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Targeting insulin and insulin-like growth factor signaling in breast cancer

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Abstract

The insulin and insulin like growth factor (IGF) signaling systems are implicated in breast cancer biology. Thus, disrupting IGF/insulin signaling has been shown to have promise in a number of preclinical models. However, human clinical trials have been less promising. Despite evidence of some activity in early phase trials, randomized phase III studies have thus far been unable to show a benefit of blocking IGF signaling in combination with conventional strategies. In breast cancer, combination anti IGF/insulin signaling agents with hormone therapy has not yet proven to have benefit. This inability to translate the preclinical findings into useful clinical strategies calls attention to the need for a deeper understanding of this complex pathway. Development of predictive biomarkers and optimal inhibitory strategies of the IGF/insulin system should yield better clinical strategies. Furthermore, unraveling the interaction between the IGF/insulin pathway and other critical signaling pathways in breast cancer biology, namely estrogen receptor- α (ER α) and epidermal growth factor receptor (EGFR) pathways, provides additional new concepts in designing combination therapies. In this review, we will briefly summarize the current strategies targeting the IGF/insulin system, discuss the possible reasons of success or failure of the existing therapies, and provide potential future direction for research and clinical trials.

Keywords

Breast cancer; insulin-like growth factor; type I receptor IGF receptor; insulin receptor; predictive biomarkers

Introduction

Breast cancer is the most common cancer and the second leading cause of cancer death among women in the US. In 2012, about 226,870 breast cancer cases will be newly diagnosed and about 39,510 women will die from this disease (www.cancer.org). In the past decade the death rate from breast cancer is decreasing, even though breast cancer incidence remains high. The wider use of adjuvant therapy for operable breast cancer partially accounts for this improvement. Targeting the estrogen receptor- α has proven to be one of the most useful methods to decrease breast cancer death mortality [1]. Targeting human epidermal growth factor receptor 2 (Her2) with trastuzumab (Herceptin®) has also been an important advance [2, 3]. The clinical success of targeting receptors critical in breast cancer biology has underlined the importance of identifying and understanding the regulatory pathways involved in breast cancer growth and metastases. Furthermore, with the awareness

of the complexity and heterogeneity of breast cancer [4], developing additional targeted therapies is critical to further improve breast cancer outcomes.

The insulin-like growth factor/insulin (IGF/insulin) system possesses potent mitogenic and pro-migratory properties and has been extensively implicated in many malignancies including breast cancer [5–7]. The type I insulin-like growth factor receptor (IGF-IR) is a component of the complex IGF/insulin signaling network. IGF-IR has been shown to regulate cell metabolism, enhance transformation, stimulate proliferation, and promote metastasis in breast cancer [5, 6, 8–10]. Numerous lines of evidence suggest that blockade of the IGF/insulin signaling pathway inhibits growth and metastasis in multiple cancer types including breast cancer both *in vitro* and *in vivo* [8, 11–14]. Collectively, IGF-IR has been viewed as a potentially valuable target for breast cancer treatment.

The IGF/insulin system consists of three ligands, IGF-I, IGF-II, and insulin; six ligand-binding proteins, IGFBP 1–6; and 2 transmembrane tyrosine kinase receptors (RTK) genes the type I IGF receptor (IGF-IR) and the insulin receptor (IR). The receptor genes encode the α and β subunits of the protein. For a fully function receptor, the gene products must be dimerized with a partner. Thus, holo-receptors and hybrid receptors composed of half IGF-IR and half (IR) are capable of forming (Figure 1). These functional receptors are composed of two extracellular α subunits covalently linked to two intracellular β subunits, which contain the tyrosine kinase domains. Following ligand binding to the extracellular α subunits, the receptors undergo a conformational change resulting in activation of its tyrosine kinase activity and trans-phosphorylation of the intracellular β subunits. The activated receptors then recruit and phosphorylate adaptor proteins including insulin receptor substrates (IRS 1–6) and Shc. This couples the initial ligand-binding event and further triggers multiple downstream signaling pathways, including phosphatidylinositol 3'-kinase (PI3K) and the mitogen-activated protein kinase (MAPK). These secondary messenger molecules result in stimulation of specific cellular functions, such as proliferation, apoptosis, metastasis, metabolism, angiogenesis, and drug resistance [15, 16] (Figure 1).

