Published in final edited form as:
Cancer Metastasis Rev. 2014 September ; 33(0): 607–617. doi:10.1007/s10555-013-9482-0.

Insulin-like growth factor receptor-1 (IGF-IR) as a target for prostate cancer therapy

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Abstract

Prostate cancer is the most commonly diagnosed cancer in men and is the second leading cause of cancer-related deaths in men each year. Androgen-deprivation therapy is and has been the gold standard of care for advanced or metastatic prostate cancer for decades. While this treatment strategy initially shows benefit, eventually tumors recur as castration-resistant prostate cancer (CRPC) for which there are limited treatment options with only modest survival benefit. Upregulation of the insulin-like growth factor receptor type I (IGF-IR) signaling axis has been shown to drive the survival of prostate cancer cells in many studies. As many IGF-IR blockades have been developed, few have been tested pre-clinically and even fewer have entered clinical trials for prostate cancer therapy. In this review, we will update the most recent pre-clinical and clinical studies of IGF-IR therapy for prostate cancer. We will also discuss the challenges for IGF-IR targeted therapies to achieve clinical benefit for prostate cancer.

Keywords

IGF-IR; Prostate Cancer; Metastasis; Mechanisms; Therapy

1 Introduction

Prostate cancer is still the most commonly diagnosed cancer in men and remains as the second leading cause of cancer-related deaths in men each year, with an estimate of over 29,000 deaths in 2013 (1). Androgen-deprivation therapy, either medical or surgical, remains the backbone for advanced or metastatic prostate cancer treatment. While this treatment strategy initially has benefit, eventually tumors become resistant to castration, necessitating additional therapeutic interventions. Improved understanding of mechanisms driving castration-resistance has led to development of multiple new therapies and improved

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outcomes. However, survival is still limited, and targeting of other dysregulated signaling pathways that promote prostate cancer cell proliferation, invasion, and survival are being explored. This review will focus on one of these pathways, specifically type I insulin-like growth factor receptor (IGF-IR) signaling and its role in prostate cancer, as well as early pre-clinical and clinical studies to inhibit this pathway with goal of anti-tumor effect.

IGF-IR activation and signaling are mainly stimulated by binding to its ligands. IGF-IR displays a hierarchical binding preference to its ligands, IGF-I > IGF-II > Insulin (2, 3). IGF-IR signaling is essential for development, survival, and proliferation of many cell types (4, 5). IGF-IR is expressed in the entire body and has important roles in cell cycle, anaerobic breathing, growth (in children), and aging (4–7). Deregulation of IGF-IR signaling, including dysregulation in IGF-IR expression itself and the ligands (IGF), has been suggested to significantly impact cancer development and progression (8). In addition, IGF-IR signaling is known to be a critical determinant of response to cancer therapy, such as radiation and chemotherapy (9–11). Increased serum levels of ligand IGF-I have been associated with increased risk and mortality of many cancer types (8, 12, 13). The expression and prognostic value of IGF-IR in malignant progression, however, has been controversial and seems to be cancer type-dependent. However, in most cancer types, such as colorectal, gastric, endometrial, and breast cancers, overexpression of IGF-IR has been associated with an aggressive phenotype, tumor progression and therapy-resistance and poor clinical outcome. In particular, targeting IGF-IR as a therapy has been extensively studied and previously reviewed in breast cancer (14).

Data from epidemiological and clinical pathological studies have generally agreed that IGF-IR signaling is elevated in prostate cancer in comparison to benign prostate tissue (15–19). However, IGF-IR expression throughout prostate cancer progression, especially with metastasis, is controversial. Analysis of clinical specimens show elevated IGF-IR expression in primary prostate cancer versus benign prostate epithelium, and the trend is persistent up through metastatic diseases (20). A majority of human prostate xenograft studies also show increased IGF-IR expression in metastatic and AI diseases over primary tumors (21, 22). Other studies with different prostate cancer models have shown conflicting results that decrease in IGF-IR expression is necessarily for progression to AI and metastatic diseases (23, 24).

Paradoxically, reports on the individual value of IGF-IR expression and serum levels of IGF in relation to prostate cancer etiology and progression are inconsistent and somewhat controversial. A large amount of clinical studies resulting from prospective and case-controlled investigation suggest a significant correlation of elevated serum levels of IGF-I with increased prostate cancer risk (13, 25–32). On the contrary, a number of other studies did not support this correlation (33, 34). A more recent large nested case-control study with 630 cases of prostate cancer and control subjects concluded that high serum levels of IGF-I only had a trend of increased risk of prostate cancer, but was not statistically significant. Instead, the study found a significant correlation of high serum IGF-I with risk of more progressive diseases (35). More provocatively, transgenic mice with prostate-specific deletion of IGF-IR in the context of compromised function of tumor suppressor gene p53 developed more aggressive prostate carcinoma than wild-type counterparts (36).

