute to improving exercise capacity[104].

GH has important regulatory effects on various aspects of lipid and lipoprotein metabolism. Lipid metabolism is strongly linked to atherosclerosis and local endothelial inflammation[105]. GH upregulates LDL receptors in the liver[106], stimulates lipolysis[107] and increases the synthesis and secretion of VLDL from the liver[108]. In addition, GH increases the ratio of plasma lecithin to cholesterol acyltransferase concentration and lipid transfer protein activities, which might explain the increase in HDL cholesterol levels seen in some GH replacement studies in adults with GHD[109]. Adults with GHD have increased concentrations of total cholesterol and LDL cholesterol, and in some studies also reduced HDL cholesterol[110,111]. Likewise, controlled studies of adult GH replacement have revealed decreased circulating levels of total cholesterol and LDL cholesterol[92], whereas effects on HDL cholesterol and triglycerides are smaller and less robust. Lipoprotein(a) is a lipoprotein that is similar to LDL in terms of its lipid and apolipoprotein B-100 content, but also contains apolipoprotein(a) covalently linked to apolipoprotein B-100. Increased plasma concentration of lipoprotein(a) is associated with increased risk of cardiovascular disease and its plasma level is mainly genetically determined, with an inverse relationship between circulating levels of lipoprotein(a) and the size polymorphism of apolipoprotein(a). Adults with GH deficiency have similar lipoprotein(a) concentrations to healthy matched control individuals, but GH replacement increases the concentration of lipoprotein(a)[112]. However, the net outcome of these changes in lipid and lipoprotein metabolism during GH replacement cannot be determined from available data.

Systemic inflammation markers such as CRP are well recognized cardiovascular risk factors[113]. Adults with GHD have increased circulating markers of inflammation such as CRP and IL-6 (REF.[114]). In one controlled study, GH replacement reduced the circulating levels of both CRP and IL-6 (REF.[115]). Also, in studies in women with abdominal obesity, GH treatment in comparison with placebo reduced biomarkers of systemic inflammation[116]. Thus, GHD is associated with a pro-inflammatory state but not with tissue fibrosis[81]. Taken together, studies of GH replacement in adults with GHD have shown beneficial effects on cardiovascular risk factors, cardiovascular function and surrogate variables for cardiovascular morbidity and mortality. However, no prospective controlled studies are available demonstrating reduced vascular morbidity and mortality. Such a study is unlikely to be performed due to the low prevalence of the disorder. However, in a retrospective meta-analysis of mortality in patients with hypopituitarism (including patients receiving GH replacement), GH replacement was associated with reduced mortality, particularly in men[117].

GH and endothelial cellular function

The vascular endothelium, which is the largest organ in the body, responds to various circulatory growth factors including GH. Angiogenesis is essential for organogenesis and successful embryonic and fetal development[118]. Disruption of the mechanisms controlling physiological angiogenesis underlies the pathophysiology and pathogenesis of various diseases including cancer, psoriasis, arthritis, retinopathies, obesity, asthma and cardiovascular disease. During angiogenesis, endothelial cells are regulated by an interplay between cells, multiple soluble factors and the ECM. For example, vascular endothelial growth factor A (VEGFA) binds to its receptor, VEGFR2, to stimulate downstream

signalling to activate endothelial nitric oxide synthase (eNOS) and nitric oxide release[119] (FIG. 2). Nitric oxide has a crucial role in angiogenesis and vasodilation, and also acts as an inhibitor of platelet adhesion and aggregation, monocyte adhesion and vascular smooth muscle cell growth. Endothelial cells express GHR, and GH, in part, regulates endothelial cell function and angiogenesis through VEGFA[120].

As discussed earlier in the article, both in vivo and in vitro studies have shown that treatment with IGF1 stimulates eNOS expression and nitric oxide release[121] (FIG. 2). Interestingly, age-dependent impairment of endothelial progenitor cells in middle-aged and older humans is corrected by treatment with hGH-mediated increases of IGF1 (REF.[32]), which supports the role of declining GH levels in ageing-associated cardiovascular dysfunction. Similarly, studies in adults with GHD have shown improved endothelial function and reduced vascular risk after GH replacement therapy[122]. As patients with GHD have reduced nitric oxide production[89], a feasible explanation of increased blood flow after GH replacement could be the improvement in endothelial function[123]. In addition, an improvement in the arterial response to induced vasodilation is observed in adolescents with GHD after GH replacement therapy[124].

Although atherosclerosis is not prevalent in acromegaly[62], GH has been found in experimental studies to directly stimulate the development of atherosclerosis in endothelial cells. For example, GH stimulates *VCAM1* and *SELE* transcripts in human umbilical vein endothelial cells (HUVECs) via the MAPK pathway, which results in augmented adhesion of a human leukaemia monocyte cell line (THP-1) and primary monocytes to HUVECs[125]. As the endothelium has a key role in the pathogenesis of atherosclerotic plaques, excess GH or IGF1 could play an active or passive part in atherosclerosis and cardiovascular dysfunction via effects on endothelial pathophysiology. These effects include endothelial proliferation, endothelial progenitor cell dysfunction or endothelial oxidative stress[126].

The effect of GH–IGF1 on endothelial cells has also been noted in other tissues and organs. In mouse endothelioma cells, GH has mitogenic effects[127]. GH also affects endothelial cell morphology and augments the deposition of the ECM molecules, laminin and fibronectin, on the cell surface[127]. In addition, human GH at physiological concentrations stimulates human retinal microvascular endothelial cells in vitro, thereby enhancing their proliferation[128]. In retinopathy, the proliferative form of retinal endothelial cells is observed during a more advanced stage of the disease and is characterized by retinal neovascularization. Although now abandoned, pituitary ablation was a method to suppress GH secretion as a potential treatment for proliferative diabetic retinopathy[129]. Interestingly, GH has an essential role in ischaemia-induced retinal neovascularization in mice[130] and a GHR antagonist prevents this effect[130]. Finally, topical application of GH accelerates the closure of skin wounds by accelerating re-epithelialization and collagen deposition, and stimulating angiogenesis[127], which occurs primarily via local production of IGF1 in the tissue[131]. Overall, these studies highlight the importance of the GH–IGF system in vascularization and angiogenesis.

Regulation of cardiac function

Studies in vitro and in rats have shown that GH and IGF1 increase cardiomyocyte gene expression and protein synthesis, which translates into cardiac hypertrophy and remodelling,

but they also inhibit apoptosis[132]. GH transgenic mice that have elevated levels of GH and IGF1 show increased organ sizes including the heart, while heart-specific IGF1 expression markedly promotes myocyte proliferation[133]. Furthermore, the removal of GH action in the heart of adult mice affects neither the local levels of IGF1 nor cardiac function, even though endocrine IGF1 levels are altered[134]. As for IGF1, loss-of-function studies using cardiac-specific *Igf1r*-knockout mice have shown that autocrine and paracrine IGF1 promotes heart repair in response to injury and conservation of cardiac function[135].

Endothelial-specific human *IGF1R*-overexpressing transgenic mice show reduced basal and insulin-stimulated eNOS activity, with no change in size or weight or whole-body glucose homeostasis[136]. These mice show normal blood pressure, an enhanced aortic response and increased endothelial cell migration and regeneration. By contrast, the *Igf1r*-knockout mice show normal glucose homeostasis with enhanced basal and insulin-stimulated eNOS phosphorylation[137] and vascular permeability in the endothelial lining[138]. These studies support an important role for IGF1R in regulating nitric oxide bioavailability and vascular repair, which are hallmarks of several human diseases involving tissue growth and vascularization. In addition, macrophage IGF1 signalling exerts anti-atherogenic effects through reducing macrophage activities, decreased atherosclerotic lesion formation and reduced plaque vulnerability[139,140].

Summary

Overall, evidence indicates that GH–IGF1 pathways have an important role in endothelial cell metabolism. Both elevated (acromegaly) and low (GHD) levels of GH are associated with cardiovascular disease. GH is a critical regulator of inflammation and immune activation. Considering that inflammation and fibrosis regulate progressive cardiac dysfunction during ischaemic heart failure[141], targeting mediators of GH action could provide an exciting therapeutic avenue for this disease. GH could also have a ‘Goldilocks effect’, where too little or too much can lead to insufficient or dysregulated immune activation and fibrotic mechanisms that lead to the exacerbation of cardiovascular disease. Comprehensive studies are warranted to fully investigate the involvement of the GH–IGF1 axis in the pathogenesis and pathophysiology of cardiovascular disease and its complications.

GH and cancer

Numerous studies in multiple cancer types since 1950 have shown that the intrinsic growth-promoting action of GH drives the growth and proliferation of cancer cells both in vitro and in vivo[142]. However, in light of our rapidly evolving understanding of different aspects of cancer as well as of GH action, a more ‘covert’ role of GH in cancer, beyond just promoting tumour growth, has also emerged. Pituitary secreted endocrine GH, critical for normal growth and development, is well known to decrease steadily in adults with age. By contrast, local or non-pituitary GH production from several non-pituitary sites (including peripheral tissues and multiple tumour types) seems to stay fairly steady or even increase with age[143,144] and exerts a profound autocrine and/or paracrine action. Fibrosis seems to be a consistent underlying theme in this action, wherein GH induces extensive

ECM remodelling by inducing expression of proteases, collagen and various cytokines[145]. Studies in cultured cells and animal models have revealed an extensive array of molecular mechanisms by which non-pituitary GH is now known to be a critical driver of a tumour supportive microenvironment and cancer therapy resistance (FIG. 3).

GH in the tumour microenvironment

Local GH production in specific tissues exerts an autocrine and/or paracrine effect, distinct from its endocrine role. In tissues such as the colon and breast, local GH production increase with age[143], forming a cellular niche in which oncogenic transformations could occur[143,146]. Furthermore, local GH production in these tissues could support the growth and survival of a tumour by affecting the tumour microenvironment (TME)[147] (TABLE 1). Melmed and colleagues have elegantly elucidated the role of autocrine and/or paracrine GH in modulating the TME in support of tumour growth and survival through the ‘field cancerization’ paradigm[147]. This model is a much overlooked but increasingly appreciated aspect of local GH action in oncology via the TME that is intuitive and critical, and supported by several observations. First, extra-pituitary sites of GH production are found in multiple tissues[144]. Second, GHR is expressed in several cell types in the TME, including cancer-associated fibroblasts, adipocytes, immune cells, stromal cells[147] and endothelial cells[148], wherein GH exerts differential effects that are supportive of tumour growth[148–151]. Third, endocrine GH-induced hepatic IGF1 has well-studied mitogenic effects that act on the tumour and TME[152,153].

