Type I Insulin-like Growth Factor Receptor as a Therapeutic Target in Cancer

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Abstract

Data from experimental model systems and population studies have implicated type I insulin-like growth factor receptor (IGF1R) signaling in many different human cancers. Drugs to disrupt IGF1R function have been developed and are now entering clinical trial. This brief review will identify key areas to consider as these clinical trials move forward. (Cancer Res 2005; 65(22): 10123-7)

Any new therapy based on targeting a specific molecule must answer three questions: why should we believe that the molecule is a target, how should we target this molecule, and what should we expect from target inhibition?

Why Target Type I Insulin-like Growth Factor Receptor?

The first identified target for cancer therapy was the estrogen receptor-α (ERα). In 1896, Beatson recognized the important link between normal mammary gland development and breast cancer growth (1). Although Beatson did not appreciate the central role of ERα in mediating this response, the idea that factors regulating normal growth and development could also serve as a cancer target was postulated.

Type I insulin-like growth factor receptor (IGF1R) is clearly involved in normal growth and development. During puberty, serum IGF-I levels increase as pituitary-derived growth hormone increases liver *igf-1* expression. Children with mutation in *igf-1* and *igf1r* have been described. These children share common features and have poor *in utero* and postnatal growth, microcephaly, and neurodevelopmental delay (2, 3). In animal model systems, disruption of IGF1R signaling results in reduced breast and prostate gland growth, implying that IGF1R mediates normal organ development (4, 5).

It has also been recognized that some cancers have abnormal expression or function of specific molecules. For example, amplification of the HER-2 oncogene in breast cancer led to the development of trastuzumab as a specific therapy directed against the target (6, 7). Although *igf1r* causes transformation *in vitro* (8), amplification of *igf1r* in human cancer is uncommon (9), and mutation has not been reported. Despite a lack of evidence that *igf1r* functions as an oncogene, population studies suggest that factors associated with IGF1R function, such as height and diet, elevate breast cancer risk (10, 11). Moreover, elevated levels of IGF-I are associated with an increased risk of developing breast, prostate, and colon cancer (12–14). Thus, *igf1r* may not be an oncogene, but findings from model systems suggest that IGF1R must function normally in order for malignant transformation to occur (15).

In the transformed cell, there are abundant data showing that IGF1R regulates cancer cell proliferation, survival, and metastasis. Expression of IGF-I, IGF-II, and all of the IGF binding proteins have been documented in primary human cancer, suggesting that tumor biology may be regulated by this system (reviewed in ref. 16). Taken together, these findings support a role for IGF1R in malignant transformation and progression. In many ways, targeting of IGF1R is similar to targeting of ERα in breast cancer. Although *erα* is not an oncogene, it is involved in normal and malignant breast epithelial biology and represents an outstanding target for cancer prevention and treatment.

How Should We Target Type I Insulin-like Growth Factor Receptor?

The IGF1R is highly homologous to insulin receptor, and this has important implications into the targeting of this receptor system (17, 18). Experimental model systems have shown that insulin receptor stimulates mitogenic signaling in cancer cells (19). Because both insulin and IGF-II (20, 21) may activate insulin receptor signaling, inhibition of IGF1R alone may be insufficient. Both insulin receptor and IGF1R require ligand stimulation for activation. Unlike members of the epidermal growth factor receptor family, overexpression alone is insufficient to trigger biochemical activation of the receptor. Thus, inhibition of ligand-receptor interactions could be a strategy to disrupt IGF1R action. The tyrosine kinase domains of IGF1R and insulin receptor are highly homologous. Development of a specific IGF1R inhibitor might be necessary, as type II diabetes, a disease of disrupted insulin receptor signaling, is a major health problem. However, if insulin receptor has a major role in regulating insulin or IGF-II action in cancer cells, then a highly specific IGF1R antagonist may be insufficient to disrupt insulin receptor action in cancer cells.

IGF1R signaling could be disrupted at many levels as shown in Fig. 1. Because serum IGF-I levels are regulated by growth hormone, disruption of the growth hormone/IGF-I axis could be a strategy to disrupt IGF1R signaling by removing the ligand. Antagonists of growth hormone–releasing hormone (22–24) or growth hormone (25) could be used to lower serum IGF-I levels. Interestingly, these drugs may directly affect tumor cells independently of their effects on serum IGF-I levels. It is notable that the growth hormone antagonist pegvisomant is already approved for treatment (26) of growth hormone excess (acromegaly), and it would not be difficult to test this drug as a cancer therapy.