These controversial reports in regards to IGF-IR expression and relationship with prostate cancer risk and progression may arise from the large amount of heterogeneity within prostate cancers, sampling bias, methods of evaluation, and/or the unique experimental system being studied. Also, an individual evaluation of IGF-IR expression or serum levels of IGF may not be sufficient to assess the association with cancer risk or progression. A more comprehensive evaluation of IGF-IR signaling pathways is needed. Nevertheless, these paradoxical observations suggest that subject-based intrinsic dysregulation of IGF-IR expression may be necessary for development of more aggressive phenotype of prostate cancer after initial transformation. Inevitably, this complexity of IGF-IR expression and signaling during prostate cancer disease progression emphasizes the dilemma and potential difficulty in effectively targeting IGF-IR for prostate cancer therapy in clinical practice. In this review, we will focus on the current understanding of IGF-IR signaling in prostate cancer and potential complexity in clinical targeting. We will also summarize recent and ongoing pre-clinical and clinical studies in targeting IGF-IR for prostate cancer therapy and strengthen the concept that co-targeting IGF-IR along with other important pathologic processes may achieve maximum therapeutic benefit for prostate cancer. Key questions to yet be answered in effectively targeting IGF-IR for prostate cancer therapy will also be addressed.

2 IGF-IR structure and signaling

The IGF-IR is a tetrameric transmembrane receptor tyrosine kinase composed of two alpha and two beta subunits linked by disulfide bond (Fig 1). The alpha subunit is extracellular and responsible for ligand binding, whereas the beta subunit composed of the transmembrane and cytoplasmic region is critical for intracellular signaling. The fully functional IGF-IR can be activated by three ligands, IGF-I, IGF-II, and insulin. Among which, IGF-I has the highest affinity and has been mostly studied in association with cancer risk and progression. Insulin has the lowest affinity for IGF-IR and has not been extensively studies in association with cancer progression (6, 37, 38). IGF-IR has 70% homology to the insulin receptor (IR), with which it shares some of the signaling pathways (38). Upon ligand binding to the alpha subunit, the intrinsic tyrosine kinase activity autophosphorylates tyrosine residues in the beta subunit and thus initiates a cascade of down-stream signaling events to activate IRS-1/PI-3 Kinase and PKB/Grb2/sos/Ras/MapK pathways (6). Activation of these pathways has been shown to be important in cell proliferation, survival, and transformation. It has also been documented as a mechanism in cancer metastasis and resistance to therapy (9–11, 39, 40).

The beta-subunit is critical for full activation of IGF-IR. The structure-functional relation of IGF-IR beta subunit has been extensively studies by Beserga's group using a variety of beta-subunit mutant receptors (Fig 2). A mutation in tyrosine 950 (Y950) or the C-terminus of the IGF-IR (roughly the last 100 amino-acids) was shown to be dispensable for mitogenesis and protection from apoptosis, but is required for differentiation and the transformation of cells *in vitro* and *in vivo* (41, 42). A mutation at the cytoplasmic lysine 1003 (the ATP-binding site) resulted in complete loss of receptor function (41). A triple mutation in the tyrosine kinase domain (Y1131, Y1135 and Y1136) resulted in defective receptor, which failed to transmit a mitogenic signal (43, 44). Based on the understanding of the functional

consequences of IGF-IR, targeting the IGF-IR kinase domain has been proposed for cancer therapy (6).

3 Regulation of IGF-IR signaling in prostate cancers

The molecular mechanism of how IGF-IR signaling is differentially regulated during prostate cancer development and progression is not well defined and remains to be an active investigation focus. To date studies are largely focusing on regulation of IGF-IR expression in prostate cancer cells at the transcriptional level although sporadic studies have reported the regulation at a post-transcriptional level. Similar to studies in many other cancer types, regulation of IGF-IR transcripts in prostate cancer cells has been reported to be mainly mediated by defective tumor suppressor genes, such as BRCA1 and transcriptional factor Kruppel-like factor 6 (KLF6) (45–47), epigenetic changes such as methylation of master regulators (48), or IGF-IR autoregulation through translocating to the nucleus (49). In this review, we will focus on tumor-suppressor-mediated regulation. We will also summarize studies on androgen-mediated regulation of IGF-IR signaling in prostate cancer.