Ageing or chemically inflicted DNA damage leads to activation of the tumour suppressor p53, which results in either apoptosis or induction of p53–p21 senescent pathway or a DNA damage repair (DDR) pathway[143]. Chromatin immunoprecipitation assays reveal *GH* as a target for p53 binding, whereas transcriptomic and proteomic analyses confirm DNA damage induces local GH production in normal colon and tumour cells[154–156]. In turn, locally produced GH exerts a feedback inhibition on p53 expression and diverts cellular commitment from senescence or apoptosis to proliferative survival[155]. Additionally, autocrine and/or paracrine GH signalling abrogates the DDR pathway, which increases the risk of oncogenic mutations, as is observed in human colonic epithelial transformation[156–158]. Increased colonic p53 expression was observed in *Ghr*-knockout (GHRKO) mice and Ames mice (which lack GH, prolactin and thyroid-stimulating hormone) compared with corresponding age-matched controls[158]. Furthermore, elevated expression of DDR genes were observed in γ-irradiated primary fibroblasts of GH-deficient Lewis dwarf rats compared with those from wild-type rats[159]. Elevated DDR gene expression was also observed in Snell mice (deficient in GH, prolactin and thyroid-stimulating hormone), GHRKO mice and *Pappa*-knockout mice (a model with alterations to the GH–IGF1 axis) compared with their respective wild-type controls[160]. Together, these findings in GH-deficient animal models support the ‘onco-promoting’ role of GH in peripheral tissues.

An analysis of the National Cancer Institute genome-wide association study identified that out of 421 pathways containing 3,962 genes, GH signalling is the third most associated pathway with breast cancer susceptibility[161]. Seminal work highlighted a concerted role

of GH and IGF1 in facilitating the functions of oestrogen and progesterone in normal mammary development[162]. The neoplastic effects of non-pituitary GH in breast cancer are particularly important, given that human GH binds to both GHR and prolactin receptor (PRLR), which are highly expressed together in ductal endothelium. These binding events result in a hyperplastic signalling cascade, which normally governs mammary development but can become an onco-driver under appropriate conditions[163]. This signalling cascade is of particular importance in the TME in the context of fibrosis, one of the hallmarks of cancer, which enables invasive and metastatic growth and compromises antitumour immunity[164,165]. As discussed above, GH is a potent inducer of fibrosis in multiple tissues, whereas the activation of the PRLR is also known to promote fibrosis in cancer via STAT3-dependent pathways[166,167]. Downstream effectors of GH action, IGF1 and TGFβ, are also strongly implicated as autocrine and/or paracrine drivers of fibrosis[168], and can therefore have profound effects in the TME. Additionally, autocrine and/or paracrine GH has been established as a prominent component of SASP, wherein it promotes DNA damage accumulation in bystander cells and predisposes senescent cells to cell cycle re-entry and neoplastic transformation[31]. Of note, congenital GHRKO mice and adult-onset GHRKO (at age 6 months) mice have markedly reduced fatal neoplasms in both sexes, compared with wild-type littermates[169,170].

GH in cancer therapy resistance

A set of key pathways observed across all types of cancer that are unresponsive to therapy are inhibition of apoptosis, active drug efflux via ATP-binding cassette (ABC) transporters and a phenotype switch via epithelial-to-mesenchymal transition (EMT). GH expression induces resistance against apoptosis in mammary and endometrial tumour cells following irradiation[171] and induces resistance against several chemotherapy treatments (mitomycin-C, doxorubicin, cisplatin, arsenic trioxide and ruxolitinib) in the same model[145]. Similar effects of GH in driving refractoriness against chemotherapy (doxorubicin, cisplatin and paclitaxel) and targeted (vemurafenib) therapies are also observed in melanoma[172]. The mechanistic validation comes from the identification that tumoural GHR activation induces a STAT5–SRC–ERK1/2-mediated upregulation of multidrug ABC transporters in human melanoma[172,173]. The ABC transporters impart resistance to a wide range of anticancer therapeutics by limiting their cytosolic retention through active efflux. Studies in human melanoma cells have shown autocrine GH signalling-induced upregulation of multidrug efflux transporters of the ABCB, ABCC and ABCG subtypes, which could be effectively blocked by GHR suppression[172]. Mouse xenograft models of human oestrogen receptor-negative breast cancer further confirm that GHR silencing reverses docetaxel resistance via downregulation of ABCG2 transporter expression[174]. Furthermore, chemically induced mammary tumour establishment was possible in spontaneous dwarf rats (GH-deficient) only when they were supplemented with exogenous GH. Moreover, when GH supplementation was stopped and the rats were treated with doxorubicin, tumours regressed in the dwarf animals but not in GH-sufficient wild-type animals, which confirms a GH-dependent chemoresistance[175]. Importantly, ABC transporters (such as ABCB1, ABCB5 and ABCG2) are known biomarkers for cancer stem cells (CSCs)[176], which are highly drug-resistant and are responsible for cancer relapse. Forced GH expression in liver cancer cells increased ABCG2 expression and conferred CSC properties by a JAK2–STAT3-mediated suppression

of the tight junction protein claudin 1 (REF.[177]). In addition forced GH expression stably increased CSC markers such as NANOG and SALL4 in both liver and colorectal cancer cells[177,178].

In cancers of the breast[179], colon[158], liver[177] and pancreas[180] and in melanoma[181], GH promotes successful metastasis from a primary tumour by the process of EMT. This process enables a switch from a well-defined, polarized, basement membrane-adherent cell phenotype to a depolarized, migrating invasive tumour cell phenotype[182]. In addition to its angiogenic and lymphangiogenic effects, GH is known to induce EMT in the overlapping pathways of tissue fibrosis and cancer metastases[183]. Suppression of the epithelial marker E-cadherin and upregulation of the mesenchymal markers N-cadherin and vimentin, and transcription factors ZEB1 and SLUG by recombinant hGH treatment occur in melanoma[173,181] and pancreatic[180] cancer cells and by autocrine GH in colorectal[178] and breast cancer cells[184]. Attenuating the GHR reverses these effects. The most extensive evidence of GH in promoting EMT is from breast cancer, where autocrine human GH expression in mammary tumour cells leads to robust EMT induction and massive ECM remodelling. This effect occurs by GH downregulating adherence factors such as plakoglobin via hypermethylation mediated by DNA methyltransferases 3A and 3B[185], by GH increasing the production of ECM-degrading MMP2 and MMP9 (REF.[184]) and by GH upregulating the microRNA (miRNA) cluster comprising miRNA-96, miRNA-182 and miRNA-183 leading to elevated ZEB1 and suppressed BRMS1L[186]. In fact, in *Dj1*-knockout mice, which have incidental high production of GH in the lungs, this local GH enhances the metastasis of disseminated melanoma cells[187]. The pronounced effect of GH in inducing fibrosis, as a part of ECM remodelling, further emphasizes a unique and critical role in promoting cancer therapy resistance[188] (TABLE 1).

Inhibition of GH action in cancer

Laron syndrome is congenital GH insensitivity due to inactivating mutations of GHR[189]. Independent long-term follow-up studies on two of the largest cohorts of individuals with Laron syndrome in Israel and in Ecuador have shown no cases of malignancy, while the incidence rate in first-degree relatives is >20%[4,190] in both cohorts. Similarly, among patients with secondary GHD due to a GHRHR defect and patients with primary congenital isolated GH deficiency, cancer incidence is considerably suppressed compared with their relatives[95]. The cohort of patients with isolated GH deficiency type 1B (arising due to GHRHR insufficiency), in Itabaianinha, Brazil, also show an absence of colorectal, prostate and breast cancers, unlike their relatives[95]. Altogether, these epidemiological findings indicate that a congenitally absent or reduced GH action seems to be onco-protective. By contrast, large-scale, long-term follow-up studies in children with GHD treated with recombinant GH do not indicate an elevated risk of neoplastic developments.

Numerous studies estimating the risks of cancer and benign neoplasia in patients with acromegaly have shown elevated risks for specific cancer types and establish cancer as a major cause of mortality in these patients[191]. However, confounding factors exist, including surveillance bias, normalization of circulating levels of IGF1 due to various treatment

options and difficulty in adequately comparing the cause of death in individuals with well-controlled acromegaly versus healthy control individuals.

Overall, the above discussion does provoke the question: can pharmacological suppression of GH action in the ageing population help tackle oncogenicity or improve cancer prognoses? Several GHR inhibitors are currently in development, which reflects a heightened pharmaceutical interest in targeting GH action in human disease[143,192,193]. So far, targeting GH action in cancer using somatostatin analogues has shown no objective response in humans, whereas GHRH antagonists so far show promising effects in several preclinical models[194]. Of note, somatostatin–GHRH control of GH production in the pituitary is seldom maintained in the context of the tumour. Pegvisomant, the first and only FDA-approved GHR antagonist, is highly successful in efficiently reducing serum concentrations of IGF1 in 70–90% of patients with acromegaly[195]. Moreover, pegvisomant has shown efficacy in attenuating growth of multiple GH-expressing and GHR-expressing human cancers in preclinical models[196].

Although clinical validation of the efficacy of GHR antagonists in monotherapy or in combination with other anticancer therapies is awaited, more clarity is needed in understanding the mutually exclusive roles of GH and IGF1, as well as the ratio of GH-induced IGF1 and insulin-like growth factor-binding protein 3 (IGFBP3)[197] in a cancer-specific manner. Importantly, several studies have revealed that endocrine GH-induced hepatic production of IGF1 and IGFBP3 is not always observed in cultured tumour cells and mouse tumour xenografts and TME, wherein autocrine and/or paracrine GH has IGF1-independent oncogenic effects[143,198]. A clinical trial in patients with cancer published in 2013 for a combination of pegvisomant and figitumumab (an anti-IGF1R monoclonal antibody) against solid tumours (breast, lung, prostate and colorectal tumours, and sarcoma) was initiated. Unfortunately, the study was terminated prematurely “due to lack of operational feasibility and halt of figitumumab development”[199]. Therefore, whether targeting GHR in cancer is a clinically relevant option remains an open question, given the large volume of provocative studies mentioned above alongside the failure of IGF1R inhibitors and monoclonal antibodies in the treatment of cancer. Patient pre-screening for tumoural GHR overexpression and serum levels of IGF1–IGFBP3 might offer an important precision factor in this approach.

Conclusions

In this Review we emphasize the importance of GH in promoting fibrosis and its association with cardiovascular and cancer pathologies. GH induces the expression of a variety of genes encoding collagen. This is not surprising, as one of the most important actions of the hormone is stimulation of longitudinal growth in children, which involves the concerted actions of systemic GH and local IGF1 on the growth plate, a specialized connective tissue[51]. Moreover, GH administration also stimulates collagen synthesis and turnover in adult humans to such an extent that quantification of IGF1 and PIIINP in serum is now an approved assay for the determination of GH doping in sport[18]. Whether GH doping causes excessive fibrosis formation in, for example, muscle is unknown. Of note, however, GH administration in healthy adults does not increase either muscle strength or aerobic exercise

capacity[200]. Indeed, after completion of longitudinal growth and somatic maturation, the major anabolic effect of GH administration seems to relate to collagen rather than muscle fibres[13]. When present in excess, GH results in fibrosis in a tissue-specific manner (FIG. 1) and the subsequent alterations to normal tissue function represent an added caution to be considered when utilizing GH supplementation in adults.

Data derived primarily from humans with elevated levels of GH (acromegaly) have shown a correlation with cardiovascular pathology, wherein fibrosis was identified as a contributor. In addition, patients with GHD often show a pro-inflammatory state without tissue fibrosis[81]. Together, the results suggest that a ‘normal’ amount of GH action is needed to ensure proper heart structure and cardiovascular function and either abnormally high or low levels of GH lead to cardiac pathology. An effect of the GH–IGF1 axis on vascular endothelial cells might be a common denominator of these effects that is reflected in adults with GHD with premature atherosclerosis.