The insulin receptors are closely related and expressed as two isoforms, insulin receptor A (IR-A) and insulin receptor B (IR-B) with a 12 amino acid difference in exon 11 [17]. IR-B is the major form expressed in adults and has high affinity for insulin, while IR-A, which is abundantly expressed during fetal development and is commonly overexpressed in tumors [17], can transmit signals by binding to both insulin and IGF-II [18].

Since deregulation of cellular energy metabolism has been considered as an emerging hallmark of cancer [19], IR and its related metabolic syndromes have become another major focus in the breast cancer research and treatment field. Both obesity and type 2 diabetes mellitus could lead to hyperinsulinemia, which has been reported to activate insulin receptors in normal breast epithelial cells [20] and in neoplastic tissues [21], increase the risk of developing breast cancer in patients with metabolic syndromes [22], promote metastatic progression, and associate with poor prognosis in breast cancer patients [23].

Strategies in targeting the IGF-I/insulin system

Blockade of ligand binding

In normal physiology, insulin is produced by pancreatic β -islet cells and arrives at target tissues through the blood circulation. For IGFs, the liver is the major producer for the circulating IGF-I, but normal tissue and tumor tissue can frequently secrete both IGF-I and IGF-II. Therefore, IGF-I and IGF-II could affect tumor biology via autocrine, paracrine, and endocrine mechanisms. As mentioned above, IGF-IR and IR require ligand binding for

receptor activation, thus reducing ligands levels becomes a reasonable and practical strategy to control the IGF-I/insulin signaling in neoplastic tissue. In normal physiology, reduction of insulin level is not practical because of the resultant metabolic effects on glucose control. In contrast, low levels of IGFs appear to be well tolerated in humans [24]. Since IGF-I is regulated by the hypothalamic-pituitary axis, via secretion of growth hormone, growth hormone-releasing hormone antagonists (e.g. JV-1–38 [25]) disrupting this pathway could be used to affect IGF-I levels. In addition, pegvisomant, a direct antagonist of the growth hormone receptor, has been developed to treat acromegaly and is also able to inhibit IGF-I levels in normal human subjects [26].

Another approach to reduce the levels of unbound ligands involves the use of monoclonal antibodies to neutralize extracellular IGFs. MEDI-573, a monoclonal antibody with high binding affinity for both IGFs selectively inhibits the activation of both the IGF1R and IR-A signaling pathways *in vitro* and in mouse models without disrupting glucose metabolism mediated by insulin and IR interaction [27]. MEDI-573 is now involved in several phase I clinical trials for different types of tumors (clinicaltrials.gov, identifier no. NCT01446159, NCT00816361). Another novel IGF ligand neutralizing antibody, BI 836845 (Boehringer Ingelheim Pharmaceuticals), was recently shown to improve preclinical antitumor efficacy of rapamycin by suppressing IGFs' bioactivity and inhibiting rapamycin-induced PI3K/AKT activation [28]. This drug is currently in a phase I clinical trial (NCT01317420).

IGFBPs regulate IGFs' bioactivity by sequestering the peptides from binding to the receptors. Most of the IGFBPs can also act in an IGF-independent fashion. IGFBP3, in particular, has been shown to directly associate with cell surface and nuclear receptors thereby inducing antiproliferative effects and apoptosis (extensively reviewed in [29]). Thus, other approaches to reduce the ligands bioactivity may include recombinant IGFBPs, namely IGFBP3 [30, 31].

Targeting the receptors

As noted above, IGF/insulin system consists of multiple receptor tyrosine kinases and nearly all of them are targetable by either dominant negative constructs or pharmacological approaches. Traditionally, IR has not been considered the primary target due to its central role in glucose metabolism. However, accumulated data suggests IR-A may play important roles in breast cancer progression and survival [32, 33]. IR-A signaling has also been suggested as a possible mechanism of resistance to IGF-IR targeted therapies [34, 35]. Thus, developing safe therapies to control IR signaling is urgently needed. Indirectly targeting IR-A activation by downregulation of one of its ligands, IGF-II, has been shown to inhibit cancer cell growth. [35]. It is possible that ligand neutralization, as opposed to receptor inhibition, could result in less disruption of glucose metabolism.