The promoter region of IGF-IR lacks the transcriptional regulatory elements TATA or CAAT box (50, 51). Like many genes that lack these regulatory elements, the proximal 5′-flanking region of the IGF-IR promoter region is highly GC-rich and contains multiple binding sites for zinc finger transcriptional factors (52). KLF6, a ubiquitous transcriptional factor and a tumor suppressor gene, has been shown to transactivate IGF-IR gene transcription through interaction with the zinc finger protein Sp1 and tumor suppressor p53 (45). The KLF6 gene is located at the chromosomal region 10p that is deleted in most sporadic prostate cancers (53). A large percentage of prostate tumors displayed loss of heterozygosity (LOH) at the KLF6 locus and mutations in the KLF6 alleles (54). Forced expression of tumor-associated mutated KLF6 led to the defect in its ability to transactivate IGF-IR transcription (55). Liu et al. discovered spliced variants of KLF6 in human prostate tumors using microdissection and array analyses and further demonstrated that androgen-dependent LnCaP cells with forced expression of KLF6 loss-of-function splicing variants displayed a survival advantage in the culture when androgen was withdrawn (55). Thus, the loss-of-function mutation of KLF6 has been implicated in prostate cancer progression to androgen-independence. Given the evidence that decrease in IGF-IR expression is associated with development of more aggressive phenotype of prostate cancer, these studies suggest that dysregulation of IGF-IR expression through KLF6 loss-of-function may be an intrinsic mechanism for prostate cancer progression to hormone independence.

In prostate cancer cells, the tumor suppressor BRCA1 is shown to interact with androgen receptor (AR) and regulate IGF-IR expression in an AR-dependent fashion (51). BRCA1 was originally identified as the familial breast and ovarian cancer susceptibility gene-1 that encodes a 220kDa phosphorylated transcriptional factor with tumor suppressor activity (56). BRCA1 mutation was initially found to be associated with the risk of breast and ovarian cancer at very young age and with the etiology of sporadic type of cancers (56–58). BRCA1 is normally targeted to the nucleus and participates in regulation of transcription and DNA damage repair pathways (19, 59). BRCA1 is expressed at a low level in normal prostate epithelium and is upregulated in prostate carcinoma (51). In AR-negative prostate cancer

cell lines, an inverse correlation of BRCA1 expression and IGF-IR expression has been found. In subsequent studies, BRCA1 can suppress IGF-IR promoter activity in AR-negative M12 prostate cancer cell lines. In AR-positive prostate cancer LuCaP and C4-2 cell lines, BRCA1 has been shown to enhance AR transcriptional activity and enhance IGF-IR expression at the transcriptional level (46).

Beyond these commonly recognized regulatory mechanisms, in prostate cancers, androgen has also been consistently shown to upregulate IGF-IR expression although the mechanisms are somewhat controversial by different studies, potentially due to the discrepancy in different cell lines. Pandini et al showed that engagement of AR by androgen upregulates IGF-IR expression in AR^+ LuCap cells and PC-3 cells overexpressing AR (60). They also showed AR mutants that lost DNA binding and transcriptional activity were still able to upregulate IGF-IR expression in HEK293 kidney cells in response to androgen. Based on these observations, Pandini et al concluded that AR regulates IGF-IR expression through non-genomic pathways. Recently, Schayek et al. (2010) consistently showed that re-expression of wild-type androgen-receptor (AR) in an AR-negative metastatic prostate cancer cell line M12 led to significant increase in IGF-IR expression (61). However, when they expressed two AR mutants that were compromised in the ability to bind to androgens or co-regulators, no effect on IGF-IR expression was seen. Schayek et al. thus concluded that androgens regulate IGF-IR expression through a genomic pathway. To further support this conclusion, they further showed that AR can directly bind to IGF-IR promoter region by CHIP assay.

4 IGF-IR signaling in Prostate Cancer Progression to Androgen-independence

The vast majority of patients with recurrent prostate cancer are responsive to standard androgen deprivation therapy. However, the disease eventually progresses to castration-resistance. Multiple mechanisms have been proposed to convey the progression (62, 63), including; 1) epigenetic mutations of androgen receptor to allow androgen-independent activation; 2) alternative splicing of AR to delete ligand-binding domain thus and allow constitutive activation of AR; 3) transactivation of AR by growth factors and cytokines; 4) sustained intratumoral androgen level through intracrine steroidogenic pathways within the prostate tumor microenvironment (64, 65). IGF-IR signaling to activate PI3K/AKT pathway has been proposed to be one of the mechanisms to transactivate AR in the absence of androgen and progression to AI diseases (66–69). Increased AKT activity has been shown to be associated with prostate cancer progression to castration-resistance through multiple pathways (70–74), including direct phosphorylation of AR, activation of wnt/GSK3 pathway, activation of NF-kB pathway, and forkhead box-O (FOXO) family of transcriptional factors. These studies suggest that co-targeting IGF-IR pathways and androgen deprivation may offer synergistic therapeutic benefits for prostate cancer.

