THEMATIC REVIEW

GH and IGF1 in cancer therapy resistance

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This paper is part of a themed collection on the role of Growth Hormone in Endocrine Cancers. The Guest Editor for this collection was John Kopchick, Ohio University, USA.

John Kopchick was not involved in the review or editorial process for this paper, on which he is listed as an author.

Abstract

Despite landmark advances in cancer treatments over the last 20 years, cancer remains the second highest cause of death worldwide, much ascribed to intrinsic and acquired resistance to the available therapeutic options. In this review, we address this impending issue, by focusing the spotlight on the rapidly emerging role of growth hormone action mediated by two intimately related tumoral growth factors – growth hormone (GH) and insulin-like growth factor 1 (IGF1). Here, we not only catalog the scientific evidences relating specifically to cancer therapy resistance inflicted by GH and IGF1 but also discuss the pitfalls, merits, outstanding questions and the future need of exploiting GH–IGF1 inhibition to tackle cancer treatment successfully.

Key Words

- growth hormone (GH)
- insulin-like growth factor 1 (IGF1)
- cancer
- therapy resistance
- radioresistance
- chemoresistance

Endocrine-Related Cancer (2023) **30**, **e220414**

Introduction

Resistance to therapy is one of the major hurdles in tackling cancer – the second highest causal factor for all-cause, all-age human mortality in the United States between the period of 2001 and 2020, as per the Center for Disease Control, USA (https://wisqars.cdc.gov/data/lcd/home). Within these last 20 years, intensive research has significantly updated the identity of cancer as a disease, by clarifying the key molecular details of inter- and intra-tumor heterogeneity (Dagogo-Jack & Shaw 2018), the tumor microenvironment (TME) (Binnewies *et al.* 2018), the epithelial-to-mesenchymal transition (EMT) process (Yang *et al.* 2020), the full spectrum of multidrug efflux (Robey *et al.* 2018), metabolic reprogramming (Tan *et al.* 2022), epigenetic reprogramming (Cheng *et al.* 2019), senescence (Wang *et al.* 2022) and immune-evasion (Thelen *et al.* 2021). Between that period, critical milestones in detection (Fitzgerald *et al.* 2022) and precision therapeutic options have been reached in cancer, including unique targeted therapies (Aggarwal 2010, Labrie *et al.* 2022), immunotherapies (Waldman *et al.* 2020), antibody–drug conjugates (ADCs) (Drago *et al.* 2021, Fu *et al.* 2022) and machine learning-based personalized therapy (Lehmann *et al.* 2021), adding to the repertoire of broader spectrum anti-cancer therapies (radiation therapy and chemotherapy) from the last century. Consequently, between 2000 and 2020, deaths due to cancers have also decreased by 27% in the US (https://seer.cancer.gov/). However, in the current year (2022), as per the National Cancer Institute, an estimated 609,360 deaths will be ascribed to cancer, only in the US (https://seer.cancer.gov/) – underlining not only unmet needs in detection, treatment and accessibility but also a re-assessment of mechanistic intervention strategies based on current knowledge of cancer therapy resistance.

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In this regard, recent empirical evidence compels a re-evaluation of targeting the growth hormone (GH) and the insulin-like growth factor 1 (IGF1) axis.

Massive amount of research over the last 70 years have established that GH and IGF1 have both overlapping and mutually exclusive roles in driving multiple aspects of cancer initiation and progression. Excellent reviews have periodically summarized these updates regarding the role of GH and IGF1 in cancer (Cohen *et al.* 2000, Chhabra *et al.* 2011, Perry *et al.* 2017, Simpson *et al.* 2017, Basu & Kopchick 2019) and will not be discussed in this review. Here we aim at providing a consolidated discussion of the specific role of these two intimately related and potent growth factors in driving a multi-modal mechanism of cancer therapy resistance. We will briefly discuss the relevant roles of GH and IGF1 in modulating each of the present-day therapeutic approaches in cancer and conclude with a discussion of the outstanding questions and our opinion on the future trajectories of scientific investigation in this area.

The GH/IGF1 axis in cancer: current knowledge

Human GH is a 191-amino acid peptide hormone secreted by the pituitary somatotroph cells of the anterior pituitary and exerts its action on many tissues in an endocrine manner (Brooks & Waters 2010). In the pituitary, somatotropic GH secretion is mainly regulated positively by hypothalamic input of GHRH or negatively by somatostatin (Finidori 2000) – a pattern seldom maintained in the peripheral sites of GH production, including tumors, wherein the secreted GH works in an autocrine/paracrine manner. Additional regulatory arms include inducing actions of the gastric peptide ghrelin and negative feedback loops to the hypothalamus and pituitary via GH and its downstream mediator IGF1 (Finidori 2000). Evidence suggests that unlike the drastic ebb of pituitary GH production at *somatopause*, non-pituitary GH production often increases with age – correlating with tumor development (Chesnokova *et al.* 2021). Endocrine GH binds and activates pre-dimerized GH receptors (GHR), expressed on almost all cells of all tissues in the body including the liver, adipose tissue, skin, brain, kidneys, spleen, intestines, stomach, heart, lung, bone, muscle, cartilage, the vasculatures and immune cells (Brooks & Waters 2010). GH plays critical roles in post-natal longitudinal growth, organ development, reproductive maturity and metabolic homeostasis and is also a determinant of net human lifespan due to its well-studied roles in several pathophysiology including but not limited to insulin resistance, cancer, glomerulosclerosis, cardiomyopathies, acromegaly, neurocognitive decline, Laron syndrome, GH deficiency (GHD) and aging (Ayuk & Sheppard 2006, Basu *et al.* 2018). Classically, GH-induced activation of the GHR enables activation of the GHR-associated Janus kinase 2 (JAK2) initiating a downstream signaling cascade of transcriptional activation via STAT5 as well as STAT1 and STAT3 in a tissue-dependent manner. GHR activation also triggers multiple SRC family kinases leading to the downstream activation of MAPK as well as the PI3K-AKT-mTOR pathways (Carter-Su *et al.* 2016). A principal physiological effect of GH is the STAT5-induced hepatic production of IGF1, a 70 amino acid long peptide with a systemic mitogenic effect. Importantly, endocrine GH-induced hepatocyte GHR activation leads to the production of ~75% of the circulating IGF1 in humans. The bioavailability of IGF1 in circulation is regulated by seven different IGFBP 1–7 (Blum *et al.* 2018). IGF1 primarily binds and activates the IGF1 receptor (IGF1R), a receptor tyrosine kinase (RTK). IGF1-induced downstream signaling primarily involves the IRS1 and 2, PI3K-AKT-mTOR, the MAPK and SRC family of kinases (Blum *et al.* 2018). IGF1 action amplifies and mediates several of the physiologic effects of GH during growth and development. GHR and IGF1R are abundantly expressed on numerous cancer cell types and share multiple downstream oncogenic signaling nodes, and the confluence of these intracellular signaling pathways drive tumor proliferation, suppress cell death, induce migration/invasion and active drug efflux, initiate metabolic and epigenetic reprogramming and promote metastasis.

Moreover, the full spectrum of GH and IGF1 action in cancer cells, beyond the mediation of GHR and IGF1R, requires relevant mention at this point. Human GH is known to exert a lactogenic effect due to its unique capacity of binding and potently activating the prolactin receptor (PRLR) as well, due to the high degree of sequence similarity of human GH and PRL (Xu *et al.* 2013). In several cancers like that of the breast and prostate, PRLR expression is often found upregulated and inversely correlated with survival. In such cancers, GH is expected to induce an oncogenic hyper-signaling cascade via activation of both GHR and PRLR (Goffin 2017).

