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Insulin-like growth factor (IGF) signaling in tumorigenesis and the development of cancer drug resistance

Sahitya K. Denduluri^{a,b}, Olumuyiwa Idowu^{a,b}, Zhongliang Wang^{b,c}, Zhan Liao^{b,d}, Zhengjian Yan^{b,c}, Maryam K. Mohammed^{a,b}, Jixing Ye^{b,e}, Qiang Wei^{b,c}, Jing Wang^{b,c}, Lianggong Zhao^{b,f}, and Hue H. Luu^{b,*}

^a The University of Chicago Pritzker School of Medicine, Chicago, IL 60637, USA

^b Molecular Oncology Laboratory, Department of Orthopaedic Surgery and Rehabilitation Medicine, 5841 South Maryland Avenue, MC 3079, Chicago, IL 60637, USA

^c Ministry of Education Key Laboratory of Diagnostic Medicine, The Affiliated Hospitals of Chongqing Medical University, Chongqing 400016, China

^d Department of Orthopaedic Surgery, Xiang-Ya Hospital of Central South University, Changsha 410008, China

^e School of Bioengineering, Chongqing University, Chongqing, China

^f Department of Orthopaedic Surgery, the Second Affiliated Hospital of Lanzhou University, Lanzhou, Gansu 730000, China

Abstract

One of the greatest obstacles to current cancer treatment efforts is the development of drug resistance by tumors. Despite recent advances in diagnostic practices and surgical interventions, many neoplasms demonstrate poor response to adjuvant or neoadjuvant radiation and chemotherapy. As a result, the prognosis for many patients afflicted with these aggressive cancers remains bleak. The insulin-like growth factor (IGF) signaling axis has been shown to play critical role in the development and progression of various tumors. Many basic science and translational studies have shown that IGF pathway modulators can have promising effects when used to treat various malignancies. There also exists a substantial body of recent evidence implicating IGF signaling dysregulation in the dwindling response of tumors to current standard-of-care therapy. By better understanding both the IGF-dependent and -independent mechanisms by which pathway members can influence drug sensitivity, we can eventually aim to use modulators of IGF signaling to augment the effects of current therapy. This review summarizes and synthesizes numerous recent investigations looking at the role of the IGF pathway in drug resistance. We offer a brief overview of IGF signaling and its general role in neoplasia, and then delve into detail about the many types of human cancer that have been shown to have IGF pathway involvement in resistance

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* Corresponding author. Tel.: +1 773 702 6216; fax: +1 773 702 4765. hluu@bsd.uchicago.edu (H.H. Luu). Peer review under responsibility of Chongqing Medical University..

Conflicts of interest

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and/or sensitization to therapy. Ultimately, our hope is that such a compilation of evidence will compel investigators to carry out much needed studies looking at combination treatment with IGF signaling modulators to overcome current therapy resistance.

Keywords

Cancer; Insulin-like growth factor; Resistance; Therapy; Tumorigenesis

Introduction

The insulin-like growth factor (IGF) signaling axis is critical to the growth, development, and maintenance of many tissues within the human body.¹ It is particularly important during neonatal and pubertal growth, and essentially carries out its effects by simulating cell proliferation and interrupting programmed cell death.^{1,2} The IGF system is comprised of two ligands, IGF-1 and IGF-2, which exhibit their effects through binding to IGF-1R (primarily), IGF-2R, and the insulin receptor (IR), all belonging to the tyrosine kinase receptor family.¹

Upon binding the IGF ligand, IGF-1R is activated through autophosphorylation, and subsequently phosphorylates insulin receptor substrate 1 (IRS-1).² Activated phosphoinositide 3-kinase (PI3K) then leads to increased phosphatidylinositol 3,4,5-trisphosphate (PIP3), which results in the activation of the critical protein AKT/PKB (AKT for short) through phosphorylation.³ AKT then performs a variety of functions, such as releasing the anti-apoptotic protein Bcl-2 from Bad, activating protein synthesis through mTOR, and promoting glucose metabolism by inhibiting GSK-3 β .^{3,4} This is commonly referred to as the PI3K/AKT pathway of IGF-1R signaling and is ultimately responsible for preventing cell death (Fig. 1).⁵

In parallel, IGF-1R signaling also promotes cell differentiation proliferation via the Ras/MAPK pathway (Fig. 1).³ IGF-1R activates the IRS protein SHC, which then stimulates Raf through the GTPase Ras. Raf then triggers a kinase cascade eventually resulting in the activation of mitogen-activated protein kinases (MAPKs), ERK1 and ERK2. These MAPKs go on to phosphorylate and activate several targets, notably the transcription factor ELK1 which promotes gene expression and therefore cell growth.^{3,6,7}

The activity of the IGF ligands and receptors is modulated in a complex fashion by six IGF binding proteins (IGFBPs), named IGFBP-1 through IGFBP-6, respectively. The IGFBPs are usually bound directly to IGF-1 (or IGF-2) in extracellular fluids, serving to mediate the half-life and localized availability of the ligands in circulation.⁸ Furthermore, extensive evidence has recently elucidated that the IGFBPs have many IGF-independent actions. By associating directly with many extracellular and cell-surface markers, these binding proteins are able to cause a variety of unique effects involving growth and differentiation.⁸

Taken as a whole, the IGF signaling axis has vast implications for cellular proliferation, apoptosis, and interactions with the microenvironment. Though these processes are critical for normal development and maintenance of tissues, it has also become increasingly evident

that dysregulation of this pathway contributes significantly to abnormal growth and disease states.