5 IGF-IR signaling in prostate cancer metastasis

The mechanism of IGF-IR signaling in mediating prostate cancer metastasis is a complex and largely site-specific. In addition, prostate cancer cells can achieve metastatic potential

through IGF-IR signaling to modify cell adhesion and mobility, independent of tumor cell growth potential (75). These complexities must be taken into when considering evaluation of IGF-IR targeting therapy for metastatic prostate cancer.

IGF-IR was shown to regulate cancer lymphatic metastasis through facilitating angiogenesis and lymphangiogenesis, by induction of VEGF-C expression (76). This has been confirmed with high level of VEGF-C detected in prostate cancer patients with lymph node metastasis (77). Li *et al* further showed that androgen-deprivation can upregulate VEGF-C expression through down-regulation of the IGF-IR pathway and activate the forkhead transcriptional factor FOXO-1 (74). In bone metastasis, bone-derived IGF-I can bridge the crosstalk between bone and metastasized cancer cells via activation of the IGF-IR/Akt/NF-κB pathway (78). Therefore, disruption of IGF-IR and NK-kB pathways may represent a promising therapeutic intervention for bone metastasis, whereas co-targeting IGF-IR and VEGF may be more effective to treat lymphatic metastasis. In liver metastasis, IGF-IR-mediated mechanism of cancer cell survival is critical for metastatic colonization (79). Normal liver cells do not express IGF-IR but secret large amount of IGF-I. When circulating cancer cells were drained to the liver, the IGF-I rich environment allows the colonization and growth of circulating tumor cells to establish metastasis. Thus, the mechanism of liver metastasis has no association with overexpression of IGF-IR on primary tumors and is more related to a hospitable liver microenvironment. In this instance, specific targeting IGF-IR signaling pathways may effectively inhibit metastatic tumor growth in the liver.

Transactivation of IGF-IR also plays a significant role in mediating inflammation-associated prostate cancer metastasis. We recently showed that chronic exposure of benign non-tumorigenic prostate epithelium cell line p69 to exogenous IL-6 can induce epithelium-mesenchymal transition and facilitate metastatic potential through transactivation of IGF-IR signaling and IL-6 autocrine pathways (80). Blocking IGF-IR signaling with an antibody IMC-A12 (cixutumumab) abolishes the effect of IL-6 and abrogates IL-6 signaling in these cells. Whether inhibition of IGF-IR can suppress IL-6-mediated metastasis in vivo and what-specific IL-6 signaling pathways could be co-targeted to suppress inflammation-mediated metastasis would be logical areas of exploration.

6 Pre-clinical studies of targeting IGF-IR for cancer therapy

IGF-IR inhibitory reagents, including a large variety of human monoclonal antibodies and few small molecules, have been developed for potential cancer therapy with distinct targeting mechanisms: target IGF-IR ligands, blocking of ligand binding, inhibits IGF-IR tyrosine kinase activity, or down regulation of IGF-IR expression through receptor internalization and degradation. These reagents have been tested in multiple pre-clinical cancer models and some are in clinical trial for multiple cancer types (81–83). Among these reagents, only few have been tested therapeutically with pre-clinical human prostate cancer models (Table 1). All the studies suggested that monotherapy with an IGF-IR antagonist can only achieve limited effect and that combined therapy of an IGF-IR antagonist with androgen deprivation therapy or cytotoxic chemotherapeutics deliver more desirable outcomes. However, all of these studies were limited to evaluation of primary tumor growth.

Cixutumumab (formerly IMC-A12), a fully human IgG1 monoclonal antibody, was shown to induce internalization of IGF-IR (84, 85). Cixutumumab was tested extensively for prostate cancer therapy with preclinical androgen-dependent (AD), androgen-independent (AI), and osseous human prostate cancer models (86–88). Alone, cixutumumab can induce cell cycle arrest of both AD and AI tumor cells and the effect of castration can be enhanced by delay of progression to AI tumors (86, 88). Cixutumumab can also enhance the effect of docetaxel as combined therapy through enhanced negative regulation of genes associated with cell cycle progression, survival and therapeutic resistance (87). Goel *et al* recently showed that the VEGF/VEGF receptor neuropilin-2 (NRP2) signaling can repress the expression of IGF-IR at transcriptional level and thus IGF-IR signaling in prostate cancer cells (89). Combined therapy of co-targeting NRP2 with shRNA and IGF-IR with cixutumumab resulted in synergistic effect and complete inhibition of PC-3 tumor growth *in vivo*, whereas mono-therapy only showed minimal or moderate effect (89). Because of the compensatory relation between NRP2 and IGF-IR expression, NRP2 is proposed to be a robust biomarker for predicting responses to IGF-IR therapy (89).