On the other hand, IGF1 can additionally bind to and activate the IGF1R-Insulin receptor A [IR(A)] hybrids

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(Belfiore *et al.* 2017). It is important to note that another member from the same family of growth factors – IGF2 – can potently activate IGF1R (Blum *et al.* 2018, Andersson *et al.* 2019). Several tumors of mesenchymal and epithelial origin secrete IGF2 which potently activates the IGF1R, IR(A) and IGF2-IR(A) hybrids and are designated as 'IGF2-omas' characterized by IGF2-induced hypoglycemia with suppressed GH and IGF1 levels (Dynkevich *et al.* 2013). Therefore, IGF2 possesses the potential to bypass IGF1R inhibition or IGF1 depletion in cancer (Baserga 2013). Extensive work on the role of IGF2 in specific types of cancer and in determining therapeutic success exists (Dynkevich *et al.* 2013, Livingstone 2013, Andersson *et al.* 2019, Belfiore *et al.* 2023) and is beyond the scope of this review. Herein, we specifically summarize the current evidence pertaining to cancer therapy resistance in the context of GH action and of IGF1 as an extension and principal target of systemic GH action.

Numerous studies with cultured cells and mouse models with either congenital deficits of GH and IGF1, as well as engineered mouse models of GH or IGF1 excess, deficit or antagonism (congenital or treatment induced) conclusively and consistently indicate that attenuation of GH/IGF1 axis suppresses tumor proliferation and invasive tumor growth, while GH excess promotes it (Cohen *et al.* 2000, Chhabra *et al.* 2011). For example, GH transgenic mice with supra-physiologic levels of GH and IGF1 develop tumors at a high frequency and rate, while the opposite is observed in mice with either GH resistance (GHR knock-out, GHRKO) or GH deficiency (Ames, Snell, lit/lit, GH knock-out or GHKO mice) (Basu *et al.* 2018). Reports from human epidemiological studies in the last 20 years, with patients of acromegaly (GH excess due to a hypersecreting pituitary adenoma leading to high serum IGF1), albeit some confounding factors (surveillance bias, normalization of serum IGF1, effects of treatments, difficulty in comparing cause-of-death against appropriate controls), corroborate the findings from corresponding mouse studies (Dal *et al.* 2018). The most compelling evidence of the involvement of GH and IGF1 in promoting cancer comes from patients with Laron syndrome (LS; GH resistance due to loss-of-function mutations of the GHR resulting in very low IGF1) from independent studies in Israel (Shevah & Laron 2007) and Ecuador (Guevara-Aguirre *et al.* 2011) spanning several decades. In both of these cohorts totaling more than 300 patients, zero cases of any malignant neoplasms were identified as the cause of death, while the rate of malignancy in their relatives were as much as 20%. Transcriptomic analyses of lymphoblasts from patients with LS have revealed upregulation of several intrinsic cancer suppressive pathways (Werner *et al.* 2019). More recently, post-natal genetic ablation of GHR in 6-month-old mice leads to a marked decrease in hepatic IGF1 output and was reported to confer an onco-protective effect and lifespan extension in the animals (Duran-Ortiz *et al.* 2021), similar to that observed in congenital GHRKO animals (Ikeno *et al.* 2009) – indicating that a late-life intervention in the GH/IGF1 axis may have beneficial effects. Furthermore, prolonged metabolic manipulations, like fasting or fasting-mimicking-diets (FMD) which lead to a blunted GH action as well as markedly reduces serum IGF1, have been found to significantly protect against cancer development or (Inagaki *et al.* 2008, Wei *et al.* 2017, Brandhorst 2021) and also abetted therapeutic resistance in clinical trials (de Groot *et al.* 2020, Ligorio *et al.* 2022). Collectively, these findings firmly establish that GH and IGF1 play a potent onco-driver role. In the wake of these reports, pharmaceutical interest first piqued toward targeting the IGF1R in cancer, resulting in scores of IGF1R inhibitors (small molecules and monoclonal antibodies) entering clinical trials in the last 20 years, with a record of remarkable results in pre-clinical models of IGF1R inhibition (Xue *et al.* 2012). To date, neither the one approved nor several other candidate GHR antagonists in development have been tried in human cancer clinical trials.

Analyses of available human cancer patient transcriptomic data reveal that while IGF1Rs are overexpressed in several cancer types almost ubiquitously, GHRs are overexpressed in selected cancers (Chhabra *et al.* 2011). This view requires an update in the light of the developing identity of cancer as a disease – with a structure and function resembling more a heterogeneous organ than a homogeneous mass of cells (Hanahan 2022). The hallmark heterogeneity of cancer cells offer the possibility of less of a uniform overexpression of GHR (or IGF1R) across the tumor but rather several sub-sets of cells within the tumor with marked overexpression of either of GH, GHR, PRLR, IGF1, IGF1R or InsR or combinations of them – setting up a very efficient autocrine/paracrine milieu. Additionally, non-tumor cells in the TME express the aforementioned proteins of the GH/IGF1 axis and the current knowledge about their actions strongly indicate a tumor-supportive action, the extent of which remains completely uninvestigated. As we know today, intercellular communication methods like exosomes now allow

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for efficient crosstalk between sub-clusters of cells with differential gene expression patterns in the TME. Revolutionary technologies like the single-cell sequencing now enables access to these unknowns. However, a mounting body of recent research is already pointing to a new and covert action of GH and IGF1 in cancer – driving therapeutic resistance. In the mechanistic modalities of this phenomenon, there are exclusive actions as well as expected overlaps between GH and IGF1. We will briefly discuss these in the following review.

GH and IGF1 in cancer radiation therapy resistance

Ionizing radiations (IRs) are one of the most extensively used anti-cancer therapies alone or in concordance with surgery and chemotherapy and is a subject well-studied to be associated with GH and IGF1. Here, we will summarize some of the salient points of these documented effects on IR specifically relating to cancer treatment. IR therapy induces cell death by inflicting extensive DNA damage, increasing DNA–protein crosslinking and increasing reactive oxygen species (ROS) levels drastically. The protective effect of GH against irradiation in non-tumor tissues has been documented in (i) GH-mediated rescue from IR-induced enteritis in adult male Wistar rats (Prieto *et al.* 1998), (ii) hGH-mediated rescue from cell death and of cytokine profile in irradiated peripheral blood lymphocytes (Lempereur *et al.* 2003) and (iii) restoration of hematologic and immune recovery by post-irradiation GH treatment in BALB/c mice and non-human primates (Chen *et al.* 2010). Only in the last study, radioprotective effects of GH were suggested to be IGF1 mediated (Chen *et al.* 2010). In cancer studies, the effect of GH in reversing irradiation challenge was consistent with that observed in non-tumor cells, as is reported in (i) GH treatment-induced post-irradiation survival and DNA damage repair in breast and endometrial cancer cells (Bougen *et al.* 2012), (ii) suppression of GH treatment induced radioprotection in colon cancer cells using anti-GHR antibody (Wu *et al.* 2014) and (iii) pegvisomant (first and only FDA-approved efficacious GHR antagonist discovered in our laboratory in the 1990s) treatment-induced reduction in angiogenesis and endometrial cancer xenograft growth following gamma irradiation in immunodeficient mice (Evans *et al.* 2016). A retrospective study comparing pre-operative biopsy and post-irradiation specimens in 98 patients of rectal cancer concluded a poorer response to therapy associated with higher GHR expression (Wu *et al.* 2006). The major underlying mechanisms of GH-induced radio-resistance, as recently described by Melmed and colleagues, largely lie in radiation-induced DNA damage, leading to a p53-induced GH production in the TME, GH-induced increased DNA damage repair (DDR) gene expression in tumor cells and upregulation of anti-apoptotic (Bcl2) and downregulation of pro-apoptotic (Bax, BAD, caspases-3, -8, -9, and PPARg) mediators (Chesnokova & Melmed 2020). Paradoxically, in non-transformed cells, GH is a p53 target gene and GH increases DNA damage in an autocrine negative feedback loop by suppressing the DDR gene ATM kinase – facilitating oncogenesis (Chesnokova *et al.* 2016, 2019*a*,*b*).