IGF signaling in cancer and the development of drug resistance

Numerous cancers have been shown to be associated with aberrant IGF signaling, including colon cancer, prostate cancer, pancreatic cancer, melanoma, osteosarcoma, and childhood malignancies, among many others.⁹ Numerous *in vitro*, *in vivo*, and clinical studies have shown that increased IGF-1R activity is implicated in cancer cell proliferation, migration, and invasion.^{9,10} IGF ligand appears to be delivered not only from distant sources (i.e. endocrine signaling), but also through paracrine/autocrine signaling in more aggressive tumors.¹⁰ In addition, increased serum levels of IGF-1 have been observed in cancers of the lung, colon, prostate, and breast.¹¹⁻¹⁴ Many other IGF pathway members are also thought to play a role in malignancies. From increased circulating levels of IGF-2 in colorectal cancer to suppressed activity of IGFBP-5 in osteosarcoma, it is clear that the IGF axis serves as an important lens to better understand and address the underlying mechanisms of neoplasia.¹⁵⁻¹⁷ In fact, several IGF signaling modulators have undergone significant basic science and translational investigations with promising results; currently, monoclonal antibodies to IGF-1R are undergoing clinical trials.¹⁸ However, it has become clear that the IGF axis is part of a much larger network of cellular signaling that ultimately results in the highly proliferative and invasive cancer phenotypes.¹⁹

Current non-surgical forms of cancer treatment are largely limited by severe systemic side effects and acquired resistance, resulting in increased morbidity and decreased survival. Of the many processes that are thought to play a role in the resistance of neoplasms to radiation or chemo-therapy, the IGF signaling axis has been recurrently deemed as a culprit.²⁰ Here, we review recent literature implicating IGF signaling in resistance to therapy among various types of human cancer. With a better grasp of the underlying mechanisms, we can one day hope to augment the efficacy of existing cancer therapy using modulators of the IGF signaling axis.

Breast cancer

Breast cancer is one of the most prevalent diseases in the world, and considered to be the most invasive cancer in women. Though there have been significant technological and public health improvements leading to early detection and surgical removal of tumors, disease-free survival remains limited due to drug resistance.²¹ Of the various mechanisms that are thought to contribute to this, IGF signaling has recently been implicated as a crucial factor.

In estrogen receptor positive (ER+) breast cancer, there appears to be a link between IGF-1R and progression of disease despite anti-estrogen therapy. In fact, IGF-1R is upregulated in cancer cells that are resistant to tamoxifen, an estrogen antagonist in breast tissue.²² This is thought to be due to crosstalk between IGF-1R and ER, as well as MAPK/ERK and PI3K/AKT signaling downstream of IGF signaling.^{23,24} One study looked at ER+ breast cancer cells resistant to long-term estrogen deprivation, showing that AKT inhibition led to compensatory upregulation of IGF-1R/IR and IGF ligands, but that simultaneous blockade

of IGF-1R/IR enhanced the anti-tumor effects of AKT inhibition.²⁵ Furthermore, variations in IGF-1R structure and function correlate with anti-estrogen resistance. In a study of 222 British patients with ER+ invasive breast cancer treated with tamoxifen, a polymorphism of the *IGF-1R* gene was found to have significantly increased risk for tumor progression (hazard ratio [HR] 2.04) and death (HR 1.84). Other polymorphisms were also found to be significantly associated with tumor size and lymph node involvement.²⁶ Finally, the activity of IGF-BPs is also implicated, but in an IGF-independent manner. For example, IGF-BP-3 appears to sensitize ER+ breast cancer cells to the anti-estrogen fulvestrant by inhibiting anti-apoptotic effects of GRP78, a binding partner of the caspase 7 complex.²⁷

Another prevalent form of breast cancer is HER2 receptor positive (HER2+), and drugs that work by targeting this marker have also met with significant tumor resistance. Trastuzumab (Herceptin) is a monoclonal antibody to HER2 that is commonly used in therapy, but limited drug efficacy appears to be, in large part, due to IGF signaling. In models of breast cancer cells that overexpress HER2, trastuzumab activity is disrupted by increased expression of IGF-1R.²⁸ Furthermore, upregulation of IGF-1R by epigenetic silencing of microRNA 375 partially leads to a trastuzumab-resistant phenotype, while overexpression of microRNA 375 restores sensitivity of HER2+ cells to the drug.²⁹ Immunohistochemistry supports that overexpression of IGF-1R and epidermal growth factor 1-receptor (EGFR), and/or dysregulation of the downstream PI3K/AKT pathway can also confer this trastuzumab resistance in a subset of patients found to have metastases.³⁰

It is clear that IGF signaling has significant implications for treatment and survival of breast cancer patients. This has led many to believe that co-targeting IGF-1R and well-known breast cancer cell receptors (e.g. ER, HER2) may circumvent drug resistance.^{31,32} However, several investigations indicate that the solution may not be so straightforward. A recent study using estrogen-resistant ER+ breast cancer cells demonstrated that dual treatment with fulvestrant and dasatinib, a nonspecific tyrosine kinase inhibitor, had superior outcomes when compared to combination fulvestrant and IGF-1R monoclonal antibody therapy.³³ This may be due to fact that tyrosine-kinases in general are upregulated in endocrine therapy-resistant breast tumors. Moreover, another study showed that ER+ cancer cells selected for tamoxifen resistance *in vitro* may actually have decreased IGF-1R expression and therefore less responsiveness to monoclonal antibodies directed against just this receptor.³⁴ The incongruence of these results with those of studies mentioned previously in this review may ultimately be due to methodology, but highlights the notion that growth factor and hormone signaling in neoplasms is incredibly complex. Nonetheless, the IGF signaling axis remains an intriguing entity in breast cancer and drug resistance.