Ganitumab (formerly AMG 479), a fully human antibody that inhibits binding of IGF-I and IGF-II to IGF-IR (90), is a newly developed IGF-IR blockade that has been tested for prostate cancer therapy in preclinical models. Ganitumab was shown to inhibit ligand-induced phosphorylation of IGF-IR and the downstream effector AKT resulting in reduced proliferation of multiple androgen-dependent and castration-resistant human prostate cancer cell lines in vitro (91). It was shown that ganitumab treatment alone retarded androgen-dependent VCaP prostate tumor growth and blocked the growth of castration-resistant VCaP xenografts for over 11.5 weeks of treatment. When combined with castration, ganitumab showed a potent therapeutic effect and achieved a long period suppression of VCaP xenograft growth (91). Ganitumab alone did not have appreciable therapeutic effect in established castration-resistant CWR-22Rv1 xenograft tumor. However, very recent study by Galet et al showed that when combined with calorie restricted diet, Ganitumab showed significant inhibition of tumor growth of CWR-22Rv1 xenografts (92).

To date the only small molecule targeting human IGF-IR for prostate cancer therapy was ATL1101, a 2′-MOE-modified antisense oligonucleotide. *In vitro* study showed that ATL1101 suppressed proliferation and increased apoptosis in PC-3 and LNCaP cells in androgen-deprived conditions. ATL1101 also showed in vivo suppression of PC-3 tumor growth and delaying castration-resistant progression of LNCaP xenografts (93).

7 Perspectives and challenges in clinical translation of targeting IGF-IR

Knowledge surrounding IGF-IR signaling in prostate cancer cell survival and the inhibitory effect of IGF-IR blocking antibodies or antagonists on the growth of human prostate cancer xenografts in pre-clinical animal models imply that IGF-IR may be an effective target for prostate cancer treatment, in particular in combination with other current standard care therapeutics. However, translation into clinical application for effectively treating prostate cancer patients may face various challenges in selection of optimal subject as well as evaluating clinical outcomes. First, as we have mentioned earlier in the introduction, reports to-date pertaining whether IGF-IR expression is persistent during prostate cancer

progression are inconsistent and controversial to some extent. This ambiguity raises the question whether targeting IGF-IR can only be selectively effective at certain disease states. If reducing IGF-IR signaling is necessary for prostate cancer progression to metastasis as have been shown by some studies (23, 24, 36), targeting IGF-IR at the inappropriate stage may result in an unfavorable clinical outcome. Second, as activation of IGF-IR is ligand dependent, valid serological or tissue markers, such as serum levels of IGF or tissue levels of activation of IGF-IR pathway, would be beneficial to distinguish potential responders versus non-responders. This issue has not been sufficiently addressed in pre-clinical studies to date. Third, as IGF-IR signaling regulates cancer cell metastasis through modulating cell mobility, independent of cell growth (75–77), evaluating whether inhibition of IGF-IR indeed withholds or delays disease progression to metastasis is clinically difficult, as prior studies in this prostate cancer disease state have necessitated extremely large studies with many patient screen failures with modest to no success (94–98). These critical challenges likely need to be resolved to achieve positive clinical outcomes with IGF-IR targeting therapy; we suggest better understanding of IGF-IR expression through metastatic biopsy studies and development/refinement of blood-based biomarkers for patient selection.

8 Clinical experience with IGF-IR inhibition for cancer therapy

Although there are many approaches to inhibition of IGF-IR, the most frequently tested approach in the clinic has been the utilization of monoclonal antibodies directed towards the external binding domain of the receptor. Although, multiple monoclonal antibodies have entered the clinical trial domain (see Table 2), only two have seen extensive testing in prostate cancer.

Cixutumumab was initially tested in a phase 2 monotherapy trial where it was dosed intravenously at 10 mg/kg every 2 weeks in men with metastatic, asymptomatic castration-resistant prostate cancer (CRPC) resulted in disease stabilization for ≥6 months in 9 of 31 (29%) patients with hyperglycemia noted in 6 (19.4%), none of which required treatment discontinuation (99). In a 10 patient dosing-schedule expansion, patients were treated with 20 mg/kg every 3 weeks, with 3 (30%) experiencing disease stabilization for ≥6 months (100). Since these were non-randomized trials, it is difficult to know the true antitumor efficacy of cixutumumab versus patient selection in the castration-resistant setting.