Targeted studies manipulating IGF1 action reports of similar radio-protective effects (Chesnokova & Melmed 2020). IGF1 treatment improves post-irradiation DDR by RAD51 recruitment and homologous recombination in multiple human and mouse cell types. Conversely, IGF1R inhibition using either antisense or siRNA or small-molecule inhibitors sensitized human prostate (Rochester *et al.* 2005, Turney *et al.* 2012, Chitnis *et al.* 2014) cancer cell lines to IR via suppression of ATM kinase and reduced DDR. In fact, an immunohistochemical assessment of diagnostic biopsies of 136 patients with prostate cancer identified increased IGF1R expression to correlate with post-radiotherapy cancer recurrence (Aleksic *et al.* 2017). Colon cancer cells either expressing a non-functional IGF1R or transfected with IGF1R-directed siRNA display reduced transcription of DDR gene *BRCA2* and sensitization of tumor cells to IR (Yavari *et al.* 2010, Venkatachalam *et al.* 2017, Zong *et al.* 2021). Moreover, analysis of human transcriptomic data in The Cancer Genome Atlas (TCGA) database (Chen *et al.* 2017*a*), as well as a retrospective analysis of pre-treatment and postoperative specimens in 87 rectal cancer patients undergoing preoperative radiotherapy followed by surgical resection (Wu *et al.* 2014), validates tumoral IGF1R expression as a predictor of radiotherapy sensitivity in colorectal cancer. Similar reports of IGF1 induced radio-resistance and IGF1R inhibition mediated radio-sensitivity have also been reported in lung cancer (Iwasa *et al.* 2009, Liu *et al.* 2018), breast cancer (Li *et al.* 2013), esophageal cancer (Zhao & Gu 2014), oral squamous cell carcinoma (Zhang *et al.* 2017), upper respiratory tract cancers (Riesterer *et al.* 2011), nasopharyngeal carcinoma (Wang *et al.* 2019), osteosarcoma (Wang *et al.* 2009) and pediatric high-grade glioma (Simpson *et al.* 2020).

Therefore, GH and IGF1 are strongly implicated as a major determinant of irradiation success in

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Table 1 GH and IGF1 in cancer radiation therapy resistance.

Cancer type	Study type	Summary of effect	Reference
Growth hormone (GH)			
Human breast and endometrial cancer	Cell lines	Autocrine GH → IR resistance GHR antagonist → IR sensitization	(Bougen *et al.* 2012)
Human colorectal cancer	Cell lines	Autocrine GH → IR resistance GHR antagonist → IR sensitization	(Wu *et al.* 2014)
Human endometrial cancer	Mouse	GHR antagonist → IR sensitization	(Evans *et al.* 2016)
Human breast cancer	Mouse	Autocrine GH → IR resistance	(Bougen *et al.* 2012)
Human rectal cancer	Human	High GHR → IR resistance	(Wu *et al.* 2006)
Insulin-like growth factor 1 (IGF1)			
Human prostate cancer	Cell lines	IGF1R depletion → IR sensitization	(Turney *et al.* 2012)
Human prostate cancer	Cell lines	IGF1R inhibition → IR sensitization	(Chitnis *et al.* 2014)
Human lung squamous carcinoma	Cell lines	IGF1R inhibition → IR sensitization	(Liu *et al.* 2018)
Human esophageal cancer	Cell lines	IGF1R inhibition → IR sensitization	(Zhao & Gu 2014)
Human oral squamous cell carcinoma	Cell lines	IGF1R inhibition → IR sensitization	(Zhang *et al.* 2017)
Human upper respiratory tract cancer	Cell lines	IGF1R inhibition → IR sensitization	(Riesterer *et al.* 2011)
Human nasopharyngeal carcinoma	Cell lines	IGF1R inhibition → IR sensitization	(Wang *et al.* 2019)
Human osteosarcoma	Cell lines	IGF1R inhibition → IR sensitization	(Wang *et al.* 2009)
Human pediatric high-grade glioma	Cell lines	IGF1R inhibition → IR sensitization	(Simpson *et al.* 2020)
Human colon cancer	Cell lines, mouse	IGF1R inhibition → IR sensitization	(Yavari *et al.* 2010, Venkatachalam *et al.* 2017, Zong *et al.* 2021)
Human non-small-cell lung cancer	Cell lines, mouse	IGF1R inhibition → IR sensitization	(Iwasa *et al.* 2009)
Human breast cancer	Cell lines, mouse	IGF1R inhibition → IR sensitization	(Li *et al.* 2013)
Human prostate cancer	Human	High IGF1R → Post-IR relapse	(Aleksic *et al.* 2017)
Human colorectal cancer	Human	High IGF1R → IR resistance	(Chen *et al.* 2017*a*)
Human colorectal cancer	Human	High IGF1R → IR resistance	(Wu *et al.* 2014)

cancer treatment (Table 1), whereas in some cases like colorectal cancer, both GHR and IGF1R have been attributed as major negative prognostic factors. Although almost none of the studies have dissected the exclusivity of GH vs IGF1 actions in this approach, it is apparent that overlapping signaling intermediates between GH and IGF1 co-operate in an irradiated tumor. Moreover, separate clusters of GH- and/or IGF1-responsive cells in the same tumor can putatively provide a heterogenic advantage in post-irradiation recovery – a postulate that awaits testing and can in turn direct appropriate combination therapeutic choices.

GH and IGF1 in cancer chemotherapy resistance

Chemotherapy compounds (alkylating agents, nitrosoureas, antimetabolites, anthracyclines, topoisomerase inhibitors, mitotic inhibitors, corticosteroids and others) exert a broad-spectrum antineoplastic effect by inducing extensive DNA damage (single- and double-strand breaks) in the highly proliferating cells of the tumor (29623040). Therefore, chemotherapy, on one hand, is indiscriminate toward all rapidly proliferating cells of the body and, on the other hand, minimally effective against dormant tumor cells. However, chemotherapy to date remains one of the most accessible and prescribed therapeutic options in cancer treatment, greatly thwarted by almost inevitable and rapid onset of intrinsic and acquired tumoral chemoresistance (Vasan *et al.* 2019). Mechanistically, as chemotherapy resembles radiation therapy in induction of DNA damage, one major pathway by which GH and IGF1 do resist the cytotoxic effects of chemotherapy involves that of radio-resistance discussed above. Additional mechanisms of GH- and IGF1-supported chemoresistance involve suppression of apoptosis, upregulation of ATP-binding cassette containing multidrug efflux pumps (ABC transporters) and activation of the EMT program (Yeldag *et al.* 2018).