Ovarian cancer

Ovarian cancer is one of the deadliest diseases in women, with diagnosis usually made after the onset of symptoms and when metastases are already present.³⁵ In addition, significant drug resistance has been reported to current chemotherapy regimens, which is particularly devastating to those patients who may not be candidates for surgical intervention.³⁶ Similar to its implications in breast cancer, the IGF signaling pathway appears to also play a role in ovarian cancer drug resistance. In A2780 ovarian carcinoma cells treated with either

cisplatin or cisplatin and taxol *in vitro*, early stages of drug resistance are correlated with upregulation of IGF-1R. Furthermore, primary tumors harvested from patients after 3–4 cycles of platinum-taxol treatment also demonstrate increased IGF-1R expression.³⁷ A gene microarray study of 28 patients with high-grade serous ovarian cancer demonstrated that samples relatively resistant to platinum chemotherapy showed enrichment of genes involving IGF1/PI3K/NFκB/ERK signaling when compared to those tumors remaining sensitive to treatment.³⁸ This finding, replicated in several studies, is thought to be the result of two distinct mechanisms beyond just IGF-1R upregulation, including loss of the tumor suppressor PTEN and IGF-2 overexpression.³⁹

Interestingly, IGF-2 is thought to be more closely associated with ovarian cancer drug resistance, despite being less prevalent than IGF-1 in signaling. An analysis of serous ovarian cancer patients using The Cancer Genome Atlas demonstrated that higher IGF-2 mRNA expression was correlated with indicators of drug resistance, including a shorter time to disease progression and death.⁴⁰ In addition, transient knockdown of IGF-2 using short-hairpin RNA restores taxol sensitivity in a xenograft model of serous papillary ovarian carcinoma.⁴⁰ Other studies have also demonstrated efficacy by inhibiting this pathway. Ganitumab, a human monoclonal antibody to IGF-1R, can augment the response to platinum-based chemotherapy by inhibiting IGF-2-dependent ovarian cancer growth.³⁹ However, blockade of IGF-1R does not seem to counteract taxol resistance.⁴⁰ This may be explained by the fact that cisplatin and taxol resistance may not arise from the same signaling mechanisms, though members of the IGF pathway appear to be critically involved in both cases. As in breast cancer, the IGF signaling axis represents a target for much needed effective therapy in ovarian cancer.

Prostate cancer

Prostate cancer remains one of the leading concerns in men's health, accounting for about 15% of all new cancer cases in the U.S. every year. When distant metastases are present, the 5-year relative survival is only 28% when compared to localized disease, making pharmacologic therapy all the more critical in these patients.⁴¹ In patients with disseminated disease, androgen deprivation therapy (ADT) is the standard approach and can be accomplished either surgically through bilateral orchiectomy or medically using a continuous gonadotropin releasing hormone (GnRH) agonist. Tumors that respond to this therapy are referred to as castration sensitive, though there are an alarming number of cases that become castration resistant (or androgen independent [AI]) [need citation].

As in other neoplasms, IGF-1R has been extensively implicated in the progression of prostate cancer, particularly through contributing to the development of AI disease. There has been considerable research into the interactions between IGF-1R and the androgen receptor (AR).⁴² Normally, AR binds to an androgen ligand and is subsequently translocated from the cytoplasm to the nucleus of cells, where it serves as a transcription factor and promotes tissue growth.⁴³ In the absence of androgen ligand, as is the case with ADT in prostate cancer, an inactive AR remains in the cytosol.⁴⁴ However, it appears that in certain cases IGF signaling actually can actually drive translocation of AR into the nucleus, even in the absence of androgen.⁴² This presents a potential mechanism by which prostate cancer

can progress to AI disease, especially if IGF signaling is upregulated. Furthermore, studies show that inhibiting IGF-1R using an antibody can prevent this transactivation of AR, establishing a potential therapy for prostate cancer progression despite castration.⁴²

It appears that IGFbps also have significant roles in driving prostate cancer development. IGFBP-1 is known to upregulate IGF-1 activity by modulating serum concentrations and tissue delivery of the ligand. Thus, it follows that in patients with metastatic disease undergoing ADT, increased levels of IGFBP-1 are associated with a shorter interval to castration resistance, and consequently, decreased survival.⁴⁵ *In vivo* studies also show that deleting *IGFBP-1* in mice actually decreases growth of prostate tumors, perhaps by activating $\alpha 5\beta 1$ integrin in an IGF-independent manner.^{46,47} There has also been significant research looking at the link between insulin-resistance/ diabetes and prostate cancer, with IGFBP-2 being recently implicated in this phenomenon. In docetaxel-treated prostate cancer cell lines, hyperglycemia significantly reduces drug-induced apoptosis through glucose-mediated upregulation of IGFBP-2. Knocking out IGFBP-2, on the other hand, reverses the survival effect caused by hyper-glycemia.⁴⁸ Finally, IGFBP-related proteins (IGFBP-rPs), similar in structure and function to IGFbps but with weaker affinity for IGF ligands, can play a role in reversing prostate cancer resistance. Restoring IGFBP-rP1 activity has been found to increase both chemosensitivity to docetaxel and radiosensitivity of prostate cancer cells *in vitro*.⁴⁹ Ultimately, it is evident that a better understanding of various members of the IGF signaling axis can help lead to more effective treatment of drug-resistant prostate cancer.

Lung cancer

Lung cancer is one of the most devastating human diseases, accounting for more than a quarter of all cancer deaths.⁵⁰ At the time of diagnosis, many patients do not qualify for surgical intervention, and those who are able to have the primary tumor resected still remain susceptible to disease progression and distant metastasis due to drug resistance.⁵¹ Again, the IGF signaling pathway appears to be implicated in this resistance, and targeting it presents a potential approach to lung cancer treatment moving forward. Gefitinib, an epidermal growth factor receptor (EGFR)-specific tyrosine kinase inhibitor (TKI), is one of the most commonly used drugs for non-small cell lung cancer (NSCLC). Many studies have demonstrated decreased response of NSCLC tumors and cell lines to gefitinib, and IGF-1R appears to be a marker associated with this resistance. Essentially, it appears as though IGF signaling is upregulated as a means of compensating for the EGFR blockade, in part contributing to a drug-resistant phenotype.