A targeted approach to maximize selection of patients with tumor biology driven by the IGF-IR axis in CRPC may be relevant. An ongoing phase 1–2 trial for metastatic CRPC combining cixutumumab with temsirolimus, a mTOR inhibitor, aims to address the paradoxical activation of IGF/AKT signaling seen with inhibition of PI3K/AKT/mTOR signaling (101). Since single agent mTOR inhibition has not been incredibly successful against prostate cancer, the approach to inhibit IGF-IR in combination could address a potential resistance mechanism.

With pre-clinical data supporting both apoptosis and G1 cell arrest in castration-sensitive C42B xenografts and only G2 arrest in castration-resistant murine models, it also makes sense to shift the treatment paradigm with IGF-IR inhibitors to a castration-sensitive disease state (88). In a neoadjuvant trial with cixutumumab combined with goserelin and

bicalutamide, serum levels of growth hormone, IGF-1, IGF-II, IGFBP-3, c-peptide and insulin increased while IGFBP-1 levels decreased significantly, without change in glucose when compared to control samples from patients in a concurrent clinical trial of neoadjuvant ADT alone (102). This showed pharmacodynamic effect, although no clear correlation could be drawn with PSA levels. A recently accrued large randomized, phase 2 trial (SWOG 0925) has treated over 200 men with newly diagnosed castration-sensitive metastatic prostate cancer either with combined ADT and cixutumumab or with combined ADT alone (NCT01120236). The primary endpoint will be evaluation of the previously described 7-month absolute PSA value as a surrogate for survival (103). Since this is the only randomized trial with IGF-IR inhibitors, we may be able to gain a sense of clinically-relevant efficacy from this cooperative group trial, especially since cixutumumab is administered in combination with ADT in the newly metastatic, previously untreated disease state. Should this trial show an improvement in the undetectable PSA endpoint at 7 months in the cixutumumab treated patients, an additional, large randomized phase 3 trial with a survival endpoint will likely be necessary for IGF-IR targeting therapy to achieve regulatory approval. However, should this trial ultimately be negative, multiple blood-based biomarkers are being evaluated to include circulating tumor cells, microRNA profiles and insulin, IGF-1, free IGF-1, growth hormone and IGFBP-3; these biomarkers may shed light on patient populations apt to have improved outcomes with cixutumumab.

Figitumumab is a highly specific IgG2 monoclonal antibody specific to IGF-IR that may have additional efficacy when added to docetaxel in men with mCRPC; however, it is difficult to ascertain the additional efficacy of IGF-IR inhibition in an open label, phase Ib dose escalation trial (104). Yet, in a small 14 patient phase II trial of preoperative figitumumab in the castration-sensitive setting, not only was pharmacodynamic activity shown by decrease in IGF-IR immunohistochemistry expression, but androgen receptor expression was also concurrently decreased (105). Most impressive is the fact that treatment with single-agent figitumumab induced ≥25% and ≥50% PSA declines from baseline in 94% and 31% of patients, respectively. This trial not only proves pharmacodynamic effect of figitumumab inhibition of IGF-IR in castration-sensitive prostate cancer tissue, but also highlights effect on clinically meaningful endpoints.

In addition to the above monoclonal antibodies, there are many other agents undergoing clinical trial testing that inhibit IGF-IR. Multiple other mechanistic approaches have involved small molecule inhibition of IGF-IR, dual monoclonal antibody inhibition of IGF-IR with the insulin receptor and IGF ligand neutralization. The agents and specific diseases they are being tested in are listed in Table 2.

9 Conclusions

The landscape for prostate cancer is changing quickly with the introduction of multiple new agents that prolong survival, all with unique mechanisms of action. However, resistance eventually develops and our understanding of the mechanisms driving resistance is limited. Additionally, most new agents are being used in patients with very advanced castration-resistant disease, and we will likely have to better understand biologically rationale

combinations to effect overall cure rates. Therefore, new agents that address alternative pathways are critical.

IGF-IR is one of the pathways with accumulating epidemiologic, pre-clinical and early clinical evidence to support this approach. Although results in the castration-resistant setting have been modest at best, pre-clinical evidence offers more hope in an earlier setting when the disease is still castration-sensitive, and clinical trials are ongoing to confirm pre-clinical findings. Our assessment, however, is that the approach to IGF-IR inhibition is probably best achieved in combination, either early with the initiation of ADT or perhaps with more extensive study with cytotoxic chemotherapy. However, whenever combination therapy is attempted, it is difficult to recognize clear efficacy in a single-arm trial without a comparator. For that reason, results from the fully-accrued SWOG 0925 trial will be critical, since it will provide randomized data from a castration-sensitive patient population and will be accompanied by many biomarker studies. We recommend only proceeding in the future with IGF-IR-targeted therapies in combination with rational agents in randomized trials supported by clear pre-clinical evidence of biologic synergism or at least additive effect. These future trials should be bolstered with supportive tissue and blood-based biomarkers to aid interpretation of overall result and inform on likely biologic heterogeneity present in regards to the IGF-IR axis in patients with prostate cancer.