In cancer, the effect of GH on fibrosis and endothelial cells makes it an important factor towards development of a detrimental TME. Clinically, cancer risks associated with GH replacement so far do not suggest any elevated risk of de novo neoplasm. However, since 1950 (REF.[142]), experimental and animal data clearly demonstrate the mechanistic links of how GH, and its partner IGF1, can influence the development, progression, therapy resistance and metastases of multiple human and animal cancers that express the GHR and, thus, depict a definite ‘oncodriver’ role. Therefore, the rational approach of targeting GH action in patients with cancer who have high tumoural GHR expression should be complemented with appropriate screening for the status of tumoural GH action, including testing tumour biopsy samples for GH or GHR expression.

Future studies that consider the surrounding tissue milieu and inherent subcellular differences associated with the covert actions of GH will ultimately define the molecular processes involved. Additionally, the question of local versus endocrine GH and IGF1 participation in these phenotypes must be determined. In terms of growth, GH and IGF1 have both independent and overlapping functions[201]. In this Review, we have updated the hidden or covert pathophysiological effects of GH and attempted to describe new molecular and cellular mechanisms responsible for them. Fibrosis is a common molecular ‘theme’ that seems to link these adverse phenotypes. Other fields of endocrinology clearly show that too much or too little exposure, or an abnormal time of exposure to a hormone, causes different adverse phenotypes. In the context of GH–IGF1, we conclude that either too much or too little of a good thing (GH) is ‘bad’ — a typical ‘Goldilocks effect’.

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References

1. Jorgensen JOL, Johannsson G & Barkan A Should patients with adult GH deficiency receive GH replacement? Eur. J. Endocrinol. 186, D1–D15 (2021). [PubMed: 34714773]
2. Ranke MB & Wit JM Growth hormone–past, present and future. Nat. Rev. Endocrinol. 14, 285–300 (2018). [PubMed: 29546874]
3. Bernardo A & Houssay MD The hypophysis and metabolism. N. Engl. J. Med. 214, 961–971 (1936).
4. Guevara-Aguirre J et al. Growth hormone receptor deficiency is associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans. Sci. Transl Med. 3, 70ra13 (2011).
5. Aguiar-Oliveira MH & Bartke A Growth hormone deficiency: health and longevity. Endocr. Rev. 40, 575–601 (2019). [PubMed: 30576428]
6. Milman S, Huffman DM & Barzilai N The somatotropic axis in human aging: framework for the current state of knowledge and future research. Cell Metab. 23, 980–989 (2016). [PubMed: 27304500]
7. Wynn TA Fibrotic disease and the T(H)1/T(H)2 paradigm. Nat. Rev. Immunol. 4, 583–594 (2004). [PubMed: 15286725]
8. Householder LA et al. Increased fibrosis: a novel means by which GH influences white adipose tissue function. Growth Horm. IGF Res. 39, 45–53 (2018). [PubMed: 29279183]
9. Fruchtman S et al. Suppressor of cytokine signaling-2 modulates the fibrogenic actions of GH and IGF-I in intestinal mesenchymal cells. Am. J. Physiol. Gastrointest. Liver Physiol 289, G342–G350 (2005). [PubMed: 15831713]
10. Ong LK et al. Growth hormone improves cognitive function after experimental stroke. Stroke 49, 1257–1266 (2018). [PubMed: 29636425]
11. Yang CW, Striker GE, Chen WY, Kopchick JJ & Striker LJ Differential expression of glomerular extracellular matrix and growth factor mRNA in rapid and slowly progressive glomerulosclerosis: studies in mice transgenic for native or mutated growth hormone. Lab. Invest. 76, 467–476 (1997). [PubMed: 9111509]
12. Nielsen RH et al. Chronic alterations in growth hormone/insulin-like growth factor-I signaling lead to changes in mouse tendon structure. Matrix Biol. 34, 96–104 (2014). [PubMed: 24080228]
13. Doessing S et al. Growth hormone stimulates the collagen synthesis in human tendon and skeletal muscle without affecting myofibrillar protein synthesis. J. Physiol. 588, 341–351 (2010). [PubMed: 19933753]
14. Gadelha MR, Kasuki L, Lim DST & Fleseriu M Systemic complications of acromegaly and the impact of the current treatment landscape: an update. Endocr. Rev. 40, 268–332 (2019). [PubMed: 30184064]
15. Constantin T et al. Calcium and bone turnover markers in acromegaly: a prospective, controlled study. J. Clin. Endocrinol. Metab. 102, 2416–2424 (2017). [PubMed: 28407138]
16. Arlien-Soborg MC et al. Fibroblast activation protein is a GH target: a prospective study of patients with acromegaly before and after treatment. J. Clin. Endocrinol. Metab. 105, dgz033 (2020). [PubMed: 31544947]
17. Nielsen RH et al. GH receptor blocker administration and muscle-tendon collagen synthesis in humans. Growth Horm. IGF Res. 21, 140–145 (2011). [PubMed: 21498100]
18. Holt RIG & Ho KKY The use and abuse of growth hormone in sports. Endocr. Rev. 40, 1163–1185 (2019). [PubMed: 31180479]
19. Coghlan RF et al. A degradation fragment of type X collagen is a real-time marker for bone growth velocity. Sci. Transl Med. 9, eaan4669 (2017). [PubMed: 29212713]
20. Antoniazzi F et al. GH in combination with bisphosphonate treatment in osteogenesis imperfecta. Eur. J. Endocrinol. 163, 479–487 (2010). [PubMed: 20592128]
21. Randeva HS et al. Growth hormone replacement decreases plasma levels of matrix metalloproteinases (2 and 9) and vascular endothelial growth factor in growth hormone-deficient individuals. Circulation 109, 2405–2410 (2004). [PubMed: 15123527]

22. Karci AC, Canturk Z, Tarkun I & Cetinarslan B Matrix metalloproteinase 2 (MMP-2) levels are increased in active acromegaly patients. Endocrine 57, 148–155 (2017). [PubMed: 28332074]
23. Imanishi R et al. GH suppresses TGF-β-mediated fibrosis and retains cardiac diastolic function. Mol. Cell Endocrinol. 218, 137–146 (2004). [PubMed: 15130518]
24. Zhang Y et al. TIMP3 modulates GHR abundance and GH sensitivity. Mol. Endocrinol. 30, 587–599 (2016). [PubMed: 27075707]
25. Amor C et al. Senolytic CAR T cells reverse senescence-associated pathologies. Nature 583, 127–132 (2020). [PubMed: 32555459]
26. Liu RM & Liu G Cell senescence and fibrotic lung diseases. Exp. Gerontol. 132, 110836 (2020). [PubMed: 31958492]
27. Baker DJ et al. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature 530, 184–189 (2016). [PubMed: 26840489]
28. Stout MB et al. Growth hormone action predicts age-related white adipose tissue dysfunction and senescent cell burden in mice. Aging 6, 575–586 (2014). [PubMed: 25063774]
29. Matsumoto R et al. Accelerated telomere shortening in acromegaly; IGF-I induces telomere shortening and cellular senescence. PLoS ONE 10, e0140189 (2015). [PubMed: 26448623]
30. Tran D et al. Insulin-like growth factor-1 regulates the SIRT1-p53 pathway in cellular senescence. Aging Cell 13, 669–678 (2014). [PubMed: 25070626]
31. Chesnokova V & Melmed S GH and senescence: a new understanding of adult GH action. J. Endocr. Soc 6, bvab177 (2022). [PubMed: 34909519]
32. Thum T et al. Age-dependent impairment of endothelial progenitor cells is corrected by growth-hormone-mediated increase of insulin-like growth-factor-1. Circ. Res. 100, 434–443 (2007). [PubMed: 17234973]
33. Luo X et al. Insulin-like growth factor-1 attenuates oxidative stress-induced hepatocyte premature senescence in liver fibrogenesis via regulating nuclear p53-progerin interaction. Cell Death Dis. 10, 451 (2019). [PubMed: 31171766]
34. Henderson NC, Rieder F & Wynn TA Fibrosis: from mechanisms to medicines. Nature 587, 555–566 (2020). [PubMed: 33239795]
35. Freeth JS et al. Human skin fibroblasts as a model of growth hormone (GH) action in GH receptor-positive Laron's syndrome. Endocrinology 138, 55–61 (1997). [PubMed: 8977385]
36. Guller S, Sonenberg M, Wu KY, Szabo P & Corin RE Growth hormone-dependent events in the adipose differentiation of 3T3-F442A fibroblasts: modulation of macromolecular synthesis. Endocrinology 125, 2360–2367 (1989). [PubMed: 2477229]
37. Thorey IS et al. Transgenic mice reveal novel activities of growth hormone in wound repair, angiogenesis, and myofibroblast differentiation. J. Biol. Chem. 279, 26674–26684 (2004). [PubMed: 15070902]
38. Fan MH et al. Fibroblast activation protein (FAP) accelerates collagen degradation and clearance from lungs in mice. J. Biol. Chem. 291, 8070–8089 (2016). [PubMed: 26663085]
39. Wang XM et al. Fibroblast activation protein and chronic liver disease. Front. Biosci. 13, 3168–3180 (2008). [PubMed: 17981786]
40. Ben-Shlomo A & Melmed S Skin manifestations in acromegaly. Clin. Dermatol. 24, 256–259 (2006). [PubMed: 16828406]
41. Lie JT Pathology of the heart in acromegaly: anatomic findings in 27 autopsied patients. Am. Heart J. 100, 41–52 (1980). [PubMed: 6446234]
42. dos Santos Silva CM et al. Low frequency of cardiomyopathy using cardiac magnetic resonance imaging in an acromegaly contemporary cohort. J. Clin. Endocrinol. Metab. 100, 4447–4455 (2015). [PubMed: 26431508]
43. Koutsou-Tassopoulou A et al. Hepatic steatosis in patients with acromegaly. Endocrinol. Diabetes Metab. 2, e00090 (2019). [PubMed: 31592448]
44. Andrioli M et al. Thyroid nodules in acromegaly: the role of elastography. J. Ultrasound 13, 90–97 (2010). [PubMed: 23396892]
45. Lai NB, Garg D, Heaney AP, Bergsneider M & Leung AM No benefit of dedicated thyroid nodule screening in patients with acromegaly. Endocr. Pract. 26, 16–21 (2020). [PubMed: 31461359]