One study found that the activity of IGF-1R predicts resistance of NSCLC to gefitinib, though it may not actually play a role in development of drug resistance itself. That is, cell lines that were already resistant to gefitinib were found to have increased total-IGF-1R and phosphorylated-IGF-1R expression, but overexpression of IGF-1R did not confer resistance to gefitinib-sensitive cells.⁵² Another study looking at IGF-1R expression using immunohistochemistry did not find any association between IGF-1R activity and clinical outcomes of gefitinib-treated NSCLC.⁵³ These disparate conclusions may ultimately be attributed to the characteristics of patient samples used in these studies, as tumor

microenvironment appears to contribute heavily to the molecular properties of cancer cells. For example, in NSCLC with an activating mutation of EGFR, IGF-1R activity promotes resistances to gefitinib in lung cancer stem cells (CSCs) under hypoxic conditions. Furthermore, inhibiting IGF-1R actually decreases the population of gefitinib-resistant CSCs in the setting of hypoxia.⁵⁴ Thus, it is possible that IGF-1R may indeed drive NSCLC tumor resistance to drugs such as gefitinib, but perhaps only in specific cell lines and under particular micro-environmental conditions.

Analogous patterns of IGF-1R overexpression in NSCLC drug resistance have been demonstrated with erlotinib, another EGFR-TKI.⁵⁵ Furthermore, in tumors that preferentially respond to erlotinib therapy due to an EGFR-activating mutation in exon 19, crosstalk between IGF-1R and epithelial-mesenchymal transition (EMT) signaling can rapidly confer drug resistance.⁵⁶ In fact, the median interval between initiation of EGFR-TKI therapy and acquired resistance is only 6–12 months in patients afflicted by tumors with this common mutation.^{57,58} Therefore, there is a significant need to block IGF-1R/EMT crosstalk in patients that are identified to have this mutation, especially since their initial response to therapy can be so pronounced.

Regardless of the mechanisms by which EGFR-TKI resistance arises, it seems that IGF-1R inhibition can play a role in re-sensitizing tumors to drugs. AG1024, which prevents autophosphorylation of IGF-1R, synergizes with gefitinib to produce pro-apoptotic and anti-proliferative effects *in vitro* in previously gefitinib-resistant NSCLC cells.⁵⁹ In mutant KRAS lung adenocarcinoma, IGF's downstream PI3K/AKT signaling is thought to be involved with both this gefitinib resistance and re-sensitization by interacting with the anti-apoptotic Ku70 and pro-apoptotic BAX proteins.⁶⁰

The IGFBPs have also been found to play a role in lung cancer resistance to chemotherapy. Apart from binding to ligands and mediating direct IGF-1R signaling, the IGFBPs are known to trigger various independent effects as well. For example, IGFBP-2 directly interacts with integrins and the extracellular matrix to stimulate growth.⁶¹ IGFBP-2 appears to be causally associated with NSCLC resistance to dasatinib, a BCR-ABL and SRC family TKI.^{62,63} Further more, focal adhesion kinase (FAK), which is downstream of IGFBP-2 and integrin binding, is correlated with increased levels of IGFBP-2 and contributes to the dasatinib-resistant phenotype. Both *in vitro* and *in vivo*, dual inhibition of IGFBP-2 and FAK reverses NSCLC resistance by restoring apoptotic sensitivity to dasatinib.⁶³ It stands to reason that both IGFBP-2 and FAK may be used as biomarkers and therapeutic targets in patients with NSCLC to predict and augment response to dasitinib.

Unlike IGFBP-2, IGFBP-3 appears to be *inversely* correlated with TKI resistance.⁶⁴ NSCLC lines with acquired resistance to gefitinib or erlotinib demonstrate decreased secretion of IGFBP-3 *in vitro*. However, upon evaluating the serum of 20 patients, there was no observed difference in IGFBP-3 levels before and after developing resistance to EGFR-TKI.⁶⁵ These disparate conclusions may be explained by understanding that IGFBP-3 levels are primarily maintained by hepatic cells.⁶⁶ That is, IGFBP-3 may serve as a marker of resistance on a cellular level in lung cancer, but this difference is washed out on an organismal level because the tumor's contribution to serum levels is proportionally insignificant. Furthermore,

it seems that the protein may not actually be involved in the pathophysiology of EGFR-TKI resistance. Adenoviral expression or small interfering RNA (siRNA) suppression of IGFBP-3 does not alter the response of NSCLC to these drugs.⁶⁵ Conversely, IGFBP-3 shows some promise in lung cancer that has become resistant to cisplatin (CDDP) therapy. In cells treated with CDDP, promoter methylation decreases expression of IGFBP-3, thereby driving signaling activity of the IGF-1R/PI3K/AKT pathway and inducing resistance.⁶⁷ Treating H640 NSCLC cells with recombinant human IGFBP-3 or IGF-1R-inhibiting siRNA can confer sensitivity to cisplatin, further demonstrating that both of these members may belong to the same drug resistance pathway.⁶⁸

Finally, IGFBP-7 is thought to be a tumor suppressor, downstream of p53, with implications for treating drug-resistant lung cancer.⁶⁹ MAP kinase phosphatase 3 (MKP3) has been found to reduce expression of IGFBP-7, driving NSCLC resistance to cisplatin therapy. Furthermore, MKP3 knockdown increases the transcriptional level of IGFBP-7, which presents a promising approach for sensitizing tumors to cisplatin.⁷⁰ Ultimately, the IGF signaling axis presents numerous opportunities for researchers to better understand and attempt to overcome drug resistance in one of deadliest forms of cancer.