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10 Key unanswered questions

- The controversial role of IGF-IR expression and signaling in prostate cancer progression is needed to understand the true relationship with IGF-IR.
- Better understanding of IGF-IR regulation is necessary to understand potential other targets or co-targets to affect IGF-IR activity.
- What is the best and most clinically meaningful approach to inhibit IGF-IR?
- What is the best agent to combine IGF-IR inhibition with to induce the greatest clinical activity?
- Do pre-clinical models of IGF-IR inhibition predict what we will see in human clinical trials of analogous settings?
- What are valid biomarkers that might predict clinical response to IGF-IR inhibition?

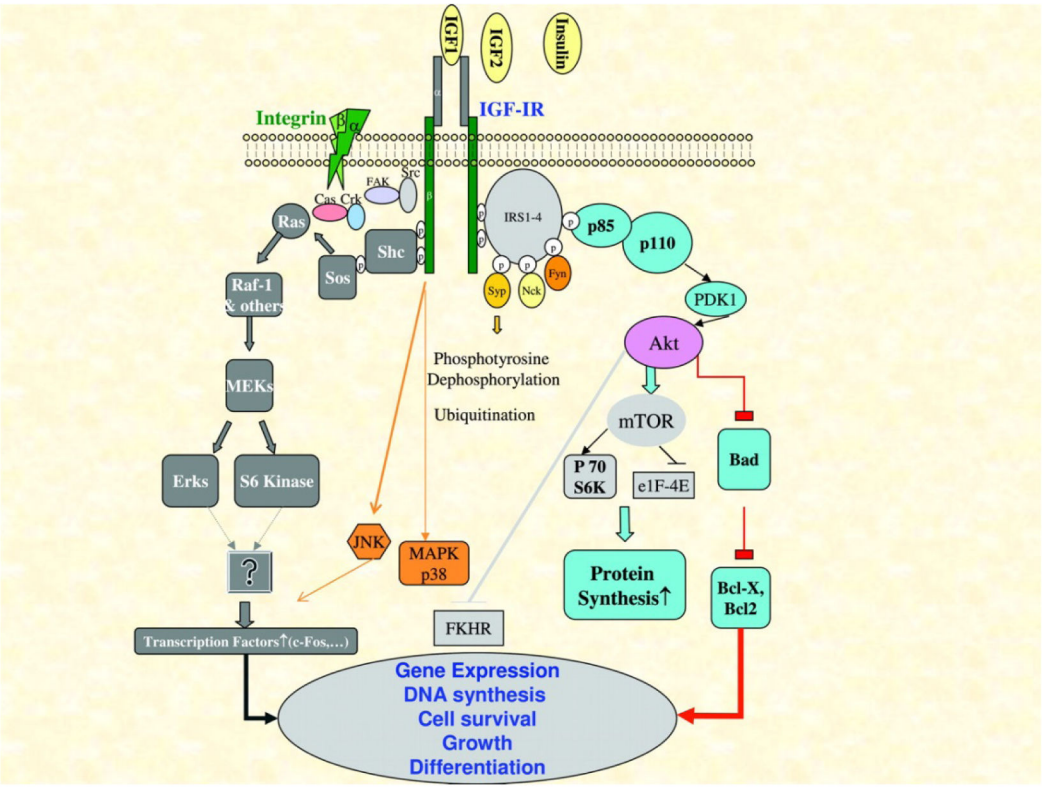

Figure 1.

IGF-IR signal transduction cascade upon ligand activation. A schematic representation of the major signaling pathways and the biological out resulted from IGF-IR activation. [Adopted from Samani A A et al. Endocrine Reviews 2007;28: 20–47.]