In the past several years, major effort has been directed toward targeting IGF-IR. Anti-IGF-IR monoclonal antibodies have been developed and several trials using such antibodies as single agents or in combination with other antitumor drugs are in phase I/II clinical trials. The antibodies are designed specifically to bind the α subunit of IGF-IR with high affinity, thus they do not directly affect IR-A or IR-B. This class of drugs shares similar mechanisms of action by interfering with ligand binding to both holo-IGF-IR and hybrid receptors [36], and causing receptor endocytosis and subsequent degradation in the endosome thereby inhibiting cancer cell proliferation and metastasis [37].

Figitumumab (CP-751, 871, Pfizer), a fully human IgG2 α -IGF-IR monoclonal antibody, generated enthusiasm in a randomized phase II clinical study (NCT00147537). The study showed that combined figitumumab with carboplatin and paclitaxel enhanced response rate and prolonged progression-free survival and overall survival in non-small-cell lung cancer

(NSCLC). However, Pfizer discontinued two phase III figitumumab clinical trials (NCT00673049, NCT00596830) due to a failure to confirm the promising phase II results and also observed substantial toxicity. Treatment of breast cancer patients with an aromatase inhibitor with or without figitumumab was studied but showed no benefit for the antibody [38]. AVE1642 (sanofi-aventis), a humanized IgG1 antibody, showed promising data in preclinical studies [39, 40] but failed in its phase II clinical trials in breast cancer patients (NCT00774878). One reason for the failure might be the lack of molecular markers that predict IGF-IR sensitive tumors.

Despite these failures, there are still several currently active trials primarily aimed to evaluate IGF-IR antibody as an adjuvant agent to other antitumor drugs in many types of cancer. Ganitumab (AMG 479, Amgen), a fully humanized IgG1 antibody, is being tested in combination with cytotoxic chemotherapy, mTOR inhibitors, and hormonal therapies in various diseases including NSCLC, colorectal, pancreatic, ovarian, and breast cancer. Similar trials have been completed with the fully humanized IgG1 IGF-IR antibody cixutumumab (IMC-A12, Imclone).

Dalotuzumab (MK 0646, Merck), another humanized IgG1 antibody with promising preliminary profiles [41, 42], is currently being studied with aromatase inhibitors and the mTOR antagonist in advanced breast cancer.

The anti-IGF-IR monoclonal antibodies also share a common effect on the disruption of normal endocrine feedback systems that have implications for phase III clinical trials. One of the common side effects using the antibodies is disruption of the negative feedback of IGF-I on growth hormone secretion by the pituitary. Administration of the antibodies results in upregulation of the growth hormone serum levels resulting in increased circulating IGF levels, hyperglycemia, and hyperinsulinemia [43]. Since the antibodies do not block IR signaling, this could explain the failure to demonstrate clinical activity when only IGF-IR signaling is disrupted. Furthermore, subsequent development of refractory tumors in IGF-IR antibody treated patients might be due to both hyperinsulinemia [44] and high free IGF [44, 45]. Certainly, activation of IR signaling could initiate pro-survival signaling to blunt the effects of cytotoxic chemotherapy. A recent clinical trial for women with ER-positive breast cancer reported combined IGF-IR antibody with the aromatase inhibitor exemestane trended toward benefit only in patients with normal hemoglobin A1C levels [38], which is an indicator for insulin resistance. In IGF-IR antibody clinical trials design, patients with pre-existing insulin resistance may need to be excluded or have their hyperinsulinemia better controlled. It would be important to state that in preclinical rodent model systems the effect of hyperinsulinemia is not seen after exposure to IGF1R monoclonal antibodies as these antibodies do not have the same affinity for murine IGF1R. Adult rodents also do not have significant level of circulating IGF-II [46], thus mouse models might not accurately model the human endocrine milieu and the effects of endocrine disruptors designed to target human receptors.