Early studies that implicated GH action to chemoresistance ascribed the effects to an observed inhibition of chemo-induced apoptosis in the tumor cells. For example, in triple negative breast cancer (TNBC) cells, GH effected an IGF1-independent suppression of doxorubicin-induced apoptosis via c-fos activation, while pegvisomant reversed these effects (Zatelli *et al.* 2009, Minoia *et al.* 2012). Autocrine GH was also found

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to dampen the efficacy of the alkylating agent mitomycin-C in breast and endometrial cancers by upregulating DDR and reducing apoptosis (Bougen *et al.* 2011). Moreover, in endometrial cancer cells, GH lowered pro-apoptotic caspase 3/7 activation via a ERK1/2- and PKC-dependent pathway and rendered resistance against doxorubicin, paclitaxel and cisplatin treatments (Minoia *et al.* 2012, Gentilin *et al.* 2017). In the same study, pegvisomant treatment reversed the endometrial chemoresistance (Gentilin *et al.* 2017). Subsequent studies from our laboratory in human melanoma cells additionally identified a GH-mediated differential upregulation of specific ABC transporters (ABCB1, ABCB5, ABCB8, ABCC1, ABCC2, ABCG1 and ABCG2) and subsequent decreased intracellular drug retention underlying melanoma resistance against doxorubicin, paclitaxel and cisplatin (Basu *et al.* 2017*a*). Knock-down of GHR expression using si-RNAs rendered acute sensitivity to the above chemotherapy treatments in melanoma cells (Basu *et al.* 2017*a*). Transcriptomic analysis of treatment-naïve murine melanoma allografts in GH transgenic mice (bGH mice; high GH, high IGF1) reveal a state of intrinsic chemoresistance by virtue of a consistently upregulated expression of ABC transporter expression compared to that in wild-type (WT) counterparts (Qian *et al.* 2020). The distinct role of GH vs IGF1 in promoting ABC transporter expression was further clarified using murine melanoma allografts in GHRKO (high GH, low IGF1) vs WT mice. Comparing the results against bGH vs WT mouse study, we identified that GH preferentially upregulates the ABCB1 and ABCG2 transporters while IGF1 drives the ABCC group of transporters as well as that of ABCB1 (Qian *et al.* 2020). We further employed another syngeneic model using mice transgenic for a GHR antagonist (GHA mice) allografted with murine melanoma cells and treated with cisplatin to study the outcome of a combination of GHR antagonism and chemotherapy. While the GHR antagonist or cisplatin alone had comparable effects in suppressing melanoma growth, the combination of cisplatin in GHA mice markedly improved cisplatin efficacy, leading to *rapid tumor shrinkage* compared to that in WT mice (Basu *et al.* 2022). An orthogonal study with a fourth syngeneic model of GHKO vs WT mice did not exhibit the chemo-sensitizing effect of GHR antagonism – highlighting the role of autocrine GH action which was effectively attenuated by the GHR antagonist in the GHA mice but not in the GHKO mice (Basu *et al.* 2022). Subsequent independent rodent studies in breast cancer corroborated these findings. For example, in one study using ER-negative breast cancer xenografts in Nude mice, GHR abrogation abetted docetaxel resistance by downregulation of ABCG2 expression (Arumugam *et al.* 2019), while in another study in GH-deficient spontaneous dwarf rats supplemented with GH, only the stoppage of GH supplementation allowed tumor regression under doxorubicin treatment, unlike that in GH-sufficient control animals which remained doxorubicin resistant (Lantvit *et al.* 2021). Furthermore, we and others have shown that chemotherapy induces GH production which temporally coincides with increased transcription of ABC transporter genes, which harbor multiple STAT5-binding sites within 500 base pairs of their transcription start sites (Basu *et al.* 2019). An upregulated ABC transporter expression serves to not only efflux the chemotherapy out of the cell but also sequesters the same away from the cytoplasm into intracellular compartments like melanosomes in case of melanoma. We found that GH drives this melanosomal drug sequestration via upregulating ABC transporters and the MITF, the master regulator of melanosomal transcription via STAT5- and SRC-dependent pathways (Basu *et al.* 2019). GHR knockdown abrogated these effects and restored chemosensitivity in melanoma cells (Basu *et al.* 2019). Lastly, a drastic increase in tumoral ABC transporter expression facilitates the generation of a sub-population of extreme drug-resistant and dormant tumor cells which are known as cancer stem cells (CSC) (Begicevic & Falasca 2017). These dormant CSCs lack the hyper-replication potential and therefore evades the chemotherapeutic challenge, only to be reactivated by cessation of treatment causing a drug-resistant relapse. Forced GH expression in tumors were found to drive upregulated ABCG2 expression and induction of CSC properties in both liver (Chen *et al.* 2017*b*) and colorectal cancer (Wang *et al.* 2017) cells.

Multiple studies have implicated IGF1 action with chemoresistance. An upregulation of IGF1R expression was observed with diminishing response to multiple cycles of platinum-taxol treatment in primary tumors of ovarian cancer patients (Singh *et al.* 2014). Early intervention with picropodophyllin, an IGF1R inhibitor, was found to alleviate this observed resistance to cisplatin and paclitaxel (Singh *et al.* 2014). An IGF1R anti-idiotypic antibody antagonist also sensitized ovarian cancer cells to cisplatin treatment (Weiwei *et al.* 2021). In another study, R1507 (mAb against IGF1R) and IR markedly sensitized small-cell lung cancer xenografts to a triple combination therapy including IR and cisplatin (Ferté *et al.* 2013). A tetravalent bi-specific antibody

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(istiratumab or MM-141) targeting both IGF1R and ErbB3 also markedly sensitized ovarian cancer cells to cisplatin and paclitaxel (Camblin *et al.* 2019) and pancreatic cancer xenograft models to gemcitabine and nab-paclitaxel treatments (Camblin *et al.* 2018) leading to subsequent human clinical trials in pancreatic cancer (Kundranda *et al.* 2020). Ganitumab (AMG479), a fully humanized anti-IGF1R mAb from Amgen, is one of the latest and highly efficacious inhibitors of IGF1, IGF2 or insulin-mediated activation of IGF1R (Calzone *et al.* 2013). Ganitumab markedly potentiates the cytotoxic effects of carboplatin or paclitaxel in ovarian cancer (Beltran *et al.* 2014) of paclitaxel along with metformin in stage 2/3 breast cancer (Yee *et al.* 2021) and multiple others leading to a slew of human clinical trials of ganitumab in combination with different types of chemotherapy in breast cancer (Robertson *et al.* 2013), ovarian cancer (Konecny *et al.* 2021), advanced solid tumors (Murakami *et al.* 2012, Rosen *et al.* 2012), metastatic pancreatic cancer (Kindler *et al.* 2012, Okusaka *et al.* 2014, Fuchs *et al.* 2015), extensive-stage small-cell lung cancer (Glisson *et al.* 2017) and metastatic colorectal cancer (Cohn *et al.* 2013). In fact, ganitumab has been approved by the US Food and Drug Administration as an orphan drug for Ewing sarcoma in 2017. The molecular mechanisms underlying IGF1-induced chemoresistance overlap largely with that of GHR – (i) inhibition of apoptosis by inducing anti-apoptotic and suppressing pro-apoptotic factors (Chesnokova & Melmed 2020), (ii) upregulation of multidrug efflux ABC transporters (Shen *et al.* 2012, Benabbou *et al.* 2013, 2014) and (iii) promoting DDR via promoting Chk1 and Chk2 phosphorylation and increased homologous recombination (Chesnokova & Melmed 2020).