Central Nervous System (CNS) tumors

Glioma comprises about 30% of all CNS tumors, with a particularly poor prognosis when diagnosed in the brain.⁷¹ Surgical resection is often not an option for many patients, who rely immensely on radio- and chemotherapy. In these cases, tumors acquire resistance within just a short interval after beginning therapy.⁷² In terms of radiation, cancer stem cells have been thought to play a critical role in tumor progression despite aggressive treatment. Not surprisingly, IGF-1R signaling seems to be involved in glioma stem cells' (GSCs) ability to adapt to repeated irradiation. One study showed that radiation exposure caused an upregulation of both IGF1 secretion and IGF-1R expression, leading to downstream AKT survival signaling in GSCs. Furthermore, treating radioresistant cells with an IGF-1R inhibitor markedly increases sensitivity to radiation.⁷³

With regards to chemotherapy and glioma, members of the IGF axis are again thought to contribute to resistance mechanisms. In GSCs, there appears to exist cooperative signaling between the Hedgehog (HH) pathway and the IGF axis that promotes resistance to temozolamide. GLI1, a transcription factor downstream of HH that targets insulin receptor substrate 1 (IRS-1), allows for activation of MAPK by IGF-1 signaling, leading to cell proliferation. Suppressing GLI1 decreases IGF-1-dependent proliferation, invasion, and angiogenesis by increasing GSC response to temozolamide.⁷⁴ Independent of HH, IGF-1-induced activation of PI3K appears to protect U251 glioma cells from tamoxifen-induced apoptosis, which can be partially overcome by combination treatment with a specific PI3K inhibitor (LY294002) or PI3K subunit P85 siRNA. Furthermore, the effects of LY294002 appear to be mediated through activation (or dephosphorylation) of GSK3, which inhibits gene transcription by β -catenin.⁷⁵ Despite this compelling evidence that IGF signaling contributes to drug resistance, other studies have muddied the waters. A recent investigation demonstrated that the transcription factor Wilms' tumor 1 (WT1) increases the survival of glioblastoma cells in the presence of cisplatin and carmustine. However, though silencing

WT1 did increase sensitivity to the drugs, there was increased IGF-1R expression as a result.⁷⁶ These disparate conclusions regarding IGF activity in glioma may be attributed to the complex and seemingly independent mechanisms by which resistance arises for different classes of drugs.

IGFBP-2, which is overexpressed in nearly 80% of all glioblastoma multiforme cases, appears to induce chemo-resistance through an IGF-independent mechanism.⁷⁷ Exogenous IGFBP-2 promotes proliferation and invasion of several glioma lines, even in the presence of temozolamide. Immunofluorescence staining and *in vitro* knockdown models show that this effect is mediated through activation of integrin β 1 and downstream phosphorylation and nuclear translocation of ERK.⁷⁸ Therefore, IGFBP-2 presents yet another promising target for overcoming drug resistance that may prove successful where direct IGF signaling inhibitors fall short. Ultimately, it will be necessary to identify reliable markers so as to determine not only the primary mechanism by which resistance arises, but also to predict the efficacy of IGF signaling inhibitors in novel combination treatment regimens for glioma.

Gastrointestinal cancers

Gastrointestinal (GI) neoplasms represent a significant proportion of all new cancers diagnosed yearly, with prognosis ranging from good to dismal based on the organs involved and the extent of invasion.^{79–81} Gastric cancer represents a form of malignancy with relatively poor outcomes, in large part due to limited efficacy of chemo-therapy. Studies have shown that drug resistance in these cases is often associated with decreased expression of microRNAs (miRs), small non-coding molecules that play a key role in post-transcriptional regulation of genes by repressing messenger RNA.^{82,83} In several cisplatin-resistant gastric cancer lines, it appears that downregulated miR-503 is correlated with increased expression of IGF-1R and the downstream anti-apoptotic Bcl-2 protein, as these genes appear to be directly regulated by the microRNA. Furthermore, overexpression of miR-503 reduces the activity of these proteins and subsequently re-sensitizes cells to cisplatin-induced apoptosis.⁸⁴ miR-1271 seems to play a similar role in gastric cancer cells, restoring cisplatin sensitivity *in vitro* by repressing IGF-1R, IRS-1, mTOR, and Bcl-2.⁸⁵ As such, these studies support a novel approach of using microRNAs to modulate IGF signaling and perhaps even overcome drug resistance.

Colorectal cancer (CRC) continues to be one of the most aggressive malignancies with roughly a third of patients succumbing to the disease within 5 years, despite recent advances leading to earlier diagnosis and treatment.⁸⁶ In general, obesity has been associated with poorer outcomes and may underlie drug resistance.⁸⁷ One study looked at the *in vitro* effects on CRC cells of low-dose oxaliplatin, 5-fluorouracil, or irinotecan in combination with obesity-related molecular phenomena, including elevated glucose, insulin, and IGF-1.⁸⁸ This was meant to emulate a frequent situation in which obese patients are under-dosed with chemotherapy.⁸⁹ Though not always observed with increased insulin or glucose concentrations, the combination of elevated IGF-1 and low-dose chemotherapy consistently increased tumor cell survival.⁸⁸ This data provides intriguing insight into how IGF signaling may serve as a link between obesity and development of drug resistance.

One of the mechanisms by which CRC cells are able to develop multidrug resistance is through active efflux by pumps, such as multidrug-resistance-associated protein 2 (MRP-2), which can reduce intracellular drug concentration.⁹⁰ IGF signaling has been thought to be involved with this pump activity. In fact, IGF-1R silencing with specific siRNA suppresses MRP-2 in CRC *in vitro*, thereby increasing intracellular drug concentration of four types of anticancer drugs separately. This effect appears to be mediated via the PI3K/AKT pathway, which causes nuclear translocation of nuclear factor-like 2 (Nrf2) and reduces expression of MRP-2.⁹¹ This study presents yet another mechanism by which resistance can arise, but offers the potential solution that modulating IGF-1R activity can overcome this by maintaining therapeutic drug levels inside target cells.