46. Jara A et al. Elevated systolic blood pressure in male GH transgenic mice is age dependent. Endocrinology 155, 975–986 (2014). [PubMed: 24424040]
47. Munoz MC et al. Downregulation of the ACE2/Ang-(1–7)/Mas axis in transgenic mice overexpressing GH. J. Endocrinol. 221, 215–227 (2014). [PubMed: 24756097]
48. Jensen EA et al. Growth hormone alters gross anatomy and morphology of the small and large intestines in age- and sex-dependent manners. Pituitary 25, 116–130 (2022). [PubMed: 34373994]
49. List EO et al. Adipocyte-specific GH receptor-null (AdGHRKO) mice have enhanced insulin sensitivity with reduced liver triglycerides. Endocrinology 160, 68–80 (2019). [PubMed: 30462209]
50. List EO et al. GH knockout mice have increased subcutaneous adipose tissue with decreased fibrosis and enhanced insulin sensitivity. Endocrinology 160, 1743–1756 (2019). [PubMed: 31099824]
51. Yakar S & Isaksson O Regulation of skeletal growth and mineral acquisition by the GH/IGF-1 axis: lessons from mouse models. Growth Horm. IGF Res. 28, 26–42 (2016). [PubMed: 26432542]
52. Dichtel LE et al. The association between IGF-1 levels and the histologic severity of nonalcoholic fatty liver disease. Clin. Transl Gastroenterol. 8, e217 (2017). [PubMed: 28125073]
53. Polyzos SA et al. Targeted analysis of three hormonal systems identifies molecules associated with the presence and severity of NAFLD. J. Clin. Endocrinol. Metab. 105, e390–e400 (2020). [PubMed: 31690932]
54. Nishizawa H et al. Nonalcoholic fatty liver disease in adult hypopituitary patients with GH deficiency and the impact of GH replacement therapy. Eur. J. Endocrinol. 167, 67–74 (2012). [PubMed: 22535644]
55. Theiss AL et al. Growth hormone reduces the severity of fibrosis associated with chronic intestinal inflammation. Gastroenterology 129, 204–219 (2005). [PubMed: 16012948]
56. de Oliveira GV et al. Growth hormone effects on hypertrophic scar formation: a randomized controlled trial of 62 burned children. Wound Repair Regen. 12, 404–411 (2004). [PubMed: 15260805]
57. Breederveld RS & Tuinebreijer WE Recombinant human growth hormone for treating burns and donor sites. Cochrane Database Syst. Rev. 2014, CD008990 (2014). [PubMed: 25222766]
58. Hu ZC et al. Expression of insulin-like growth factor-1 receptor in keloid and hypertrophic scar. Clin. Exp. Dermatol. 39, 822–828 (2014). [PubMed: 25154292]
59. Doi T et al. Progressive glomerulosclerosis develops in transgenic mice chronically expressing growth hormone and growth hormone releasing factor but not in those expressing insulinlike growth factor-1. Am. J. Pathol. 131, 398–403 (1988). [PubMed: 3132856]
60. Bengtsson BA, Eden S, Ernest I, Oden A & Sjogren B Epidemiology and long-term survival in acromegaly. A study of 166 cases diagnosed between 1955 and 1984. Acta Med. Scand. 223, 327–335 (1988). [PubMed: 3369313]
61. Dal J et al. Acromegaly incidence, prevalence, complications and long-term prognosis: a nationwide cohort study. Eur. J. Endocrinol. 175, 181–190 (2016). [PubMed: 27280374]
62. Colao A, Grasso LFS, Di Somma C & Pivonello R Acromegaly and heart failure. Heart Fail. Clin. 15, 399–408 (2019). [PubMed: 31079698]
63. Thuesen L et al. Increased myocardial contractility following growth hormone administration in normal man. An echocardiographic study. Dan. Med. Bull. 35, 193–196 (1988). [PubMed: 2896102]
64. Thuesen L et al. Short and long-term cardiovascular effects of growth hormone therapy in growth hormone deficient adults. Clin. Endocrinol. 41, 615–620 (1994).
65. Napoli R et al. Acute effects of growth hormone on vascular function in human subjects. J. Clin. Endocrinol. Metab. 88, 2817–2820 (2003). [PubMed: 12788893]
66. Kamenicky P, Mazziotti G, Lombes M, Giustina A & Chanson P Growth hormone, insulin-like growth factor-1, and the kidney: pathophysiological and clinical implications. Endocr. Rev. 35, 234–281 (2014). [PubMed: 24423979]
67. Moller J, Jorgensen JO, Frandsen E, Laursen T & Christiansen JS Body fluids, circadian blood pressure and plasma renin during growth hormone administration: a placebo-controlled study with

two growth hormone doses in healthy adults. Scand. J. Clin. Lab. Invest. 55, 663–669 (1995). [PubMed: 8903836]

68. Thuesen L, Christensen SE, Weeke J, Orskov H & Henningsen P A hyperkinetic heart in uncomplicated active acromegaly. Explanation of hypertension in acromegalic patients? Acta Med. Scand. 223, 337–343 (1988). [PubMed: 3369314]
69. Ikkos D, Luft R & Sjogren B Body water and sodium in patients with acromegaly. J. Clin. Invest. 33, 989–994 (1954). [PubMed: 13174654]
70. Moller N et al. Basal- and insulin-stimulated substrate metabolism in patients with active acromegaly before and after adenomectomy. J. Clin. Endocrinol. Metab. 74, 1012–1019 (1992). [PubMed: 1569148]
71. Bolfi F, Neves AF, Boguszewski CL & Nunes-Nogueira VS Mortality in acromegaly decreased in the last decade: a systematic review and meta-analysis. Eur. J. Endocrinol. 181, L5–L6 (2019). [PubMed: 31539872]
72. Jaffrain-Rea ML et al. Impact of successful transsphenoidal surgery on cardiovascular risk factors in acromegaly. Eur. J. Endocrinol. 148, 193–201 (2003). [PubMed: 12590638]
73. Maison P, Tropeano AI, Macquin-Mavier I, Giustina A & Chanson P Impact of somatostatin analogs on the heart in acromegaly: a metaanalysis. J. Clin. Endocrinol. Metab. 92, 1743–1747 (2007). [PubMed: 17311857]
74. Yuen KCJ et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care. Endocr. Pract. 25, 1191–1232 (2019). [PubMed: 31760824]
75. Hammarstrand C et al. Higher glucocorticoid replacement doses are associated with increased mortality in patients with pituitary adenoma. Eur. J. Endocrinol. 177, 251–256 (2017). [PubMed: 28596421]
76. Klose M et al. Central hypothyroidism and its replacement have a significant influence on cardiovascular risk factors in adult hypopituitary patients. J. Clin. Endocrinol. Metab. 98, 3802–3810 (2013). [PubMed: 23796569]
77. Tomlinson JW et al. Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. Lancet 357, 425–431 (2001). [PubMed: 11273062]
78. Abe SY et al. Metabolic syndrome and its components in adult hypopituitary patients. Pituitary 23, 409–416 (2020). [PubMed: 32418172]
79. Rosen T & Bengtsson BA Premature mortality due to cardiovascular disease in hypopituitarism. Lancet 336, 285–288 (1990). [PubMed: 1973979]
80. Isgaard J, Wahlander H, Adams MA & Friberg P Increased expression of growth hormone receptor mRNA and insulin-like growth factor-I mRNA in volume-overloaded hearts. Hypertension 23, 884–888 (1994). [PubMed: 8206622]
81. Ratku B et al. Effects of adult growth hormone deficiency and replacement therapy on the cardiometabolic risk profile. Pituitary 25, 211–228 (2022). [PubMed: 35106704]
82. Johannsson G & Ragnarsson O Growth hormone deficiency in adults with hypopituitarism — What are the risks and can they be eliminated by therapy? J. Intern. Med. 290, 1180–1193 (2021). [PubMed: 34605087]
83. Moller N & Jorgensen JO Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. Endocr. Rev. 30, 152–177 (2009). [PubMed: 19240267]
84. Zierler KL & Rabinowitz D Roles of insulin and growth hormone, based on studies of forearm metabolism in man. Medicine 42, 385–402 (1963). [PubMed: 14085535]
85. Press M, Notarfrancesco A & Genel M Risk of hypoglycaemia with alternate-day growth hormone injections. Lancet 1, 1002–1004 (1987). [PubMed: 2883344]
86. Johansson JO, Fowelin J, Landin K, Lager I & Bengtsson BA Growth hormone-deficient adults are insulin-resistant. Metabolism 44, 1126–1129 (1995). [PubMed: 7666785]
87. Hew FL et al. Insulin resistance in growth hormone-deficient adults: defects in glucose utilization and glycogen synthase activity. J. Clin. Endocrinol. Metab. 81, 555–564 (1996). [PubMed: 8636267]

88. Berryman DE, Glad CA, List EO & Johannsson G The GH/IGF-1 axis in obesity: pathophysiology and therapeutic considerations. Nat. Rev. Endocrinol. 9, 346–356 (2013). [PubMed: 23568441]

89. Boger RH et al. Nitric oxide may mediate the hemodynamic effects of recombinant growth hormone in patients with acquired growth hormone deficiency. A double-blind, placebo-controlled study. J. Clin. Invest. 98, 2706–2713 (1996). [PubMed: 8981915]

90. Sverrisdottir YB, Elam M, Herlitz H, Bengtsson BA & Johannsson G Intense sympathetic nerve activity in adults with hypopituitarism and untreated growth hormone deficiency. J. Clin. Endocrinol. Metab. 83, 1881–1885 (1998). [PubMed: 9626113]

91. Moller J, Frandsen E, Fisker S, Jorgensen JO & Christiansen JS Decreased plasma and extracellular volume in growth hormone deficient adults and the acute and prolonged effects of GH administration: a controlled experimental study. Clin. Endocrinol. 44, 533–539 (1996).

92. Maison P et al. Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a metaanalysis of blinded, randomized, placebo-controlled trials. J. Clin. Endocrinol. Metab. 89, 2192–2199 (2004). [PubMed: 15126541]

93. Sverrisdottir YB et al. The effect of growth hormone (GH) replacement therapy on sympathetic nerve hyperactivity in hypopituitary adults: a double-blind, placebo-controlled, crossover, short-term trial followed by long-term open GH replacement in hypopituitary adults. J. Hypertens. 21, 1905–1914 (2003). [PubMed: 14508197]

94. Evans LM et al. The effect of GH replacement therapy on endothelial function and oxidative stress in adult growth hormone deficiency. Eur. J. Endocrinol. 142, 254–262 (2000). [PubMed: 10700719]

95. Aguiar-Oliveira MH & Salvatori R Disruption of the GHRH receptor and its impact on children and adults: the Itabaianinha syndrome. Rev. Endocr. Metab. Disord. 22, 81–89 (2021). [PubMed: 32935264]

96. Johannsson G, Sverrisdottir YB, Ellegard L, Lundberg PA & Herlitz H GH increases extracellular volume by stimulating sodium reabsorption in the distal nephron and preventing pressure natriuresis. J. Clin. Endocrinol. Metab. 87, 1743–1749 (2002). [PubMed: 11932310]

97. Kamenicky P et al. Body fluid expansion in acromegaly is related to enhanced epithelial sodium channel (ENaC) activity. J. Clin. Endocrinol. Metab. 96, 2127–2135 (2011). [PubMed: 21508131]

98. Moller J et al. Blockade of the renin-angiotensin-aldosterone system prevents growth hormone-induced fluid retention in humans. Am. J. Physiol. 272, E803–E808 (1997). [PubMed: 9176179]

99. Yokota N, Bruneau BG, Kuroski de Bold ML & de Bold AJ Atrial natriuretic factor significantly contributes to the mineralocorticoid escape phenomenon. Evidence for a guanylate cyclase-mediated pathway. J. Clin. Invest. 94, 1938–1946 (1994). [PubMed: 7962539]

100. Moller J, Jorgensen JO, Marqversen J, Frandsen E & Christiansen JS Insulin-like growth factor I administration induces fluid and sodium retention in healthy adults: possible involvement of renin and atrial natriuretic factor. Clin. Endocrinol. 52, 181–186 (2000).