In the study of GH- and IGF1-regulated cancer chemoresistance, a review of the above information (Table 2) hints at definite IGF1-independent actions of GH, which had not been addressed by any studies, except two, of which only one identified a GH-specific upregulation of ABCB1 and ABCG2 and an IGF1-specifc upregulation of ABCB1 and ABCC group of transporters (Qian *et al.* 2020). Given the substantial overlap in substrate specificity among the ABC transporters, it appears that a targeted attenuation of IGF1R may not be adequate to restrict drug efflux from the tumor. A GHR blockade, on the other hand, attenuates both the GH action and the IGF1 supply from the liver – effectively rendering a 'double whammy' in suppressing ABC

Table 2 GH and IGF1 in cancer chemotherapy resistance.

Cancer type	Study type	Summary of effect	Reference
Growth hormone (GH)			
Human breast cancer	Cell lines	GH → doxorubicin resistance	(Minoia *et al.* 2012)
Human breast cancer	Cell lines	GH → doxorubicin resistance GHR antagonist → doxorubicin sensitization	(Zatelli *et al.* 2009)
Human breast and endometrial cancer	Cell lines	Autocrine GH → mitomycin-C resistance	(Bougen *et al.* 2011)
Human endometrial cancer	Cell lines	Autocrine GH → doxorubicin, cisplatin, resistance GHR antagonist → chemotherapy sensitization	(Gentilin *et al.* 2017)
Human melanoma	Cell lines	GH → doxorubicin, cisplatin, paclitaxel resistance GHR silencing → chemotherapy sensitization	(Basu *et al.* 2017*a*)
Human liver cancer	Cell lines	Autocrine GH → cancer stem cell	(Chen *et al.* 2017*b*)
Human colorectal cancer	Cell lines, mouse	Autocrine GH → cancer stem cell	(Wang *et al.* 2017)
Mouse melanoma	Mouse	High GH → intrinsic chemoresistance	(Qian *et al.* 2020)
Mouse melanoma	Mouse	GHR antagonist → cisplatin sensitization	(Basu *et al.* 2022)
Human breast cancer	Mouse	GHR silencing → docetaxel sensitization	(Arumugam *et al.* 2019)
Rat breast cancer	Rat	GH treatment → doxorubicin resistance	(Lantvit *et al.* 2021)
Insulin-like growth factor 1 (IGF1)			
Human prostate cancer	Cell lines	IGF1R inhibition → mitoxantrone, etoposide sensitization	(Rochester *et al.* 2005)
Human ovarian cancer	Cell lines	IGF1R inhibition → chemotherapy sensitization	(Camblin *et al.* 2019)
Human ovarian cancer	Cell lines, mouse	IGF1R inhibition → cisplatin sensitization	(Weiwei *et al.* 2021)
Human small cell lung cancer	Cell lines, mouse	IGF1R inhibition → IR + cisplatin sensitization	(Ferté *et al.* 2013)
Human pancreatic cancer	Cell lines, mouse	IGF1R inhibition → gemcitabine, paclitaxel sensitization	(Camblin *et al.* 2018)
Human ovarian cancer	Cell lines, mouse	IGF1R inhibition → cisplatin, carboplatin, paclitaxel sensitization	(Beltran *et al.* 2014)
Human ovarian cancer	Human	High IGF1R → chemotherapy resistance IGF1R inhibition → cisplatin, paclitaxel sensitization	(Singh *et al.* 2014)

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transporter increase at the tumor cell surface. Notably, although a plethora of combination therapy clinical trials involving IGF1R inhibition and chemotherapy ensued in the last 20 years, there has been none involving GHR antagonism yet.

GH and IGF1 in cancer-targeted therapy response

The expression of cancer-specific neo-antigens as well as overexpression of specific growth factor receptors on specific types of cancer have allowed the first inroads toward a precision therapeutic approach in the form of targeted therapies, prime examples of which are imatinib (BCR-ABL inhibitor), Herceptin/trastuzumab (anti-HER2 mAb) and Avastin/bevacizumab (anti-VEGFR2 mAb). Cytokine receptors like GHR and RTKs like IGF1R often harbor cross-talks with other receptors and regulate mutual intracellular signaling and trafficking (Huang *et al.* 2003). For example, GH action is well studied to increase EGFR levels in mouse liver (Johansson *et al.* 1989, González *et al.* 2010, 2021). Moreover, not only GH acts as an almost equipotent ligand for both GHR and PRLR but also hybrid hetero-multimeric receptors of GHR–PRLR have been postulated (Liu *et al.* 2016). Similar correlates exist between IGF1R and InsR as well as between IGF1R and EGFRs (Roudabush *et al.* 2000). In an entity necessitating a sustained proliferative signaling, like a tumor, such receptor cross-talks are upregulated and exert insurmountable resistance to targeted therapies, including endocrine/hormone therapies in cancer (Osborne *et al.* 2005).

Despite the known association between GHR and EGFR, as well as that of GHR and PRLR, no studies have as yet focused on their extent and implications in any cancer types. In our studies with human melanoma cells, we had reported a GHR-associated change in the ErbB3 and HGF (Basu *et al.* 2017*b*), although the therapeutic ramifications of this observation await a systematic investigation. However, multiple reports provocatively implicate GH action in anti-cancer therapy resistance. For example, GHR expression inversely correlates with ruxolitinib (JAK2 inhibitor) efficacy in endocrine-resistant breast cancer cells (Holtz *et al.* 2018), whereas GH inhibits apoptotic effects of PPARg ligands in human colon cancer cells (Bogazzi *et al.* 2004). In human melanoma cells, we observed a GH-dependent increase in EC50 of the BRAF-V600E inhibitor vemurafenib as well as increased vemurafenib sensitivity following a GHR knockdown-mediated suppression of ABCC2 and ABCG2 (Basu *et al.* 2017*a*). In a recent *in vivo* study, we reported the role of GH in augmenting sorafenib resistance in human liver cancer cells (Basu *et al.* 2022). Using the GHA and WT mice implanted with murine hepatoma cells, we observed notable improvement in sorafenib efficacy in the GHA mice, wherein the combination of GHR antagonist with sorafenib achieved a markedly superior tumor clearance compared to the same in the WT counterparts (Basu *et al.* 2022). Most recent studies from MD Anderson Cancer Center in hepatocellular carcinoma (HCC) strongly validate these findings. Following the establishment of a definite role of GH in promoting hepatocarcinogen-induced liver tumors in GHRKO vs WT mice (Haque *et al.* 2022), the group observed a more aggressive disease and poorer clinical outcomes correlated with higher serum GH levels in a cohort of 767 HCC patients compared against 200 healthy controls (Kaseb *et al.* 2022). *In vitro* and *in vivo* studies using nude mice confirmed a sorafenib-sensitizing effect of pegvisomant, which they then extended to two human patients presenting advanced stage HCC with sorafenib resistance. Pegvisomant treatment at 10 mg/day for 6 weeks resulted in 'stable disease' and halted tumor progression (Kaseb *et al.* 2022).