The role of IGF signaling is also apparent in hepatic and pancreatic cancers resistant to treatment. HA22T, a hepatocellular carcinoma (HCC) cell line resistant to the histone deacetylase inhibitor apicidin, was found to display increased levels of activated IGF-1R, PI3K, AKT, and Bcl-2. Furthermore, the highly proliferative nature of these cells could be attenuated by AKT knockdown.⁹² In addition, IGF signaling seems to maintain the self-renewal capacity of cancer stem cells (CSCs) within these tumors.⁹³ In oxaliplatin-resistant HCC, the stemness of a subpopulation of tumor cells is associated with autocrine signaling of IGF-1, whereas treatment with an IGF-1R inhibitor suppresses CSC-related markers.⁹⁴ In pancreatic cancer, IGF-1R knockdown enhances the efficacy of gemcitabine *in vitro*, likely due to inhibition of the downstream PI3K/AKT and NF- κ B activity.⁹⁵ K-Ras, a GTPase belonging to the Ras family, is frequently mutated into a constitutively active form in pancreatic ductal adenocarcinoma (PDAC).⁹⁶ This mutation also confers resistance to experimental drugs such as rapalog and everolimus, which are mTOR inhibitors, by causing feedback activation of the IGF-1-Ras-ERK pathway. In these cases, K-Ras knockdown blocks IGF-induced ERK signaling and thereby enhances sensitivity to everolimus.⁹⁷ Furthermore, targeting IGF signaling may offer another way to overcome drug resistance in tumors identified to have a K-Ras mutation. Overall, there is clear evidence that multiple GI malignancies can be made more responsive to current therapy regimens by better understanding and working to modulate the underlying IGF signaling abnormalities.

Head and neck cancers

Head and neck cancers can have debilitating effects on quality of life, often due to aggressive surgical resection at the time of diagnosis.^{98,99} Despite these efforts, outcomes still remain poor due to the dwindling response of tumors to chemotherapy.^{100,101} IGF signaling remains under considerable investigation for its contributions to this drug resistance. In head and neck squamous cell cancer (HNSCC), similar to lung cancer, EGFR-TKIs have had elicited poor response in tumors, likely due to compensatory pro-survival signaling caused by IGF-1R. In five HNSCC cell lines, IGF-1R activation decreases apoptotic sensitivity to gefitinib *in vitro* through downstream activation of AKT and ERK.¹⁰² Other studies have demonstrated that IRS-1 may be at the root of this chemoresistance, showing that treatment with gefitinib alters its binding and phosphorylation properties which ultimately requires less IGF ligand for AKT activation.¹⁰³ Keeping with these findings, direct IGF-1R inhibition of HNSCC does indeed result in increased response to treatment with EGFR antagonists.¹⁰⁴ Furthermore, various *in vitro* and

in vivo studies have indicated that IGF signaling blockade can augment the response to histone deacetylase inhibitors, rapamycin, gemcitabine (a nucleoside analog), and even radiation treatment by targeting similar resistance mechanisms.¹⁰⁵ It is clear that HNSCC represents yet another disease for which IGF modulation may be a suitable adjuvant therapy for overcoming drug resistance.

Bone and soft tissue tumors

Unique to most types of cancer, primary bone and soft tissue tumors have a tendency to preferentially affect children and adolescents. This is thought to be due to the underlying mechanisms involved in both normal skeletal growth and the development of these tumors, such as the extensively-studied IGF pathway.¹ In addition to contributing to the malignant phenotype of bone diseases like osteosarcoma (OS) and Ewing's sarcoma, IGF signaling now appears to be implicated in tumor response to pharmacologic agents.¹⁰⁶ For example, IGF-1R inhibition has been shown to inhibit OS proliferation and invasion while increasing sensitivity to both radiation and chemotherapy with docetaxel, cisplatin, or doxorubicin.¹⁰⁷⁻¹¹⁰ Furthermore, IGFBP-5 is significantly downregulated in OS, with overexpression of the N- and C-terminal domains of the protein specifically inhibiting tumor growth and invasion, respectively.^{16,17} These effects appear to be mediated through both IGF-dependent and -independent pathways, indicating a potential role for IGFBP-5 in mono- or combination therapy to overcome various mechanisms of drug resistance.¹¹¹

Rhabdomyosarcoma (RMS) is a soft tissue tumor of muscle that also appears to be influenced by IGF signaling.¹¹² In addition to increased activity of IGF-1R, downregulation of IGFBP-2 is associated with resistance of RMS cells to therapy. Furthermore, it has been found that resistance to IGF-1R inhibitors *in vivo* is actually mediated by decreased IGFBP-2 through IGF-independent activation of PI3K and mTOR.¹¹³ Another study found that IGF-2 mRNA binding protein 1 (IGF2BP1) is implicated in driving translation of cellular inhibitor of apoptosis 1 (cIAP1), which promotes resistance to tumor necrosis factor- α (TNF α). Inhibiting cIAP1 through IAP antagonists or knockdown of IGF2BP1 promotes sensitivity to TNF α , essentially by preventing proliferative NF- κ B signaling and allowing for caspase-8-mediated cell death.¹¹⁴ It seems that studying members of the IGF axis, even those that do not directly mediate IGF-dependent signaling, offers various opportunities for treating tumors that have become resistant to both pre-existing and novel therapeutics.