101. Widdowson WM & Gibney J The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: a metaanalysis. J. Clin. Endocrinol. Metab. 93, 4413–4417 (2008). [PubMed: 18697875]

102. Jorgensen JO et al. Beneficial effects of growth hormone treatment in GH-deficient adults. Lancet 1, 1221–1225 (1989). [PubMed: 2566779]

103. Johannsson G, Grimby G, Sunnerhagen KS & Bengtsson BA Two years of growth hormone (GH) treatment increase isometric and isokinetic muscle strength in GH-deficient adults. J. Clin. Endocrinol. Metab. 82, 2877–2884 (1997). [PubMed: 9284713]

104. Amato G et al. Body composition, bone metabolism, and heart structure and function in growth hormone (GH)-deficient adults before and after GH replacement therapy at low doses. J. Clin. Endocrinol. Metab. 77, 1671–1676 (1993). [PubMed: 8263158]

105. Hansson GK Inflammation, atherosclerosis, and coronary artery disease. N. Engl. J. Med. 352, 1685–1695 (2005). [PubMed: 15843671]

106. Rudling M et al. Importance of growth hormone for the induction of hepatic low density lipoprotein receptors. Proc. Natl Acad. Sci. USA 89, 6983–6987 (1992). [PubMed: 1495990]

107. Sharma VM et al. Growth hormone acts along the PPARγ-FSP27 axis to stimulate lipolysis in human adipocytes. Am. J. Physiol. Endocrinol. Metab 316, E34–E42 (2019). [PubMed: 30325658]
108. Elam MB, Wilcox HG, Solomon SS & Heimberg M In vivo growth hormone treatment stimulates secretion of very low density lipoproteins by the perfused rat liver. Endocrinology 131, 2717–2722 (1992). [PubMed: 1446613]
109. Beentjes JA, van Tol A, Sluiter WJ & Dullaart RP Effect of growth hormone replacement therapy on plasma lecithin:cholesterol acyltransferase and lipid transfer protein activities in growth hormone-deficient adults. J. Lipid Res. 41, 925–932 (2000). [PubMed: 10828084]
110. Rosen T, Bosaeus I, Tolli J, Lindstedt G & Bengtsson B-Å Increased body fat mass and decreased extracellular fluid volume in adults with growth hormone deficiency. Clin. Endocrinol. 38, 63–71 (1993).
111. Cuneo RC, Salomon F, Wiles CM, Hesp R & Sönksen PH Growth hormone treatment in growth hormone-deficient adults. II. Effects on exercise performance. J. Appl. Physiol. 70, 695–700 (1991). [PubMed: 2022561]
112. Olivecrona H, Ericsson S, Berglund L & Angelin B Increased concentrations of serum lipoprotein (a) in response to growth hormone treatment. BMJ 306, 1726–1727 (1993).
113. Ridker PM, Hennekens CH, Buring JE & Rifai N C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N. Engl. J. Med. 342, 836–843 (2000). [PubMed: 10733371]
114. Leonsson M et al. Increased Interleukin-6 levels in pituitary-deficient patients are independently related to their carotid intima-media thickness. Clin. Endocrinol. 59, 242–250 (2003).
115. Sesmilo G et al. Effects of growth hormone administration on inflammatory and other cardiovascular risk markers in men with growth hormone deficiency. A randomized, controlled clinical trial. Ann. Intern. Med. 133, 111–122 (2000). [PubMed: 10896637]
116. Franco C et al. Growth hormone treatment reduces abdominal visceral fat in postmenopausal women with abdominal obesity: a 12-month placebo-controlled trial. J. Clin. Endocrinol. Metab. 90, 1466–1474 (2005). [PubMed: 15598680]
117. Pappachan JM, Raskauskiene D, Kutty VR & Clayton RN Excess mortality associated with hypopituitarism in adults: a meta-analysis of observational studies. J. Clin. Endocrinol. Metab. 100, 1405–1411 (2015). [PubMed: 25658016]
118. Drake CJ Embryonic and adult vasculogenesis. Birth Defects Res. C. Embryo Today 69, 73–82 (2003). [PubMed: 12768659]
119. Bouloumie A, Schini-Kerth VB & Busse R Vascular endothelial growth factor up-regulates nitric oxide synthase expression in endothelial cells. Cardiovasc. Res. 41, 773–780 (1999). [PubMed: 10435050]
120. Brunet-Dunand SE et al. Autocrine human growth hormone promotes tumor angiogenesis in mammary carcinoma. Endocrinology 150, 1341–1352 (2009). [PubMed: 18974274]
121. Walsh MF et al. Insulin-like growth factor I diminishes in vivo and in vitro vascular contractility: role of vascular nitric oxide. Endocrinology 137, 1798–1803 (1996). [PubMed: 8612517]
122. Setola E et al. Effects of growth hormone treatment on arginine to asymmetric dimethylarginine ratio and endothelial function in patients with growth hormone deficiency. Metabolism 57, 1685–1690 (2008). [PubMed: 19013291]
123. Lilien MR, Schroder CH, Levtchenko EN & Koomans HA Growth hormone therapy influences endothelial function in children with renal failure. Pediatr. Nephrol. 19, 785–789 (2004). [PubMed: 15173937]
124. Lanes R et al. Endothelial function, carotid artery intima-media thickness, epicardial adipose tissue, and left ventricular mass and function in growth hormone-deficient adolescents: apparent effects of growth hormone treatment on these parameters. J. Clin. Endocrinol. Metab. 90, 3978–3982 (2005). [PubMed: 15870123]
125. Ishikawa M et al. Role of growth hormone signaling pathways in the development of atherosclerosis. Growth Horm. IGF Res. 53–54, 101334 (2020).
126. Maffei P, Dassie F, Wennberg A, Parolin M & Vettor R The endothelium in acromegaly. Front. Endocrinol. 10, 437 (2019).

127. Messias de Lima CF, Dos Santos Reis MD, da Silva Ramos FW, Ayres-Martins S & Smaniotto S Growth hormone modulates in vitro endothelial cell migration and formation of capillary-like structures. Cell Biol. Int. 41, 577–584 (2017). [PubMed: 28205281]
128. Rymaszewski Z, Cohen RM & Chomczynski P Human growth hormone stimulates proliferation of human retinal microvascular endothelial cells in vitro. Proc. Natl Acad. Sci. USA 88, 617–621 (1991). [PubMed: 1988956]
129. Speakman JS et al. Pituitary ablation for diabetic retinopathy. Can. Med. Assoc. J. 94, 627–635 (1966). [PubMed: 5907943]
130. Smith LE et al. Essential role of growth hormone in ischemia-induced retinal neovascularization. Science 276, 1706–1709 (1997). [PubMed: 9180082]
131. Steenfos HH & Jansson JO Growth hormone stimulates granulation tissue formation and insulinlike growth factor-I gene expression in wound chambers in the rat. J. Endocrinol. 132, 293–298 (1992). [PubMed: 1311749]
132. Isgaard J, Arcopinto M, Karason K & Cittadini A GH and the cardiovascular system: an update on a topic at heart. Endocrine 48, 25–35 (2015). [PubMed: 24972804]
133. Santini MP et al. Enhancing repair of the mammalian heart. Circ. Res. 100, 1732–1740 (2007). [PubMed: 17525368]
134. Jara A et al. Cardiac-specific disruption of GH receptor alters glucose homeostasis while maintaining normal cardiac performance in adult male mice. Endocrinology 157, 1929–1941 (2016). [PubMed: 27035649]
135. Kim J et al. Insulin-like growth factor I receptor signaling is required for exercise-induced cardiac hypertrophy. Mol. Endocrinol. 22, 2531–2543 (2008). [PubMed: 18801929]
136. Imrie H et al. Novel role of the IGF-1 receptor in endothelial function and repair: studies in endothelium-targeted IGF-1 receptor transgenic mice. Diabetes 61, 2359–2368 (2012). [PubMed: 22733797]
137. Abbas A et al. The insulin-like growth factor-1 receptor is a negative regulator of nitric oxide bioavailability and insulin sensitivity in the endothelium. Diabetes 60, 2169–2178 (2011). [PubMed: 21677284]
138. Liang M et al. Protective role of insulin-like growth factor-1 receptor in endothelial cells against unilateral ureteral obstruction-induced renal fibrosis. Am. J. Pathol. 185, 1234–1250 (2015). [PubMed: 25783760]
139. Higashi Y et al. Insulin-like growth factor-1 receptor deficiency in macrophages accelerates atherosclerosis and induces an unstable plaque phenotype in apolipoprotein E-deficient mice. Circulation 133, 2263–2278 (2016). [PubMed: 27154724]
140. Spadaro O et al. Growth hormone receptor deficiency protects against age-related NLRP3 inflammasome activation and immune senescence. Cell Rep. 14, 1571–1580 (2016). [PubMed: 26876170]
141. Nehra S, Gumina RJ & Bansal SS Immune cell dilemma in ischemic cardiomyopathy: to heal or not to heal. Curr. Opin. Physiol. 19, 39–46 (2021). [PubMed: 33103020]
142. Moon HD, Simpson ME, Li CH & Evans HM Neoplasms in rats treated with pituitary growth hormone; pulmonary and lymphatic tissues. Cancer Res. 10, 297–308 (1950). [PubMed: 15414480]
143. Chesnokova V et al. Local non-pituitary growth hormone is induced with aging and facilitates epithelial damage. Cell Rep. 37, 110068 (2021). [PubMed: 34910915]
144. Harvey S, Aramburo C & Sanders EJ Extrapituitary production of anterior pituitary hormones: an overview. Endocrine 41, 19–30 (2012). [PubMed: 22169962]
145. Basu R & Kopchick JJ The effects of growth hormone on therapy resistance in cancer. Cancer Drug Resist. 2, 827–846 (2019). [PubMed: 32382711]
146. Waters MJ & Conway-Campbell BL The oncogenic potential of autocrine human growth hormone in breast cancer. Proc. Natl Acad. Sci. USA 101, 14992–14993 (2004). [PubMed: 15479760]
147. Chesnokova V & Melmed S Growth hormone in the tumor microenvironment. Arch. Endocrinol. Metab 63, 568–575 (2019). [PubMed: 31939481]

148. Lincoln DT, Singal PK & Al-Banaw A Growth hormone in vascular pathology: neovascularization and expression of receptors is associated with cellular proliferation. Anticancer Res. 27, 4201–4218 (2007). [PubMed: 18225592]

149. Dos Santos Reis MD, Dos Santos YMO, de Menezes CA, Borbely KSC & Smaniotto S Resident murine macrophage migration and phagocytosis are modulated by growth hormone. Cell Biol. Int. 42, 615–623 (2018). [PubMed: 29363842]

150. Kopchick JJ, Berryman DE, Puri V, Lee KY & Jorgensen JOL The effects of growth hormone on adipose tissue: old observations, new mechanisms. Nat. Rev. Endocrinol. 16, 135–146 (2020). [PubMed: 31780780]

151. Lee SW, Kim SH, Kim JY & Lee Y The effect of growth hormone on fibroblast proliferation and keratinocyte migration. J. Plast. Reconstr. Aesthet. Surg. 63, e364–e369 (2010). [PubMed: 20022575]