The association of IGF1R with other RTKs, especially the EGFR, has been more frequently exploited in anti-cancer drug development. For example, in ovarian and breast cancer cells, IGF1R inhibitors sensitize the cells to PARP-inhibitor treatment by suppressing RAD51 levels (Amin *et al.* 2015). It was found that a concomitant activation of IGF1R with ErbB3 induce ovarian cancer resistance to trastuzumab (Herceptin, anti-HER2 mAb) (Jia *et al.* 2013), which was reversed by LMAb1, an IGF1R-targeted mAb (Wang *et al.* 2014). Similarly, based on their highly consistent co-expression profile, the approach of dual inhibition of IGF1R and EGFR/HER2 was adopted and have shown significant success in multiple pre-clinical models of different cancer – viz. (i) a bi-specific (anti-IGF1R and -EGFR) antibody XGFR in pancreatic cancer (Schanzer *et al.* 2016), (ii) IGF1R inhibitor linsitinib with EGFR inhibitors lapatinib or gefitinib in esophageal squamous cell carcinoma (Kang *et al.* 2022), (iii) a ligand-based enediyne-energized bi-specific fusion protein (anti-IGF1R and -EGFR) in esophageal (Cao *et al.* 2017) and non-small-cell lung cancer (Guo *et al.* 2017), (iv) AVE1642 (anti-IGF1R mAb) and gefitinib in HCC (Desbois-Mouthon *et al.* 2009), (v) ganitumab and panitumumab (anti-EGFR mAb) in advanced cancers (non-small-cell lung cancer and sarcoma) (Vlahovic *et al.* 2018) and (vi) ganitumab

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and panitumumab in metastatic colorectal cancer (Van Cutsem *et al.* 2014), to name a few. Interestingly, the anti-diabetic 'wonder drug' metformin is reported to affect a downregulation of IGF1R and thereby enhance the efficacy of figitumumab (mAb against IGF1R) in small-cell lung cancer (Cao *et al.* 2015) and non-small-cell lung cancer (Cao *et al.* 2016). IGF1R inhibition has additional therapy-sensitizing effects in the case of endocrine therapy-resistant breast and prostate cancers (Fahrenholtz *et al.* 2013), which have been comprehensively summarized in other excellent reviews (Hua *et al.* 2020).

The above discussion collectively emphasizes that the combination of GHR antagonism or IGF1R inhibition with targeted therapies presents untapped potential in sensitizing tumors to treatment effects (Table 3). An assessment of compensatory changes in receptor expression pre- and posttreatment with targeted therapies in different types of cancer might help to identify effective drug combination partners from the existing repertoire of antineoplastic agents.

GH and IGF1 in cancer immunotherapy resistance

Immunotherapy, which involves augmenting the body's intrinsic immune system to detect and eliminate tumor growth, has revolutionized anti-cancer therapy in the 21st century. However, the response of cancer patients to immunotherapy, at different stages of the disease, vary considerably based on several factors including but not limited to age and immune fitness of the patient, the type of cancer, the composition of the TME, loss of antigen processing in the tumor, tumor mutational burden and tumor heterogeneity (Wang *et al.* 2021*a*). Moreover, the target of immune checkpoint inhibitors (ICIs) is often expressed by a small fraction of the total cells of the tumor offering a strictly limited response (Wang *et al.* 2021*a*). Over the last 2 years, a growing line of scientific evidence have started to indicate that not only is circulating GH/IGF1 status a prognostic marker of immunotherapy response but also that attenuation of GH action or IGF1 action or both might significantly enhance immunotherapy success across multiple cancers.

Plasma GH levels in human patients have been found to be associated with poorer response to immunotherapy combinations in at least two different human cancers – (i) in the first study, in 31 male and 6 female HCC patients undergoing the combination therapy of atezolizumab (anti-PDL1 mAb) and bevacizumab (anti-VEGFR2 mAb) at the MD Anderson Cancer Center, the 1-year survival rate was significantly lower at 33% in the patients with higher GH levels (>0.9 µg/L in men and >3.7 µg/L in women) compared to 70% in the ones

Table 3 GH and IGF1 in cancer-targeted therapy resistance.

Cancer type	Study type	Summary of effect	Reference
Growth hormone (GH)			
Human breast cancer	Cell lines	High GHR → JAK2-inhibitor resistance	(Holtz *et al.* 2018)
Human colorectal cancer	Cell lines	Autocrine GH → PPARg ligand resistance	(Bogazzi *et al.* 2004)
Human melanoma	Cell lines	GH → V600E-BRAF inhibitor resistance GHR silencing → V660E-BRAF inhibitor sensitization	(Basu *et al.* 2017*a*)
Mouse liver cancer	Mouse	GHR antagonist → kinase inhibitor sensitization	(Basu *et al.* 2022)
Human liver cancer	Human	High GH → kinase inhibitor resistance	(Kaseb *et al.* 2022)
Human liver cancer	Human	GHR inhibition → kinase inhibitor sensitization	(Kaseb *et al.* 2022)
Insulin-like growth factor 1 (IGF1)			
Human breast and ovarian cancer	Cell lines	IGF1R inhibition → PARP inhibitor sensitization	(Amin *et al.* 2015)
Human ovarian cancer	Cell lines	IGF1R → HER2 inhibitor resistance	(Jia *et al.* 2013)
Human ovarian cancer	Cell lines	IGF1R inhibition → HER2 inhibitor sensitization	(Wang *et al.* 2014)
Human pancreatic cancer	Cell lines	IGF1R inhibition → EGFR inhibition sensitization	(Schanzer *et al.* 2016)
Human esophageal cancer	Cell lines, mouse	IGF1R inhibition → EGFR, Lidamycin inhibition sensitization	(Cao *et al.* 2017, Kang *et al.* 2022)
Human non-small cell lung cancer	Cell lines, mouse	IGF1R inhibition → EGFR, Lidamycin inhibition sensitization	(Guo *et al.* 2017)
Human liver cancer	Cell lines	IGF1R inhibition → EGFR inhibition sensitization	(Desbois-Mouthon *et al.* 2009)
Human non-small cell lung cancer and sarcoma	Human	IGF1R inhibition → EGFR inhibition sensitization	(Vlahovic *et al.* 2018)
Human small cell lung cancer	Cell lines	IGF1R inhibition → MEK/ERK inhibitor sensitization	(Cao *et al.* 2015)

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with lower GH (Mohamed *et al.* 2022). Median overall survival also showed a similar significant difference (18.9 vs 9.3 months; P =0.014), while progression-free survival was marginal (6.6 vs 2.9 months; P=0.053) between GH-high and GH-low patients (Mohamed *et al.* 2022). (ii) In the second study, 75 patients of advanced gastric cancer in the Hebei Medical University, China, were treated with anti-PD1 mAb and post-treatment serum GH levels were measured and correlated with treatment outcome (Zhao *et al.* 2022). Between the high-GH and the low-GH groups of patients, significant differences in disease control rate (30% vs 53.3%, P=0.046), overall survival (P=0.052) and progression free survival (P=0.016) were observed (Zhao *et al.* 2022). In both of these studies, despite the confounding factor that due to the short half-life of GH in circulation (~15 min) a once daily GH sampling often does not elicit the GH status accurately, the implications of the observation are profound. Knowledge of the serum IGF1 status can further clarify if this is an IGF1 independent effect of GH.

There are no direct studies implicating IGF1 with immunotherapeutic success, but the current circumstantial evidences are highly suggestive. A pharmacologic caloric restriction using the FMD, which markedly lowers serum IGF1 among other effects, has been shown to improve anti-PDL1 and anti-OX40 therapy in poorly immunogenic TNBC (Cortellino *et al.* 2022). Similarly, short-term starvation was found to dampen IGF1R signaling and IGF1 levels and was associated with sensitization of lung tumor allografts in syngeneic mouse models to anti-PD1 ICIs via a CD8 T-cell-dependent process (Ajona *et al.* 2020). The same study observed resistance to anti-PD1-PDL1 immunotherapy in patients with non-small-cell lung cancer to be associated with higher plasma IGF1 or higher tumoral IGF1R levels (Ajona *et al.* 2020). Reduced caloric intake associated with a marked reduction in IGF1 has also been reported to augment immunotherapy, especially in glucose-resistant, overweight individuals (Eriau *et al.* 2021). Overall, the results indicate that IGF1 action can be a therapeutic target of interest in boosting immunotherapeutic outcomes in selected cancers.