Another major class of drugs to target IGF-IR activation is small-molecule tyrosine kinase inhibitors (TKI), which compete for the ATP binding site in the catalytic domain of the β subunit of IGF-IR and IR. Most TKIs show limited selectivity of IGF-IR over IR *in vitro* or *in vivo* [47, 48]. The high degree of homology of the intracellular β subunits of the IGF-IR and IR may account for this relative lack of selectivity of the TKIs. However, this dual targeting might have some benefits given the potential role for IR in cancer. Specifically, upregulated serum levels of insulin after IGF1R monoclonal antibody treatment might not have as much effect on the tumor if both IGF1R and IR are blocked by a TKI. Studies showed that these TKIs inhibited IGF-IR/IR phosphorylation and AKT activation, enhanced apoptosis, decreased *in vitro* cell proliferation, and tumor suppression in xenograft models

[42, 49, 50]. A dual IGF-IR/IR dual tyrosine kinase inhibitor BMS-754807 (BMS) showed better antitumor efficacy in combination with hormonal therapies in hormone sensitive breast cancer model systems [50]. BMS-754807 and OSI-906 are two promising examples of small molecule inhibitors, being tested in several breast cancer clinical trials.

The cyclolignan picropodophyllin (AXL1717 or PPP, Axelar) is reported to specifically inhibit IGF-IR specific tyrosine kinase activity, although the exact mechanism is uncertain. The compound reportedly possesses both signal inhibitory properties and downregulates IGF-IR *in vitro* [51]. A phase I trial of this drug has been completed showing favorable safety and pharmacokinetics profiles of PPP in patients with advanced cancer (NCT01062620).

Other novel approaches to target IGF/insulin system at the receptor level include using small interfering RNA (siRNA) and microRNA to suppress IGF-IR expression and function. Recently, an interesting preclinical study showed that 2'-O-methyl modified IGF-IR specific siRNA are able to downregulate IGF-IR expression, block IGF-IR signaling, and suppress tumor growth *in vivo* by triggering antitumor immune responses [51]. siRNA-based therapies face two major barriers: the delivery of the large and highly charged molecules to the targets [52] and the transient effects of the downregulation of the target gene. In pre-clinical *in vivo* studies, the latter could be solved by developing *in vivo* stable and inducible long-term expression of target short hairpin RNA under the control of doxycycline, tetracycline, or other dimerizing drugs [53]. Specific microRNAs inhibited cancer cell proliferation, motility, invasion, xenograft tumor growth, and metastasis in different cancers by downregulation of IGF-IR expression [54, 55]. Typically these microRNAs have approximately 22 nucleotides and usually have more than one target; potential drug candidates need to be carefully examined to exclude off-target effects before evaluation in clinical trials. Introduction of kinase deficient mutation into IGF-IR as a gene transfer strategy could also be an alternative approach to suppress IGF-IR signaling pathway and result in tumor suppression [56].

Targeting IGF/insulin downstream signaling pathways

As noted, PI3K/AKT and Ras-MAPK axis are two well-established intracellular signal networks downstream of IGF/insulin signaling. Therefore, several key molecules in these pathways might be relevant targets for drug development including mammalian target of rapamycin (mTOR), a serine/threonine protein kinase. Activation of mTOR upon growth factor stimulation subsequently induces the activation of ribosomal p70 S6 kinase (S6K1) and eukaryotic initiation factor 4E-binding protein-1 (4EBP1). Phosphorylated 4EBP1 releases eIF4E, the latter recruits eIF4G to form eIF4F complex, which then binds to the 5' mRNA cap and initiates cap-dependent mRNA-protein translation, thereby regulating cell growth and proliferation. Rapamycin and its analogs, everolimus (Novartis), temsirolimus (Pfizer) and ridaforolimus (Merck), have been developed to inhibit mTOR. Based on preclinical data using breast cancer cell lines [57–60] and mouse tumor models [61], both temsirolimus and everolimus have been approved for cancer treatment. Two recently published reports showed that everolimus combined with endocrine therapies were of benefit. In hormone refractory patients, tamoxifen plus everolimus resulted in increased clinical benefit compared to tamoxifen alone with improved time to progression and overall survival in hormone receptor (HR)-positive, human epidermal growth factor receptor (EGFR) 2-negative metastatic breast cancer patients [62]. In a similar patient population, everolimus combined with the aromatase inhibitor exemestane showed improved progression-free survival in HR positive advanced breast cancer patients [63].