152. Hua H, Kong Q, Yin J, Zhang J & Jiang Y Insulin-like growth factor receptor signaling in tumorigenesis and drug resistance: a challenge for cancer therapy. J. Hematol. Oncol. 13, 64 (2020). [PubMed: 32493414]

153. Pollak M Insulin and insulin-like growth factor signalling in neoplasia. Nat. Rev. Cancer 8, 915–928 (2008). [PubMed: 19029956]

154. Basu R et al. Growth hormone upregulates melanocyte-inducing transcription factor expression and activity via JAK2-STAT5 and SRC signaling in GH receptor-positive human melanoma. Cancers 11, 1352 (2019). [PubMed: 31547367]

155. Chesnokova V et al. Growth hormone is a cellular senescence target in pituitary and nonpituitary cells. Proc. Natl Acad. Sci. USA 110, E3331–E3339 (2013). [PubMed: 23940366]

156. Ben-Shlomo A et al. DNA damage and growth hormone hypersecretion in pituitary somatotroph adenomas. J. Clin. Invest. 130, 5738–5755 (2020). [PubMed: 32673291]

157. Chesnokova V et al. Excess growth hormone suppresses DNA damage repair in epithelial cells. JCI Insight 4, e125762 (2019). [PubMed: 30728323]

158. Chesnokova V et al. Growth hormone is permissive for neoplastic colon growth. Proc. Natl Acad. Sci. USA 113, E3250–E3259 (2016). [PubMed: 27226307]

159. Podlutsky A et al. The GH/IGF-1 axis in a critical period early in life determines cellular DNA repair capacity by altering transcriptional regulation of DNA repair-related genes: implications for the developmental origins of cancer. Geroscience 39, 147–160 (2017). [PubMed: 28233247]

160. Dominick G, Bowman J, Li X, Miller RA & Garcia GG mTOR regulates the expression of DNA damage response enzymes in long-lived Snell dwarf, GHRKO, and PAPPA-KO mice. Aging Cell 16, 52–60 (2017). [PubMed: 27618784]

161. Menashe I et al. Pathway analysis of breast cancer genome-wide association study highlights three pathways and one canonical signaling cascade. Cancer Res. 70, 4453–4459 (2010). [PubMed: 20460509]

162. Kleinberg DL & Barcellos-Hoff MH The pivotal role of insulin-like growth factor I in normal mammary development. Endocrinol. Metab. Clin. North Am. 40, 461–471 (2011). [PubMed: 21889714]

163. Lombardi S et al. Growth hormone is secreted by normal breast epithelium upon progesterone stimulation and increases proliferation of stem/progenitor cells. Stem Cell Rep. 2, 780–793 (2014).

164. Boulter L, Bullock E, Mabruk Z & Brunton VG The fibrotic and immune microenvironments as targetable drivers of metastasis. Br. J. Cancer 124, 27–36 (2021). [PubMed: 33239677]

165. Piersma B, Hayward MK & Weaver VM Fibrosis and cancer: a strained relationship. Biochim. Biophys. Acta Rev. Cancer 1873, 188356 (2020). [PubMed: 32147542]

166. Chakraborty D et al. Activation of STAT3 integrates common profibrotic pathways to promote fibroblast activation and tissue fibrosis. Nat. Commun. 8, 1130 (2017). [PubMed: 29066712]

167. Tandon M et al. Prolactin promotes fibrosis and pancreatic cancer progression. Cancer Res. 79, 5316–5327 (2019). [PubMed: 31395607]

168. Sun W et al. Regulation of the IGF1 signaling pathway is involved in idiopathic pulmonary fibrosis induced by alveolar epithelial cell senescence and core fucosylation. Aging 13, 18852–18869 (2021). [PubMed: 34329195]

169. Duran-Ortiz S et al. Growth hormone receptor gene disruption in mature-adult mice improves male insulin sensitivity and extends female lifespan. Aging Cell 20, e13506 (2021). [PubMed: 34811874]
170. Ikeno Y et al. Reduced incidence and delayed occurrence of fatal neoplastic diseases in growth hormone receptor/binding protein knockout mice. J. Gerontol. A Biol. Sci. Med. Sci. 64, 522–529 (2009). [PubMed: 19228785]
171. Bougen NM et al. Autocrine human GH promotes radioresistance in mammary and endometrial carcinoma cells. Endocr. Relat. Cancer 19, 625–644 (2012). [PubMed: 22807498]
172. Basu R, Baumgaertel N, Wu S & Kopchick JJ Growth hormone receptor knockdown sensitizes human melanoma cells to chemotherapy by attenuating expression of ABC drug efflux pumps. Horm. Cancer 8, 143–156 (2017). [PubMed: 28293855]
173. Qian Y et al. Growth hormone upregulates mediators of melanoma drug efflux and epithelial-to-mesenchymal transition in vitro and in vivo. Cancers 12, 3640 (2020). [PubMed: 33291663]
174. Arumugam A et al. Silencing growth hormone receptor inhibits estrogen receptor negative breast cancer through ATP-binding cassette sub-family G member 2. Exp. Mol. Med. 51, 1–13 (2019).
175. Lantvit DD et al. Mammary tumors growing in the absence of growth hormone are more sensitive to doxorubicin than wild-type tumors. Endocrinology 162, bqab013 (2021). [PubMed: 33475144]
176. Begicevic RR & Falasca M ABC transporters in cancer stem cells: beyond chemoresistance. Int. J. Mol. Sci. 18, 2362 (2017). [PubMed: 29117122]
177. Chen YJ et al. Autocrine human growth hormone promotes invasive and cancer stem cell-like behavior of hepatocellular carcinoma cells by STAT3 dependent inhibition of CLAUDIN-1 expression. Int. J. Mol. Sci. 18, 1274 (2017). [PubMed: 28617312]
178. Wang JJ et al. Autocrine hGH stimulates oncogenicity, epithelial-mesenchymal transition and cancer stem cell-like behavior in human colorectal carcinoma. Oncotarget 8, 103900–103918 (2017). [PubMed: 29262609]
179. Subramani R, Nandy SB, Pedroza DA & Lakshmanaswamy R Role of growth hormone in breast cancer. Endocrinology 158, 1543–1555 (2017). [PubMed: 28379395]
180. Subramani R et al. Growth hormone receptor inhibition decreases the growth and metastasis of pancreatic ductal adenocarcinoma. Exp. Mol. Med. 46, e117 (2014). [PubMed: 25301264]
181. Basu R, Wu S & Kopchick JJ Targeting growth hormone receptor in human melanoma cells attenuates tumor progression and epithelial mesenchymal transition via suppression of multiple oncogenic pathways. Oncotarget 8, 21579–21598 (2017). [PubMed: 28223541]
182. Yang J et al. Guidelines and definitions for research on epithelial-mesenchymal transition. Nat. Rev. Mol. Cell Biol. 21, 341–352 (2020). [PubMed: 32300252]
183. Brittain AL, Basu R, Qian Y & Kopchick JJ Growth hormone and the epithelial-to-mesenchymal transition. J. Clin. Endocrinol. Metab. 102, 3662–3673 (2017). [PubMed: 28938477]
184. Mukhina S et al. Phenotypic conversion of human mammary carcinoma cells by autocrine human growth hormone. Proc. Natl Acad. Sci. USA 101, 15166–15171 (2004). [PubMed: 15353581]
185. Shafiei F et al. DNMT3A and DNMT3B mediate autocrine hGH repression of plakoglobin gene transcription and consequent phenotypic conversion of mammary carcinoma cells. Oncogene 27, 2602–2612 (2008). [PubMed: 17998942]
186. Zhang W et al. Autocrine/paracrine human growth hormone-stimulated microRNA 96–182-183 cluster promotes epithelial-mesenchymal transition and invasion in breast cancer. J. Biol. Chem. 290, 13812–13829 (2015). [PubMed: 25873390]
187. Chien CH, Lee MJ, Liou HC, Liou HH & Fu WM Growth hormone is increased in the lungs and enhances experimental lung metastasis of melanoma in DJ-1 KO mice. BMC Cancer 16, 871 (2016). [PubMed: 27825319]
188. Chandler C, Liu T, Buckanovich R & Coffman LG The double edge sword of fibrosis in cancer. Transl Res. 209, 55–67 (2019). [PubMed: 30871956]
189. Leslie M Genetics and disease. Growth defect blocks cancer and diabetes. Science 331, 837 (2011). [PubMed: 21330503]
190. Steuerman R, Shevah O & Laron Z Congenital IGF1 deficiency tends to confer protection against post-natal development of malignancies. Eur. J. Endocrinol. 164, 485–489 (2011). [PubMed: 21292919]

191. Boguszewski CL & Boguszewski M Growth hormone's links to cancer. Endocr. Rev. 40, 558–574 (2019). [PubMed: 30500870]
192. Lu M, Flanagan JU, Langley RJ, Hay MP & Perry JK Targeting growth hormone function: strategies and therapeutic applications. Signal Transduct. Target. Ther. 4, 3 (2019). [PubMed: 30775002]
193. Basu R et al. A novel peptide antagonist of the human growth hormone receptor. J. Biol. Chem. 296, 100588 (2021). [PubMed: 33774052]
194. Wang H et al. Inhibition of experimental small-cell and non-small-cell lung cancers by novel antagonists of growth hormone-releasing hormone. Int. J. Cancer 142, 2394–2404 (2018). [PubMed: 29435973]
195. Paisley AN, Trainer P & Drake W Pegvisomant: a novel pharmacotherapy for the treatment of acromegaly. Expert Opin. Biol. Ther. 4, 421–425 (2004). [PubMed: 15006735]
196. 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. 178, R155–R181 (2018). [PubMed: 29459441]
197. Cohen P, Clemmons DR & Rosenfeld RG Does the GH-IGF axis play a role in cancer pathogenesis? Growth Horm. IGF Res. 10, 297–305 (2000). [PubMed: 11161960]
198. Chesnokova V, Zonis S, Barrett RJ, Gleeson JP & Melmed S Growth hormone induces colon DNA damage independent of IGF-1. Endocrinology 160, 1439–1447 (2019). [PubMed: 31002310]
199. US National Library of Medicine. ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT00976508 (2013).
200. Hermansen K, Bengtsen M, Kjaer M, Vestergaard P & Jorgensen JOL Impact of GH administration on athletic performance in healthy young adults: a systematic review and meta-analysis of placebo-controlled trials. Growth Horm. IGF Res. 34, 38–44 (2017). [PubMed: 28514721]
201. Lupu F, Terwilliger JD, Lee K, Segre GV & Efstratiadis A Roles of growth hormone and insulin-like growth factor 1 in mouse postnatal growth. Dev. Biol. 229, 141–162 (2001). [PubMed: 11133160]
202. Wang Z et al. Disruption of growth hormone signaling retards early stages of prostate carcinogenesis in the C3(1)/T antigen mouse. Endocrinology 146, 5188–5196 (2005). [PubMed: 16141391]
203. Zhang X et al. Inhibition of estrogen-independent mammary carcinogenesis by disruption of growth hormone signaling. Carcinogenesis 28, 143–150 (2007). [PubMed: 16916863]
204. Swanson SM & Unterman TG The growth hormone-deficient Spontaneous Dwarf rat is resistant to chemically induced mammary carcinogenesis. Carcinogenesis 23, 977–982 (2002). [PubMed: 12082019]
205. Bugni JM, Poole TM & Drinkwater NR The little mutation suppresses DEN-induced hepatocarcinogenesis in mice and abrogates genetic and hormonal modulation of susceptibility. Carcinogenesis 22, 1853–1862 (2001). [PubMed: 11698349]
206. Snibson KJ, Bhathal PS & Adams TE Overexpressed growth hormone (GH) synergistically promotes carcinogen-initiated liver tumour growth by promoting cellular proliferation in emerging hepatocellular neoplasms in female and male GH-transgenic mice. Liver 21, 149–158 (2001). [PubMed: 11318985]
207. Emerald BS et al. αCP1 mediates stabilization of hTERT mRNA by autocrine human growth hormone. J. Biol. Chem. 282, 680–690 (2007). [PubMed: 17085453]
208. Snibson KJ, Bhathal PS, Hardy CL, Brandon MR & Adams TE High, persistent hepatocellular proliferation and apoptosis precede hepatocarcinogenesis in growth hormone transgenic mice. Liver 19, 242–252 (1999). [PubMed: 10395045]
209. Zhang X et al. Human growth hormone-regulated HOXA1 is a human mammary epithelial oncogene. J. Biol. Chem. 278, 7580–7590 (2003). [PubMed: 12482855]
210. Zhu T et al. Oncogenic transformation of human mammary epithelial cells by autocrine human growth hormone. Cancer Res. 65, 317–324 (2005). [PubMed: 15665309]