Immunotherapy is one of the latest approaches in cancer treatment and studies relating it to the pathophysiology of GH and IGF1 have only just begun (Table 4). We are yet to understand the underlying mechanisms, for example, how the different immune checkpoint protein expression varies under GH or IGF1 action or inhibition, in tumor cell subsets. The first results, as listed above, are highly provocative and promising enough for large-scale investigations, as the field of anti-cancer therapy has begun to turn toward immunotherapy as a standard for cure.

GH and IGF1 in anti-cancer therapy: present and future

Scores of human cancer clinical trials have been conducted with a multitude of IGF1R inhibitors (small molecule or biologics). Highly promising IGF1R inhibitors like linsitinib, ganitumab, figitimumab and xentuzumab were tried in several different types of cancers, alone or in combination with chemo- or targeted-therapies. Almost all of them have failed in sustaining the promising efficacies shown in pre-clinical models as well as in early phase clinical trials. Later phase trials encountered either high toxicity or sub-optimal improvements in prognostic parameters with the best outcome being disease stabilization in selected cancers, which in most cases were not reproducible in subsequent larger clinical trials – leading majority of the pharmaceutical organizations to abandon their pursuit of targeting IGF1R in cancer. Importantly, several of the candidate IGF1R inhibitors were clinically potent, and subsequent re-purposing in other disease areas like thyroid eye disease has earned them FDA approval

Table 4 GH and IGF1 in cancer immunotherapy resistance.

Cancer type	Study type	Summary of effect	Reference
Growth hormone (GH)			
Human liver cancer	Human	High GH → anti-PDL1 + anti-VEGFR2 resistance	(Mohamed *et al.* 2022)
Human gastric cancer	Human	High GH → anti-PD1 resistance	(Zhao *et al.* 2022)
Insulin-like growth factor 1 (IGF1)			
Human breast cancer	Mouse	IGF1 suppression → anti-PDL1, anti-OX40 sensitization	(Cortellino *et al.* 2022)
Human lung cancer	Mouse	IGF1R inhibition → anti-PD1 sensitization	(Ajona *et al.* 2020)
Human lung cancer	Human	High IGF1, high IGF1R → anti-PD1-PDL1 sensitization	(Ajona *et al.* 2020)

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(Dolgin 2020). Post-mortem of the astounding disappointment of IGF1R inhibitors in cancer has been done in several excellent reviews (Baserga 2013, Chen & Sharon 2013, Beckwith & Yee 2015, Crudden *et al.* 2015). Indeed, this stunning failure of IGF1R targeting imparted some salvageable lessons and novel opportunities. Some of the notable reasons for the lack of success of IGF1R inhibition in the human trials against cancer include (i) elevated secretion of GH due to inhibition of the IGF1-regulated negative feedback loop in the hypothalamic–pituitary axis, (ii) the aforementioned ligand-receptor promiscuity in the IGF system which allow mainly local IGF2-mediated sustained autocrine/paracrine signaling via IR(A), and the IGF1R-IR(A) and IGF2-IR(A) hybrids and the shared nodes in downstream signaling cascade, (iii) compensatory over-expression and activation of IGF1R-associated RTKs like EGFR as well as G-protein-coupled receptors, (iv) increased integrin signaling by accumulating IGF1 in the event of non-availability of IGF1R binding, (v) constitutive activation of AKT due to loss of PTEN and (vi) lack of appropriate patient selection, stratification and follow-up biomarker for therapeutic efficacy. Moreover, Chesnokova *et al.* have recently reported a marked increase in colon GHR levels following IGF1R inhibition (Chesnokova *et al.* 2019*b*), which increases the GH action in the pre-tumoral niche as well as the TME and remains to be verified in other tissues of the body. These assessments, however, point us toward a unique target – the GHR.

The anti-cancer effects of abrogating IGF1 action can be partly exploited by targeting the GHR instead. As stated earlier, no GHR antagonist have ever been into any cancer clinical trial, except one initiated by Pfizer in 2013, for figitumumab–pegvisomant combination for six different solid tumors but was discontinued midway as Pfizer shelved the figitumumab project. It is apparent from our discussion that the actions of GH and IGF1 are intimately related, and targeted IGF1R blockage in turn upregulates the GH effects tremendously causing a cascade of cancer supportive consequences – (i) increased GH production due to a de-repression of negative feedback, (ii) increased GH action leading to systemic insulin resistance (an effect of GH known since the 1930s) and hyperinsulinemia, (iii) increase of multiple direct tumor-supportive effects of the excess GH and insulin and lastly (iv) the overlooked effects of GH on the TME. The effects of GH (as well as IGF1) in the TME are remarkably understudied to date despite long-standing knowledge of GH being produced in the tumor and surrounding tissues (Harvey 2010, Perry *et al.* 2017) and the effects of GH on several components of the TME. For example, GH is known to (i) drive angiogenesis (Brunet-Dunand *et al.* 2009), lymphangiogenesis (Banziger-Tobler *et al.* 2008) and fibrosis (Kopchick *et al.* 2022), which are hallmarks of the TME; (ii) promote fibroblast proliferation (Lee *et al.* 2010) and fibrosis (Kopchick *et al.* 2022), which allow tumoral expansion and immune evasion (Sahai *et al.* 2020); (iii) lipolysis in adipocytes leading to production of free fatty acids (Kopchick *et al.* 2020), which allow tumor metabolic reprogramming and cancer associated fibroblast generation (Cao 2019, Wu *et al.* 2021); and (iv) polarization of macrophage to an anti-inflammatory M2-type (Lu *et al.* 2013), which are one of the most negative prognostic factors in cancer due to profound and multi-factorial immune-suppressive effects (Pittet *et al.* 2022). In addition to this, Melmed and colleagues have proposed a 'field cancerization' model of GH action in promoting cancer in the TME by dint of its role in promoting DNA damage in aging non-transformed cells (Chesnokova *et al.* 2019*a*, 2021), repairing DNA damage in tumor cells (Chesnokova & Melmed 2020) and as a significant member of the senescence-associated secretory phenotype (SASP) (Chesnokova *et al.* 2013, Chesnokova & Melmed 2022). Also relevant are the totally understudied effects of GH–PRLR interactions at the TME. In addition to this, one of the most important systemic effects of GH remains hepatic IGF1 production – which is responsible for up to 75% of the circulating IGF1 in humans (Blum *et al.* 2018). Importantly, GH parallelly increases hepatic IGFBP3 production which is argued to limit IGF1 availability and thus its effect (Cohen *et al.* 2000). However, it is now understood that elevated presence of matrix metalloproteinases in the TME cleave IGFBPs to generate bio-available IGF1 feeding the tumoral IGF1Rs (Mañes *et al.* 1997, 1999, Egeblad & Werb 2002). Moreover, IGF1 action at the TME has also not been investigated adequately and includes critical prognostic factors like immune-suppression (Somri-Gannam *et al.* 2020). Therefore, distilation of the information we present here above clearly directs us to a simple yet transformative and feasible solution – human trials of GHR attenuation in cancer to achieve *a dual inhibition* of GH and IGF1 actions in tumor growth and therapy resistance without the detriments of IGF1R blockade. Notably, as we mentioned before, GHR-blockade-induced IGF1 depletion (as part of our proposed strategy) can be bypassed by IGF2 (Dynkevich *et al.* 2013). However, incidentally, Pfizer pegvisomant trial