These promising clinical studies provide important evidence that anti-ER therapies can be combined with anti-signaling strategies. However, some caution is warranted in using

mTOR inhibitors with the IGF system. Normally, IGF stimulation results in activation of S6K1, which negatively regulates adaptor protein insulin receptor substrate-1 (IRS1) function by phosphorylation. IRS1 phosphorylation results in degradation of IRS1 protein and suppression of IRS1 gene expression [64]. mTOR inhibitors disrupt this negative feedback loop and enhance IGF/insulin signaling and subsequent PI3K/AKT activation [65].

Combination therapy with anti-IGF-IR agents might be needed to address this problem and will be discussed later. Beyond mTOR inhibitors, other small molecule inhibitors of the downstream pathways, such as PI3K inhibitor LY294002 [66], S6K1 inhibitor H89 [57], MAPK inhibitor U0126 [57, 67], and dual PI3K/mTOR inhibitor NVP-BEZ235 [68] are currently in preclinical and clinical studies. The important translation initiation protein 4EBP1 could also be a potential drug target to terminate IGF/insulin signaling induced cap-dependent translation.

Crosstalk and combination therapies

IGF-IR monoclonal antibodies and mTOR inhibitors

As noted above, mTOR inhibitors affect the S6K1-IRS1 negative feedback loop and result in enhanced PI3K- AKT activation through IGF-IR signaling [69]. If this pathway represents a resistance mechanism for the mTOR inhibitors, then co-targeting IGF-IR and mTOR might result in enhanced clinical benefit over mTOR inhibitor monotherapy. Studies showed that dual inhibition of IGF-IR and mTOR improved antitumor activity *in vitro* and in breast cancer and other cancer patient tumor samples [69, 70]. Currently, Merck is determining the benefits of IGF-IR monoclonal antibody (dalotuzumab) and mTOR inhibitor (ridaforolimus) combination therapy in breast cancer patients with ER-positive tumors (NCT01220570, NCT01234857). Amgen is evaluating the clinical benefits of combining ganitumab with everolimus in patients having advanced cancers (NCT01061788, NCT01122199). The results of these clinical trials are expected to reveal the benefits of co-targeting IGF-IR and mTOR [71]. It is worth noting that drugs acting as dual inhibitors of PI3K and mTOR, such as NVP-BEZ235, also demonstrated improved antitumor efficacy compared to mTOR inhibitors alone [68, 72, 73].

Targeting IGF-IR/IR and estrogen receptor- α (ER α)

Cross talk between IGF/insulin system and estrogen receptor signaling pathway is well established [42, 57, 74]. IGF/insulin signaling activates ER α via PI3K/AKT and/or MAPK pathways respectively by phosphorylating ER α ^{serine167} and/or ER α ^{alanine118} [57, 75–77]. Estrogen increases expression of several key genes in the IGF signaling pathway including IGF-II [78], IGF-IR, and IRS1 [79], while decreasing expression of other genes, such as IGFBP-3 [80] and IGF-IIR [81]. Thus, the overall effect of estrogen on the IGF/insulin system is to positively regulate signaling.

Acquired resistance to anti-estrogen therapies is an important clinical problem. Since ER α may function together with IGF-IR signaling to enhance cell survival [82], targeting both pathways may have value. More recently, microarray data suggest that a gene signature co-regulated by IGF-I and estrogen correlated with poor prognosis in human breast cancer [67], which also implies dual inhibition of IGF-IR and ER pathway may be necessary in certain breast cancer subtypes.

However, the clinical trials using the combination therapy for patients with endocrine-resistant breast cancer have been disappointing [83]. In these trials, most women had already developed resistance to anti-ER therapies. In most of the reported trials, the anti-IGF-IR strategies were tested as the second or third line endocrine therapies.