211. Ma Y et al. Dysregulation and functional roles of miR-183–96-182 cluster in cancer cell proliferation, invasion and metastasis. Oncotarget 7, 42805–42825 (2016). [PubMed: 27081087]
212. Mertani HC et al. Autocrine human growth hormone (hGH) regulation of human mammary carcinoma cell gene expression. Identification of CHOP as a mediator of hGH-stimulated human mammary carcinoma cell survival. J. Biol. Chem. 276, 21464–21475 (2001). [PubMed: 11297545]
213. Chen YJ et al. Autocrine human growth hormone stimulates the tumor initiating capacity and metastasis of estrogen receptor-negative mammary carcinoma cells. Cancer Lett. 365, 182–189 (2015). [PubMed: 26070963]
214. Divisova J et al. The growth hormone receptor antagonist pegvisomant blocks both mammary gland development and MCF-7 breast cancer xenograft growth. Breast Cancer Res. Treat. 98, 315–327 (2006). [PubMed: 16541323]
215. Kaulsay KK et al. Autocrine stimulation of human mammary carcinoma cell proliferation by human growth hormone. Exp. Cell Res. 250, 35–50 (1999). [PubMed: 10388519]
216. Takahara K et al. Human prostate cancer xenografts in lit/lit mice exhibit reduced growth and androgen-independent progression. Prostate 71, 525–537 (2011). [PubMed: 20878948]
217. Recouvreux MV et al. Androgen receptor regulation of local growth hormone in prostate cancer cells. Endocrinology 158, 2255–2268 (2017). [PubMed: 28444169]
218. Friend KE, Radinsky R & McCutcheon IE Growth hormone receptor expression and function in meningiomas: effect of a specific receptor antagonist. J. Neurosurg. 91, 93–99 (1999). [PubMed: 10389886]
219. McCutcheon IE et al. Antitumor activity of the growth hormone receptor antagonist pegvisomant against human meningiomas in nude mice. J. Neurosurg. 94, 487–492 (2001). [PubMed: 11235955]
220. Yan HZ et al. GHR is involved in gastric cell growth and apoptosis via PI3K/AKT signalling. J. Cell Mol. Med. 25, 2450–2458 (2021). [PubMed: 33492754]
221. Evans A, Jamieson SM, Liu DX, Wilson WR & Perry JK Growth hormone receptor antagonism suppresses tumour regrowth after radiotherapy in an endometrial cancer xenograft model. Cancer Lett. 379, 117–123 (2016). [PubMed: 27241667]
222. Wu X et al. Growth hormone receptor overexpression predicts response of rectal cancers to pre-operative radiotherapy. Eur. J. Cancer 42, 888–894 (2006). [PubMed: 16516462]
223. Wu XY et al. Growth hormone protects colorectal cancer cells from radiation by improving the ability of DNA damage repair. Mol. Med. Rep. 10, 486–490 (2014). [PubMed: 24788673]
224. Minoia M et al. Growth hormone receptor blockade inhibits growth hormone-induced chemoresistance by restoring cytotoxic-induced apoptosis in breast cancer cells independently of estrogen receptor expression. J. Clin. Endocrinol. Metab. 97, E907–E916 (2012). [PubMed: 22442272]
225. Zatelli MC et al. Growth hormone excess promotes breast cancer chemoresistance. J. Clin. Endocrinol. Metab. 94, 3931–3938 (2009). [PubMed: 19622619]
226. Bougen NM, Yang T, Chen H, Lobie PE & Perry JK Autocrine human growth hormone reduces mammary and endometrial carcinoma cell sensitivity to mitomycin C. Oncol. Rep. 26, 487–493 (2011). [PubMed: 21567106]
227. Gentilin E et al. Growth hormone differentially modulates chemoresistance in human endometrial adenocarcinoma cell lines. Endocrine 56, 621–632 (2017). [PubMed: 27585662]
228. Bogazzi F et al. Growth hormone inhibits apoptosis in human colonic cancer cell lines: antagonistic effects of peroxisome proliferator activated receptor-gamma ligands. Endocrinology 145, 3353–3362 (2004). [PubMed: 15070854]
229. Arnold RE & Weigent DA The inhibition of apoptosis in EL4 lymphoma cells overexpressing growth hormone. Neuroimmunomodulation 11, 149–159 (2004). [PubMed: 15067206]

Key points

- Growth hormone (GH) is important for growth and tissue remodelling, extracellular matrix formation and fibrosis.
- Patients with acromegaly, which is characterized by excessive circulating levels of GH, have increased cardiovascular mortality that is associated with hypertension and heart failure.
- Patients with GH deficiency have an increased risk of cardiovascular morbidity and mortality that is associated with cardiovascular risk factors and premature atherosclerosis.
- GH actions in cancer are particularly implicated in mechanisms of therapy resistance; for example, active drug efflux, the epithelial-to-mesenchymal transition, apoptosis inhibition and development of a tumour-supportive microenvironment.
- GH has a ‘Goldilocks effect’, where too little or too much can lead to poor clinical outcomes.

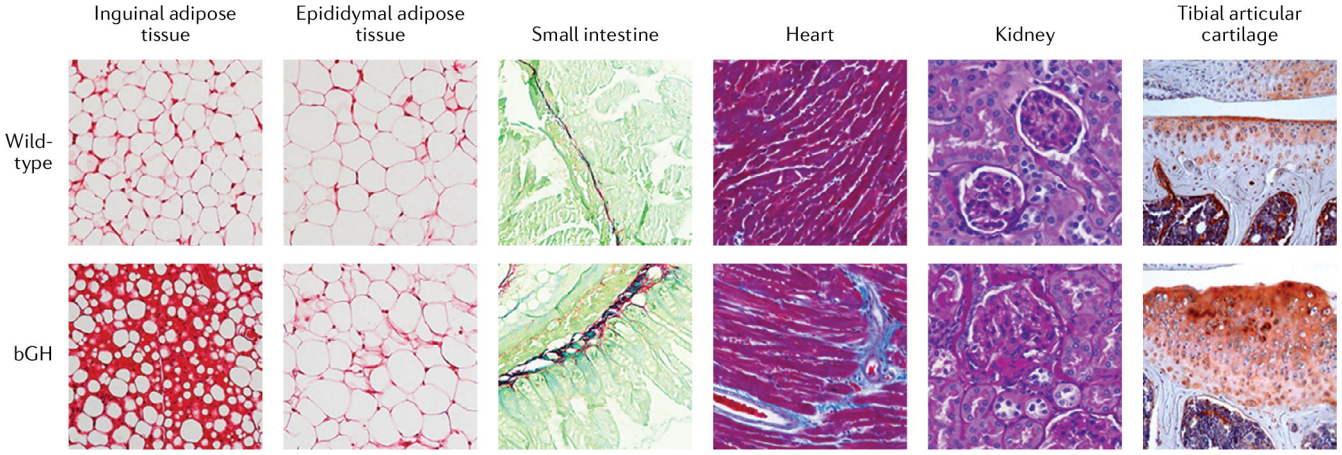

Fig. 1 |. GH overexpression in mice induces tissue fibrosis.

Histology of assorted tissues in aged male mice (10–13 months of age) overexpressing bovine growth hormone (bGH) and wild-type control mice. White adipose tissue from inguinal or epididymal adipose depots was stained with Sirius red (a non-specific red collagen stain), Swiss rolls of the small intestine were stained using Sirius Red and Fast Green (which stains non-collagenous protein), heart was stained with Masson's trichrome (which stains connective tissue blue) and kidney sections were stained with periodic acid Schiff stain (which stains connective tissue a purple–magenta colour). The tibial articular cartilage images were generated via immunostaining with a type X collagen (a bone-specific collagen)-specific antibody (orange–red colour). In bGH mice, the increased GH activity results in increased fibrosis in the tissues shown. The histological images of tibial articular cartilage are courtesy of S. Zhu, Ohio University.

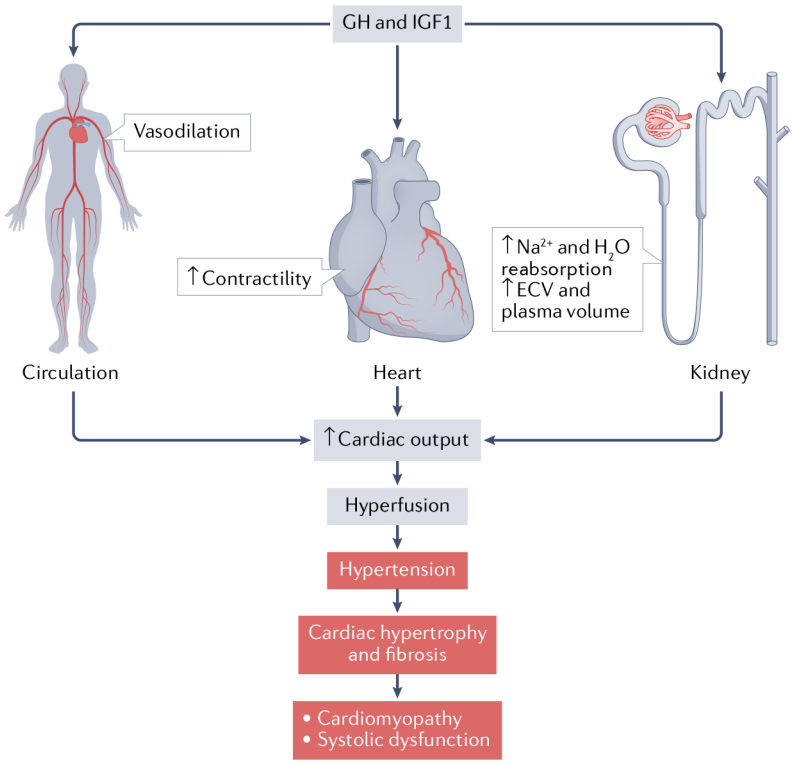

Fig. 2 |. The pleiotropic actions of GH–IGF1 on the cardiovascular system, and electrolyte and water balance in humans.