Hematologic malignancies

Affecting patients of all ages, various cancers of the blood and bone marrow are usually not amenable to surgical treatment and unfortunately tend to show erratic response to chemotherapy.^{115,116} Interestingly, though, downstream components of the IGF signaling axis, including PI3K, AKT and mTOR have been heavily implicated in conferring this drug resistance.¹¹⁷⁻¹²⁰ For example, in multiple myeloma, IGF-1/IGF-1R activity is thought to reduce cell sensitivity to bortezomib, a proteasome inhibitor. Exogenous IGF-1 is shown to amplify this effect, whereas inhibiting IGF-1R using small hairpin RNA increases the apoptotic effect of the drug.¹²¹ In contrast, other studies have actually shown that IGF-1 enhances the cytotoxic effect of proteasome inhibitors, augmenting the effect of bortezomib

on both pro-apoptotic and anti-apoptotic protein levels.¹²² These conflicting conclusions may be attributed to varying experimental designs and use of different cell lines/tumors in experiments. Regardless, the role of IGF in myeloma drug resistance is quite intriguing and warrants further investigation to develop novel therapies.

Patients with acute myeloid leukemia (AML) only have a 30–40% survival five years after diagnosis, most often due to development of chemotherapy resistance.¹²³ When studying 99 adult patients with AML found to be non-responsive to cytarabine and anthracycline, one group found that high IGFBP-2 mRNA levels are not only associated with, but predictive of, poor response to therapy due to upregulation of genes involved in leukemogenesis.¹²⁴ In addition, IGFBP-7 has been found to sensitize AML to cell death induced by doxorubicin, etoposide, and cytarabine through an IGF-independent mechanism of promoting G2 cell cycle arrest.¹²³ However, in acute lymphoblastic leukemia (ALL), an opposite effect is seen as IGFBP-7 has been found to promote resistance to asparaginase through interactions with bone marrow stromal cells, even correlating with decreased leukemia-free survival in patients.¹²⁵ Overall, it seems that molecular therapy targeting members of the IGF pathway can one day be developed to enhance response to drugs based on disease-specific mechanisms.

Conclusions and future directions

In conclusion, during a time when cancer treatment has seemingly reached a plateau due to drug resistance, it is critically important to not only understand the underlying mechanisms of this phenomenon but also identify novel therapeutic agents to overcome it. As evidenced by the numerous studies reviewed above (summarized in Table 1), IGF signaling demonstrates significant promise in both of these aims. IGF-mediated effects, as well as IGF-independent signaling by pathway-related molecules, are undoubtedly involved in the response of various tumors to radio- and chemotherapy regimens. Though an important element of normal tissue growth and homeostasis, the IGF pathway appears just as important to cancer disease progression through aberrant signaling. As discussed above, this dysregulation can occur at multiple levels, from crosstalk between IGF and other hormone receptors to constitutive activation of downstream proteins. What is most compelling is that members of this pathway have the ability to promote (or reverse) resistance of various cancer cells to many different classes of drugs (and even radiotherapy) with unique mechanisms of action. Therefore, it can be argued that the IGF axis should be one of the most important foci of research efforts.

Previously, investigators have found the IGF pathway to be implicated in the malignant phenotypes of various neoplasms, focusing their efforts on treating tumors with modulators of this pathway. Many potential drugs, such as IGF-1R inhibitors, have now even made it to clinical trials, but the outcomes of these studies have been largely under-whelming.¹²⁶ Used as monotherapy, these drugs may not prove superior to current standard-of-care chemotherapy, but there exists considerable potential for use of these agents in combination therapy to improve existing treatment regimens. In light of the compelling evidence presented here, future directions seem abundantly clear: understand the effects of IGF signaling modulators in combination with existing drugs in translational and clinical studies.

In addition, more emphasis needs to be placed on studying members of the pathway that exert IGF-independent effects, such as the IGFBPs. We cannot ignore the possibility that such investigations might offer a wide array of therapeutic benefits for drug-resistant tumors. In parallel, researchers should seek to better understand how dysregulation of IGF signaling occurs. This may eventually help clinicians to prevent tumors from becoming not only more aggressive, but also resistant to early therapy. Ultimately, IGF signaling plays a remarkable role in the development and progression of cancer despite therapy, so we must seek to better control its properties if there are to be substantial improvements in patient outcomes in the future.

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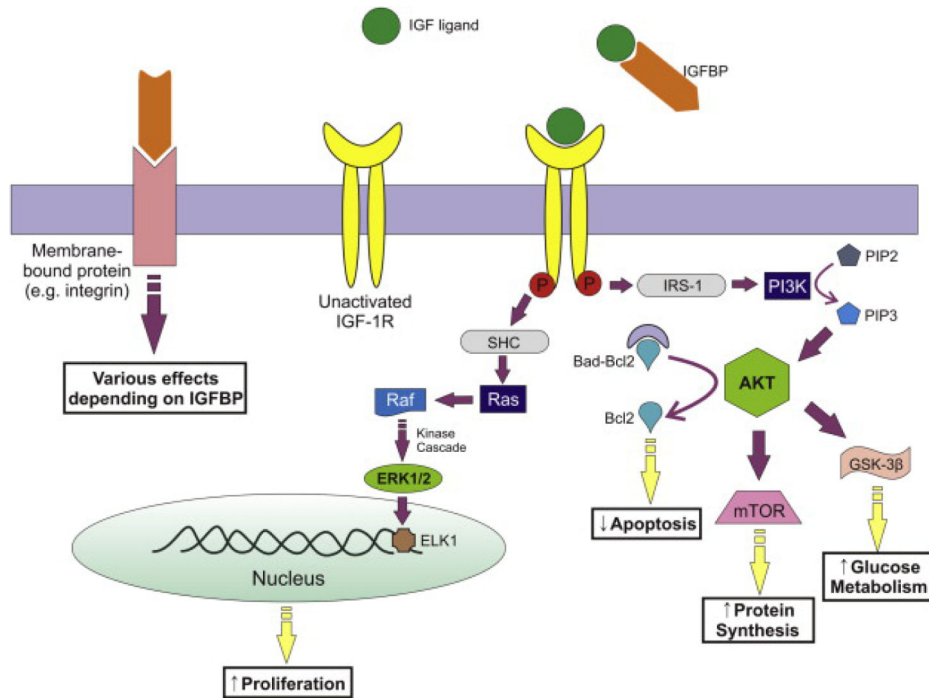


Figure 1.