We have recently shown that tamoxifen-resistant (TamR) cells and tumors lose expression of IGF-IR while maintaining IR expression. These findings suggest IGF-IR is a poor target in tamoxifen resistant tumors and IR might be an alternative option in treating TamR breast cancer [42]. Patients with tamoxifen resistant tumors also show loss of IGF-IR at the time of progression on tamoxifen [84]. Thus, endocrine resistant patients might not be the best candidates for anti-IGF-IR therapies. However, there are other ways to target IGF-IR and IR with small molecule TKIs, ligand neutralizing antibodies, or even growth hormone receptor antagonists, so the final word about the clinical relevance of these cross talk pathways is not yet settled.

Targeting IGF-IR and human epidermal growth factor receptor (EGFR)

About 30% of the patients with invasive breast cancers have amplification or overexpression of EGFR2 (HER2), which is associated with poor prognosis breast cancer [85–87]. Trastuzumab is a recombinant humanized monoclonal antibody that targets the extracellular domain of RTK HER2 [88]. Trastuzumab initially showed outstanding anti-tumor efficacy in patients with HER2 positive breast cancer in combination with cytotoxic chemotherapy. However, not all patients benefit from this regimen and in advanced breast cancer, resistance develops in about one year [89, 90]. IGF-IR and HER2 are reported to form heterodimers in trastuzumab-resistant breast cells [86]. Further, IGF-I was shown to activate HER2 signaling in trastuzumab-resistant breast cancer cells but not parental cells. Inhibition of IGF signaling resulted in restoration of trastuzumab sensitivity to resistant cells [86, 91, 92]. These preclinical findings led to several clinical trials aimed at evaluating the benefits of co-targeting IGF-IR and HER2 in trastuzumab-resistant breast cancer patients (NCT01479179, NCT00788333, NCT00684983, and NCT01111825).

Other combination therapy strategies

IGF/insulin signaling and chemotherapy—Combining either IGF-IR monoclonal antibodies or IGF-IR TKI could enhance doxorubicin drug efficacy [39, 93]. We demonstrated that giving cytotoxic chemotherapy first or concurrently with IGF-IR inhibitors resulted in a better tumor response. In contrast, IGF-IR prior to cytotoxic chemotherapy did not improve the benefits of doxorubicin and may represent an interference pathway between cytotoxic chemotherapy and IGF-IR inhibitors. These results suggest a combination of IGF-IR blockade and chemotherapy works in a sequencing-dependent fashion [39].

IGF/insulin system therapy and metformin—As noted above, IGF-IR blockade is predicted and proven to result in compensational upregulation of circulating IGFs and insulin. These effects may cause hyperinsulinemia and be clinically manifested as metabolic syndrome or frank type-2 diabetes [6, 43, 59, 94–96]. Therefore, combining insulin sensitizing drugs to decrease serum levels of insulin with metformin might be necessary to attenuate the metabolic effects of the anti-IGF-IR/IR drugs. The I-SPY2 trial of neoadjuvant breast cancer therapy will test the therapeutic value of combining ganitumab, metformin and paclitaxel. The metformin will help to manage any acquired insulin resistance induced by ganitumab [97]. Metformin also reduces reactive oxygen species in mitochondria, which potentially would be important to inhibit tumorigenesis independent of the effects on glucose metabolism [43, 98]. Thus metformin combined with IGF-IR blockades may not only attenuate the drug-induced hyperglycemia and hyperinsulinemia, but may also exhibit antitumor efficacy.

Future Directions

In order to maximize patient response to the emerging anti-IGF/insulin signaling therapies and accelerate developments of these antitumor drugs, the identification of therapeutic predictive biomarkers will need great attention.