Growth hormone (GH) and insulin-like growth factor 1 (IGF1) promote renal reabsorption of sodium and water and thereby increase the extracellular volume (ECV) and plasma volume. This effect is accompanied by nitric oxide-mediated vasodilation and increased myocardial contractility, which translate into increased cardiac output. This increase results in hyperperfusion and reduced total peripheral resistance. Pathological GH–IGF1 excess (such as in uncontrolled acromegaly) results in hypertension and cardiac hypertrophy. We hypothesize that GH–IGF1-induced fibrosis eventually contributes to the development of cardiomyopathy and heart failure (systolic dysfunction). Pathological processes are highlighted in the figure in red.

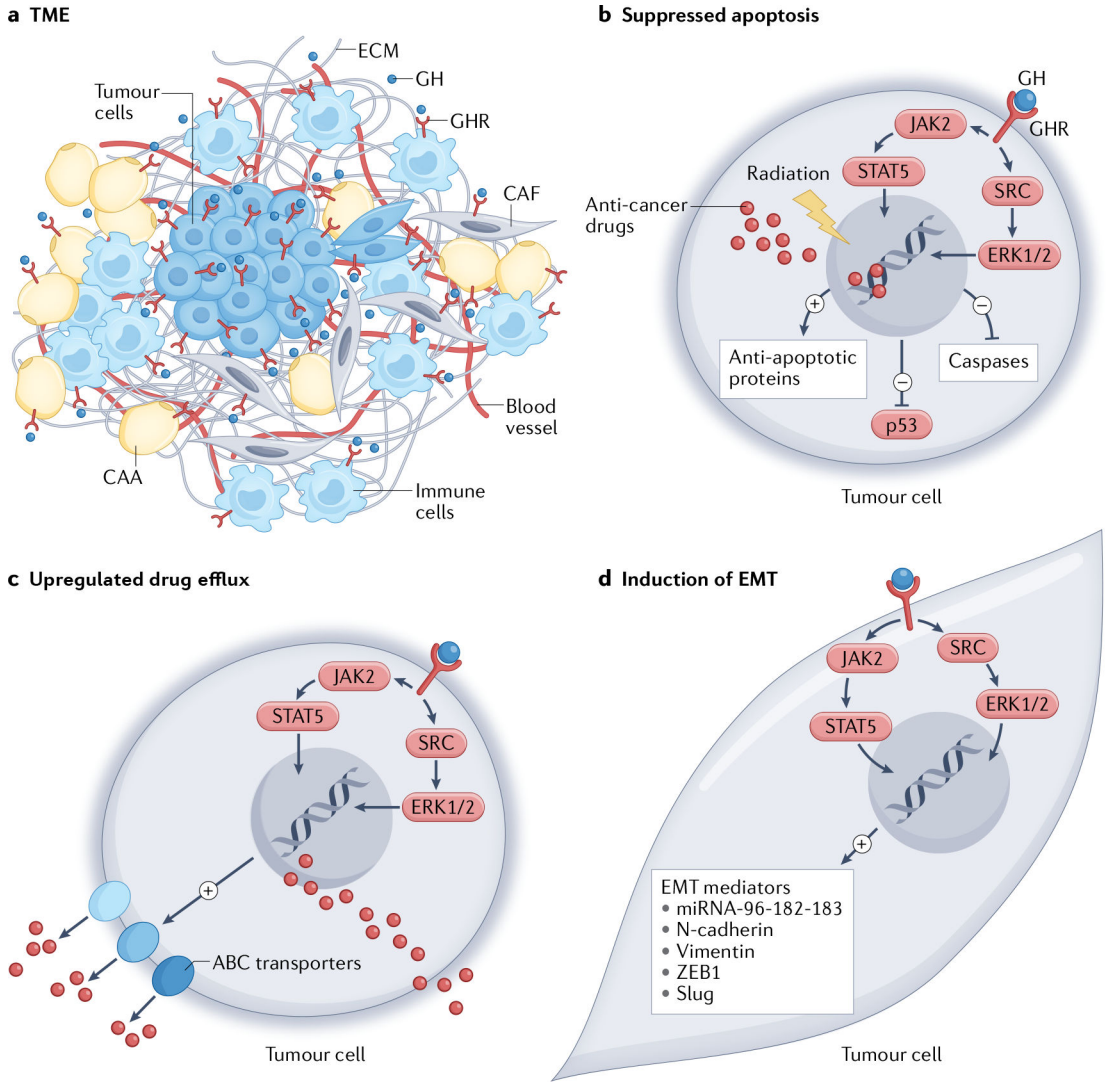

Fig. 3 |. Covert actions of GH in cancer.

The emerging covert actions of growth hormone (GH) in cancer as evidenced from reports in the literature to date. **a** | GH promotes a tumour-supportive microenvironment via the crosstalk of tumour cells and multiple types of cells in the tumour microenvironment (TME), such as immune cells, cancer-associated adipocytes (CAA) and cancer-associated fibroblasts (CAF). This crosstalk occurs via autocrine and/or paracrine GH actions, which promote fibrosis and extracellular matrix (ECM) remodelling via matrix metalloproteases and collagen turnover, production of pro-inflammatory cytokines and immune-suppressive molecules such as transforming growth factor-β (TGFβ). Parts **b**–**d** illustrate the process of tumour therapy resistance through various mechanisms involving GH. **b** | Suppression of apoptosis due to radiotherapy-induced or chemotherapy-induced DNA damage, via downregulation of p53 and apoptotic mediators including caspases and upregulation of anti-apoptotic factors including BCL-2. **c** | Increased ATP-binding cassette (ABC) transporter multidrug efflux pump expression (ABCB1, ABCC1, ABCC2 and ABCG2), which actively removes multiple anti-cancer drugs out of the tumour cells. **d** | Induction of the metastatic

process of epithelial-to-mesenchymal transition (EMT) by GH acting to upregulate EMT mediators, including vimentin, N-cadherin, ZEB1, SLUG and the microRNA (miRNA) cluster comprising miRNA-96, miRNA-182 and miRNA-183 (miRNA-96–182-183), which altogether enable a phenotype switch of the tumour cells. The above processes are induced by autocrine and/or paracrine GH binding to GH receptor (GHR)-expressing cells in the tumour and TME, activating downstream signalling mediators JAK2, STAT5, SRC and ERK1/2. Therefore, a combination of a GHR antagonist with anticancer drugs is a transformative approach for highly effective tumour clearance, which has already been validated in preclinical models.

Table 1 |

Molecular actions of GH in human cancers

Molecular action	Effect	Cancer type	Refs.
Oncogenesis and tumour microenvironment			
GH is a p53 target and in turn blocks p53 by a negative feedback loop	Tumour initiation	Colon cancer	158
GH induces DNA damage and suppresses DNA damage repair in normal colon tissue	Tumour initiation	Colon cancer	156,157,198
GH resistance reduces number and size of neoplasms in C3(1)/Tag-GHRKO mice	Tumour initiation	Breast cancer, prostate cancer	202,203
GH deficiency suppress DMBA-induced tumour development	Tumour initiation	Breast cancer	204
bGH mice have a higher DEN-induced hepatoma incidence while *lit/lit* (*Ghrhr*-knockout) mice have a lower one	Tumour initiation	Liver cancer	205,206
GH supplementation enables MNU-induced tumours in GH-deficient rats; tumours regress on GH withdrawal	Tumour initiation	Breast cancer	175
GH stabilizes hTERT through αCP1 and αCP2	Tumour initiation	Breast cancer	207
GH supports spontaneous neoplastic growth with age	Tumour initiation	Liver cancer	208
GH expression in mammary epithelia promotes oncogenic transformation via HOXA1	Tumour initiation	Breast cancer	209,210
GH produced in ageing colon accumulates DNA damage	Tumour initiation	Colon cancer	143
Invasive tumour growth			
GH increases miRNA-96, miRNA-182 and miRNA-183 cluster targeting BRMS1L	EMT induction	Breast cancer	186,211
GH induces CHOP expression via p38 MAPK activation	EMT induction	Breast cancer	212
GH supports tumour angiogenesis	Invasive growth	Breast cancer	120
GH drives migration, invasion and metastasis in tumour xenografts	Invasive growth and EMT induction	Breast cancer	213–215
GH deficiency reduces tumour growth rate in *lit/lit* mice	Tumour progression	Prostate cancer	216
GH increases migration, invasion, proliferation and MMP levels	Invasive growth	Prostate cancer	217
GH blockade reduces xenograft growth rate	Invasive growth	Colon cancer, meningioma	218,219
GH blockade reduces migration, invasion and markers of EMT	EMT induction	Melanoma, pancreatic cancer	180,181
GH production in lungs guides melanoma metastases in mice	Metastasis	Melanoma	187
GH inhibits tumour apoptosis via PI3K–AKT signalling	Invasive growth	Gastric cancer	220
Therapy resistance			
GH increases ABC transporter expressions via JAK2-STAT5 and SRC signalling	Multidrug resistance	Melanoma	172

GH increases MITF-dependent melanogenesis and drug sequestration via JAK2–STAT5 and SRC	Multidrug resistance	Melanoma	154
GH increases ABCG2 levels via JAK2–STAT5	Docetaxel resistance	Breast cancer	174
GH increases PI3K–AKT–MAPK and JAK2 signalling	Ruxolitinib resistance	Breast cancer	145
GH reduces tumour apoptosis and increase proliferation	Doxorubicin resistance	Breast cancer	175
GH increases post-irradiation clonogenicity and reduces radiation-induced DNA damage	Radiation resistance	Colorectal cancer, breast cancer, endometrial cancer	171,221–223
GH induces FOS expression	Doxorubicin resistance	Breast cancer	224,225
GH suppress DNA damage and apoptosis	Mitomycin-C resistance	Breast cancer, endometrial cancer	226
GH activates ERK1/2 and PKC and suppresses caspase activation	Multidrug resistance	Endometrial cancer	227
GH reduces pro-apoptotic BAX and PPARγ via STAT5B activation	PPARγ ligand resistance	Colon cancer	228
GH reduces BAX, BAD, caspase 3, caspase 8 and caspase 9	Methylmethanosulfonate resistance	Lymphoma	229
GH increases ABCG2 and markers of cancer stem cells (NANOG, ALDH1, CD24 and CD44)	Increased stemness	Liver cancer, breast cancer, colon cancer	163,177,178,184,213
GH is a part of senescence-associated secretory phenotype	Therapy evasion and relapse	Colon cancer	31

ABC, ATP-binding cassette; bGH, bovine growth hormone; C3(1)/Tag-GHRKO mice, mice from a cross between *Ghr*-knockout (GHRKO) mice and C3(1)/Tag mice, where females develop spontaneous mammary tumours; DEN, diethylnitrosamine; DMBA, dimethylbenz[a]anthracene; EMT, epithelial-to-mesenchymal transition; GH, growth hormone; hTERT, human telomerase reverse transcriptase; miRNA, microRNA; MMP, matrix metalloproteinases; MNU, *N*-methyl-*N*-nitrosourea.

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