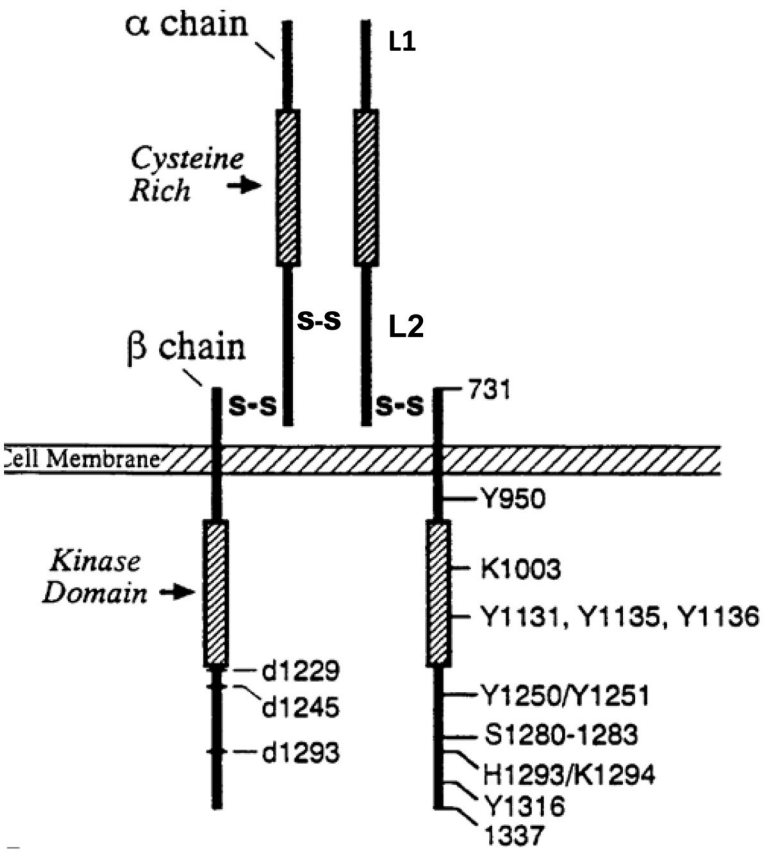

Figure 2.

Structure and Function of IGF-IR. The IGF-IR ectodomain contains two homologous domains (L1 and L2), separated by a Cys-rich region (Cys152 to Cys298) containing 22 cysteine residues. Intracellularly, each IGF-IR monomer contains a tyrosine kinase catalytic domain (residues 973–1229) flanked by two regulatory regions: a juxtamembrane region, residues 930–972, and the C-tail, residues 1230–1337 that contain the phosphotyrosine binding sites for signaling molecules.

Table 1

Preclinical Targeting IGF-IR signaling in Prostate Cancer

Antagonist	Property	Model	Therapy Effect	Ref
IMC-A12 (*Cixutumumab)*	Full human mAb induce IGF-IR internalization	LuCaP35-AD and LuCaP35v-AI	Inhibits AD and AI tumor growth by inducing cell cycle arrest Enhance castration effect on AD tumor growth Combined therapy with Docetaxel enhanced treatment effect on AI LuCaP35V and LuCaP 23.1 in comparison to monotherapy	(86–88)
AMG479 (Genitumab)	Full human mAb, Inhibits IGF binds to IGF-IR	VCaP and CWR22Rv1	Treatment alone retard VCaP growth with enhanced therapeutic effect when combined with castration. No effect on AI CWR- 22RV1	(91, 92)
ATL 1101	Antisense oligonucleotide, suppress IGF-IR expression	LNCaP and PC-3	Monotherapy suppress PC-3 tumor growth and delays LNCaP progression to CRPC	(93)

Table 2

Agents targeting IGF-IR in clinical trials (derived from clinicaltrials.gov on June 20, 2013)

Drug	Mechanism	Phase	Malignancies
Cixutumumab (IMC- A12)	IgG1 monoclonal antibody	II	Prostate, breast, non-small cell lung, neuroendocrine, mesothelioma, head & neck squamous, esophageal, colon, hepatocellular, thymic, sarcoma, adrenocorticol
Figitumumab (CP-751,871)	IgG2 monoclonal antibody	II	Prostate, breast, non-small cell lung, small cell lung, colon, myeloma
Ganitumab (AMG 479)	IgG1 monoclonal antibody	II	Breast, non-small cell lung, small cell lung, colon, pancreatic, PNET/carcinoid, ovarian, Ewing's sarcoma
Dalotuzumab (MK-0646)	Monoclonal antibody	II	Breast, non-small cell lung, small cell lung, colon, NET, myeloma
RG1507	Monoclonal antibody	II	Breast, non-small cell lung, sarcoma
AVE 1642	Monoclonal antibody	I	Breast, hepatocellular, myeloma
Linsitinib (OSI 906)	Monoclonal antibody with dual IGF-IR and insulin receptor inhibition	III	Prostate, non-small cell lung, small cell lung, head & neck squamous, colon, hepatocellular, pancreatic, myeloma, adrenocorticol
Picropodophyllin (AXL 1717)	Small molecule	II	Non-small cell lung, astrocytoma
BI 836845	IGF ligand neutralizing antibody	I	Non-specific solid tumors