The ‘figitumumab downfall’ raises an important question: what molecular attributes will likely be predictive of tumor dependence on IGF-IR? In these figitumumab clinical trials patients were not selected based upon any molecular markers. Microarray analysis has been used to determine sarcoma and neuroblastoma cell lines either sensitive or resistant to a TKI of IGF1R/IR, (BMS-536924). These data show that the mRNA levels of IGF-I and IGF-II highly correlated with cell response to BMS-536924 [99, 100]. Interestingly, the mRNA level of IGF1R did not meet the stringent statistical significance threshold to serve as an independent predictive biomarker, suggesting hybrid receptor mediated some of the IGF-I/IGF-II effects in these cells. Similarly, in a report addressing the sensitivity profile of another anti-IGF1R TKI, OSI-906 in colorectal cancer, the level of the phosphorylation status of IGF1R alone did not have positive correlation with cell sensitivity to OSI-906 [101]. These findings suggest a more complete definition of the IGF system signaling components is likely to assist in the clinical evaluation of anti-IGF1R therapies. Distinct receptor composition on the cell surface may influence cancer cell biology and predict sensitivity to anti-IGF1R therapy. Many studies have supported the important role of holo-IGF1R in cancer [9, 10, 102], yet the function of the IGF1R/IR hybrid receptor has not been well studied. The function of hybrid receptor signaling [18, 35] compared to holo-IGF1R and holo-IR receptors needs further characterization in order to serve as predictive biomarkers in breast cancer patients.

In addition, the IGF/insulin downstream signaling molecules may be important to predict a patient’s response to the anti-IGF1R therapy. As adaptor molecules are important components to transduce IGF1R signaling, the preferential expression of specific IRS isoforms in breast cancer cells has been linked to distinct signal transduction pathways and shown to mediate distinct biological behavior [103–106]. Our laboratory studied the gene expression profiles of a series of T47D variant cell lines with differential IRS adaptor protein expression to develop predictive IGF-I pathway biomarkers in breast cancer cells (submitted, Becker et al.). The results have suggested IGF-induced gene expression is IRS-dependent and highly conserved. In addition, this previous study has revealed several genes regulated specifically by either IRS-1 or IRS-2.

Besides cell surface composition of the receptors and preferential expressions of IRS adaptor proteins, other components of the IGF/insulin system may serve as predictive biomarkers for therapeutic outcomes and disease prognosis. Pre-treatment level of free IGF-I has been shown to predict NSCLC patients’ benefit from IGF-IR monoclonal antibody [107]. IGF-IR nuclear staining has been reported to associate with a better progression-free survival and overall survival in a small group of soft tissue sarcoma patients treated with IGF-IR antibody [108]. A recent report suggested IGFBP5 expression was associated with resistance to IGF-IR/IR targeted therapy. Furthermore, increased IGFBP5/IGFBP4 ratio is associated with decreased sensitivity to IGF-IR/IR inhibition and worse prognosis in breast cancer patients [109].

In sum, the IGF/insulin system is complex. Simply targeting one receptor may not be sufficient enough to completely inhibit tumor behavior. Additional preclinical data are needed to unravel the true clinical benefit of the anti-IGF/insulin targeted agents in breast cancer patients.

Conclusion

Although preclinical evidence provides strong rationale for clinically targeting IGF/insulin signaling, the withdrawal of figitumumab from phase III clinical trials raised significant concerns about the clinical utility of targeting IGF-IR with a monoclonal antibody. However, we still believe that IGF-IR antibodies can be clinically beneficial in a subset of breast cancer patients through the use of appropriate predictive biomarkers coupled with cautious monitoring of insulin levels during the therapy. Other drugs affecting IGF/insulin signaling such as TKIs, ligand neutralizers, and mTOR inhibitors show promise, most likely in combination with conventional and novel agents. A more insightful understanding of IGF/insulin system and its crosstalk with other critical signaling pathways in breast cancer cells is needed to optimize the targeting of the IGF/insulin system in breast cancer.

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Figure 1.

Schematic representation of the IGF/insulin system. In the extracellular environment, ligands IGF-I, IGF-II and insulin bind to distinct members of the IGF-IR and IR receptor family (as indicated by arrows). These transmembrane tetrameric receptors (three types of holo-receptors and three types of hybrid receptors) are composed of two extracellular α -subunits, which function as binding domains; and membrane-spanning β -subunits, which possess tyrosine kinase activity. The bioactivity of IGF-I and IGF-II are negatively influenced by IGF-BPs and IGF-IIR. Following the ligand binding and receptor activation, the phosphorylated adaptor proteins IRS and Shc provide a platform to initiate multiple downstream signaling pathways, namely PI3K/Akt and MAPK axis, ultimately influence tumor cell biology.