Schematic of IGF signaling and major downstream effects. Activation of IGF-1R can result in signaling via two pathways: PI3K/AKT and Ras/MAPK. PI3K/AKT results in decreased apoptosis, increased protein synthesis, and increased glucose metabolism, among various other effects not represented here. Ras/MAPK contains an elaborate kinase cascade that ultimately leads to increased cellular proliferation by promoting the activity of transcription factors, such as ELK1. The activity of IGF ligands is modulated by IGFBPs through direct binding in the extracellular space. IGFBPs also exert several IGF-independent effects via direct interaction with cell membrane-bound proteins, such as integrins.

Table 1

Summary of IGF pathway members and their implications in promoting resistance or sensitivity to therapy among various human cancers.

IGF pathway member	Observed or experimental change	Confers resistance or increases sensitivity?	Affected cancer: Drug/Treatment			
IGF-1R	↑	Resistance	Breast ER+: Tamoxifen ²²			
			Breast HER2+: Trastuzumab ²⁸			
			Gastric: Cisplatin ⁸⁴			
			Glioma: Radiation, ⁷³ Temozolamide ⁷⁴			
			Hepatocellular: Apicidin ⁹²			
			HNSCC: Gefitinib ¹⁰²			
			NSCLC: Gefitinib, ⁵² Erlotinib, ⁵⁵			
	↓	Sensitivity	Osteosarcoma: Radiation, ¹⁰⁸ Docetaxel, Cisplatin, ¹⁰⁷ Doxorubicin ^{109,110}			
			Ovarian: Cisplatin ± taxol ³⁷			
			Prostate: Androgen deprivation therapy ⁴²			
			Colorectal: Multiple ⁹¹			
			Gastric: Cisplatin ^{84,85}			
			Glioma: Radiation ⁷³			
			Hepatocellular: Oxaliplatin ⁹⁴			
IGF-1	↑	Resistance	HNSCC: Methotrexate, Cetuximab, ¹⁰⁴ histone deacetylase inhibitors, Rapamycin, Gemcitabine, Radiation ¹⁰⁵			
			Multiple myeloma: Bortezomib ¹²¹			
			NSCLC: Gefitinib ⁵⁴			
			Ovarian: Platinum-based drugs ³⁹			
			Pancreatic: Gemcitabine ⁹⁵			
			Prostate: Androgen deprivation therapy ⁴²			
			Colorectal: Oxaliplatin, 5-Fluorouracil, Irinotecan ⁸⁸			
	↑	Sensitivity	Glioma: Tamoxifen ⁷⁵			
			Hepatocellular: Oxaliplatin ⁹⁴			
			Multiple myeloma: Bortezomib ¹²¹			
			Pancreatic: Everolimus ⁹⁷			
			Multiple myeloma: Bortezomib ¹²²			
			IGF-2	↑	Resistance	Ovarian: Platinum-based drugs ³⁹
				↓	Sensitivity	Ovarian: Taxol ⁴⁰
PI3K/AKT	↑	Resistance	NSCLC: Gefitinib ⁶⁰			
	↓	Sensitivity	Glioma: Tamoxifen ⁷⁵			
			Hepatocellular: Apicidin ⁹²			
Ras/ERK	↑	Resistance	NSCLC: Gefitinib ⁶⁰			
	↓	Sensitivity	Pancreatic: Everolimus ⁹⁷			
			Pancreatic: Everolimus ⁹⁷			

IGF pathway member	Observed or experimental change	Confers resistance or increases sensitivity?	Affected cancer: Drug/Treatment
IGFBP-1	↑	Resistance	Prostate: Androgen deprivation therapy ⁴⁵
	↓	Sensitivity	Prostate: Androgen deprivation therapy ^{46,47}
IGFBP-2	↑	Resistance	AML: Cytarabine, Anthracycline ¹²⁴ Glioma: Temozolamide ⁷⁸ NSCLC: Dasatinib ^{62,63} Prostate: Docetaxel ⁴⁸
	↓	Sensitivity	NSCLC: Dasatinib ⁶³ Prostate: Docetaxel ⁴⁸
	↓	Resistance	RMS: IGF-1R antibody ¹¹³
	↓	Resistance	NSCLC: Gefitinib, Erlotinib, ⁶⁵ Cisplatin ⁶⁷
IGFBP-3		Sensitivity	Breast ER+: Fulvestrant ²⁷
	↑		NSCLC: Cisplatin ⁶⁸
IGFBP-7	↓	Resistance	NSCLC: Cisplatin ⁷⁰
	↑	Sensitivity	AML: Doxorubicin, Etoposide, Cytarabine ¹²³ NSCLC: Cisplatin ⁷⁰
IGFBP-rP1	↑	Resistance	ALL: Asparaginase ¹²⁵
	↑	Sensitivity	Prostate: Docetaxel, Radiation ⁴⁹
IGF2BP1	↑	Resistance	RMS: TNF α ¹¹⁴
	↓	Sensitivity	RMS: TNF α ¹¹⁴

Abbreviations – ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; ER+: estrogen receptor positive; HNSCC: Head and neck squamous cell cancer; IGF2BP1: insulin-like growth factor 2 mRNA binding protein 1; IGFBP-rP1: insulin-like growth factor binding protein related peptide 1; NSCLC: Non-small cell lung cancer; RMS: rhabdomyosarcoma

The upward arrows represent either upregulation, overexpression, or otherwise increased activity of the specific IGF pathway member as observed or experimentally changed in the study. The downward arrows represent either downregulation, underexpression, or otherwise decreased activity of the specified IGF pathway member.