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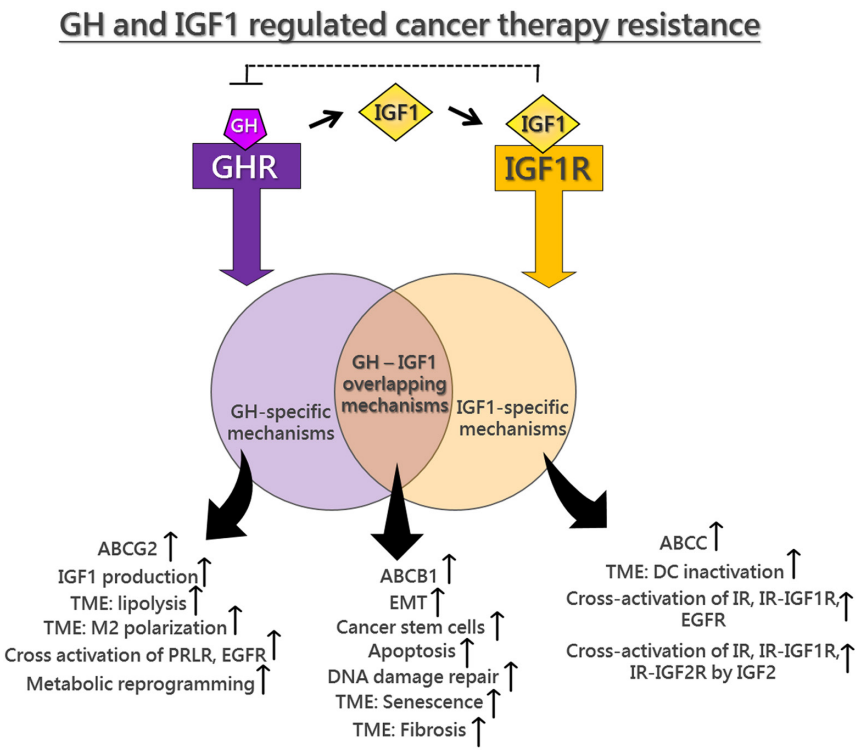

Figure 1
Growth hormone (GH) and insulin-like growth factor 1 (IGF1) regulation of cancer therapy resistance. GH binding and activation of the GH receptor (GHR) exert multiple direct tumor-supportive actions as well as production of hepatic (and extra-hepatic?) IGF1 production. Circulating IGF1-mediated activation of the IGF1 receptor (IGF1R) in turn exerts multiple direct tumor-promoting effects. Particular therapy refractory effects, exclusive to either GH or IGF1, as well as those overlapped by both GH and IGF1, from the tumor and TME as the source, drive ABC multidrug transporter levels, epithelial-to-mesenchymal transition (EMT) activation, apoptosis inhibition, increased DNA damage repair, increased stemness and metabolic re-programming of the tumor cells. Additionally, GH and IGF1 inflict cross-activation of related growth factor receptors including PRLR, PRLR-GHR hybrids, insulin receptors (InsR) and InsR-IGF1R hybrids exerting pro-tumorigenic, anti-therapeutic effects on the tumor and the tumor microenvironment (TME). Moreover, in the TME, autocrine/paracrine GH potentially drives lipolysis in the cancer-associated adipocytes, proliferation in cancer-associated fibroblasts, macrophage polarization in tumor-associated macrophages, immune-suppression and production of IGF1, while autocrine/paracrine IGF1 is known to promote clonal proliferation of TME cells and induce immune-suppression via dendritic cell (DC) inactivation. Importantly, IGF1 exerts a systemic effect of reducing pituitary GH production via a negative feedback loop – which is inhibited by IGF1R inhibitors leading to increased GH production. Therefore, GHR inhibition is a putatively superior and breakthrough approach in not only attenuating direct effects of GH on the tumor and TME but also in suppressing systemic and peripheral IGF1 production, thus largely inhibiting IGF1-regulated therapy refractory effects in cancer as well. A full color version of this figure is available at https://doi.org/10.1530/ERC-22-0414.

in healthy human subjects have shown that even a 14-day pegvisomant treatment leads to a consistent and significant sustained suppression of free IGF1 (up to 33%), IGFBP3 (up to 46%) and IGF2 (up to 35%), implicating GHR antagonist use in IGF1 and IGF2 responsive cancers (Yin *et al.* 2007).

Targeting the GH action is unique due to its multi-pronged (GHR activation, PRLR activation, IGF1 production) anti-cancer effects not only on the tumor but also tumor supportive cells in the TME which altogether orchestrate therapy resistance as discussed above. Increased tumoral GHR expression correlates significantly with patient mortality in TNBC, prostate cancer, endometrial cancer, ovarian cancer, bladder cancer and gastric cancer (The Cancer Genome Atlas database), while the effects of GHR expression and action in the TME and its correlation with patient survival is anticipated with the expansion of single-cell-sequencing techniques. It is essential to remember that tumors are markedly heterogeneous in composition and sub-populations of cells with differential expression of ligands and receptors of the GH/IGF1 axis can be a key determinant in predicting the outcome of GHR targeting in any specific cancer type and individual patient. Lastly, we would like to emphasize that the evidence compiled in this review appears to justify the need for well-designed clinical studies to validate if GHR inhibition can be an effective adjuvant for multiple antineoplastic approaches to significantly enhance their respective efficacies.

The current landscape of development of GHR antagonists and inhibitors is encouraging and has been reviewed recently (Lu *et al.* 2019). Our laboratory had pioneered the first ever GHR antagonist in the early 1990s, termed pegvisomant, which won FDA approval for the treatment of acromegaly and was marketed by Pfizer under the brand name Somavert (pegvisomant for injection) (Kopchick *et al.* 2014). Pegvisomant is known to normalize plasma IGF1 safely and effectively in almost 90% of patients (Paisley *et al.* 2004). Moreover, pegvisomant has a reported beneficial side effect of lowering insulin resistance (Higham *et al.* 2009), which can be a beneficial indirect effect in anti-cancer therapy. Development of multiple additional small-molecule and peptide-based GHR antagonists are currently underway in our laboratory (Basu *et al.* 2021) as well as in others (Chen *et al.* 2020, Tamshen *et al.* 2020, Wang *et al.* 2020, 2021*b*, van der Velden *et al.* 2022) – which should be powerful tools in subsequent cancer clinical trials to effect therapeutic sensitization as discussed in this review.

Conclusion

Targeting GH and IGF1 action via GHR inhibition is a scientifically sound and beneficial strategy for anti-cancer therapy (Fig. 1), with the potential of transforming cancer prognosis in patients, not only due to their well-documented proliferative effects on tumors but more due to their role in driving therapy refractory disease, an intrinsic hallmark of cancer. The reasons behind the falter of IGF1R inhibition in cancer trials also strongly justify the need of GHR antagonism in cancer trials – which exerts a dual effect of blocking both GH and IGF1 actions, as well as imparting insulin sensitivity – a rarely encountered 'win–win' situation in pharmacology. There is indeed rarely a cancer target which encompasses the multifactorial nature of cancer as a disease. Cancer drug discovery is thwarted largely by cancer drug resistance, costing human lives around the globe, every minute. Attenuating GH and IGF1 actions by targeting GHR is steadily becoming 'the elephant in the room' in tackling this hurdle in cancer treatment and deserves appropriate human clinical trials in the immediate future.

Declaration of interest

The authors declare no conflict of interest.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

JJK is supported by the state of Ohio's Eminent Scholar Program that includes a gift from Milton and Lawrence Goll, AMVETS, NIH 1RO1AG059779-01 and The Edison Biotechnology Institute and Diabetes Institute at Ohio University.

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Received 4 May 2023
Accepted 5 June 2023
Available online 7 June 2023
Version of Record published 28 July 2023