However, methods to lower growth hormone–stimulated IGF-I serum levels do not account for paracrine expression of IGF-I nor do they address serum IGF-II. To address this concern, Goya et al. used an IGF-I- and IGF-II-neutralizing antibody to inhibit the growth of prostate cancer cells in human bone (27). By implanting human

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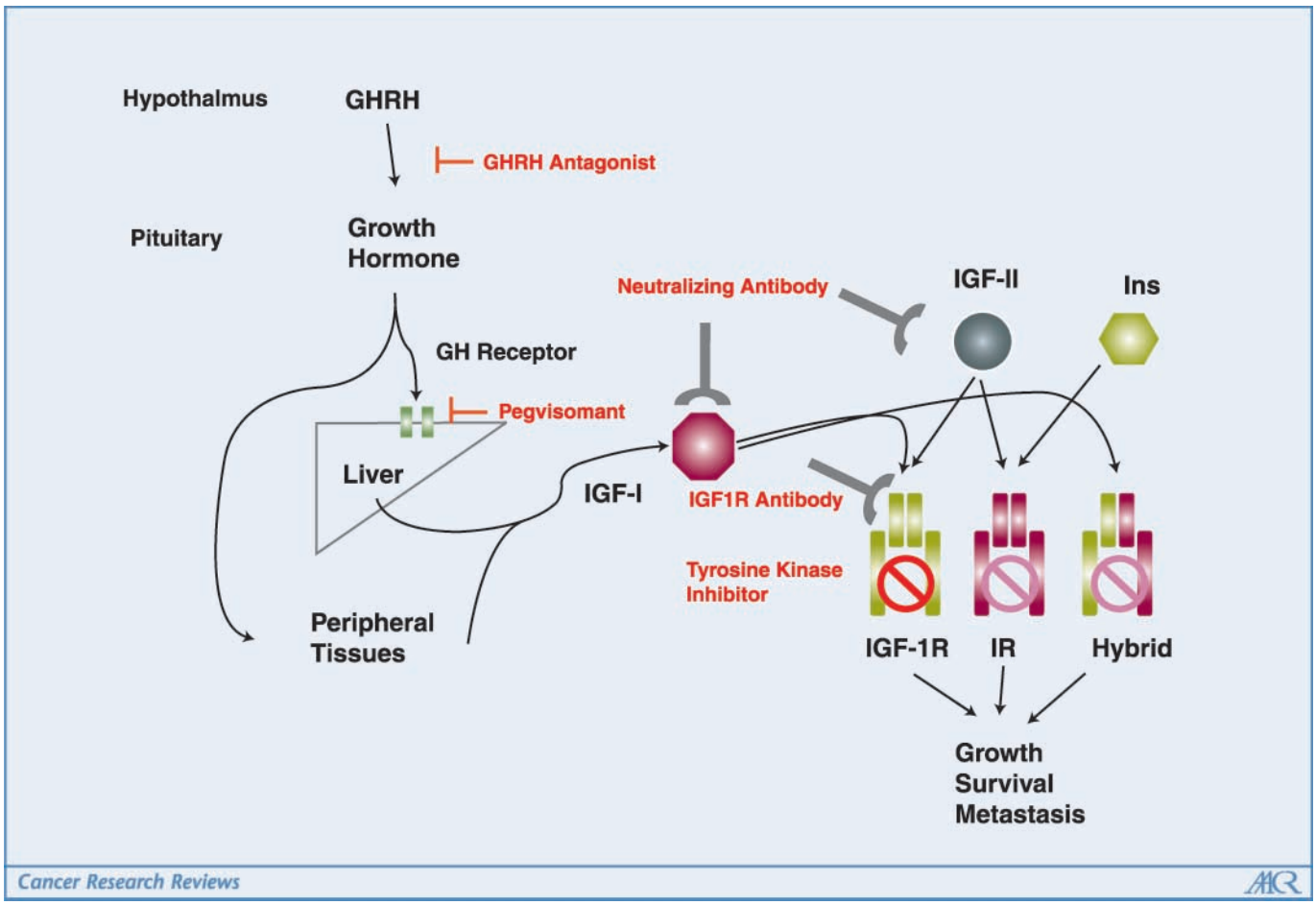

Figure 1. IGF system. Serum IGF-I is regulated by growth hormone (*GH*). Disruption of the hypothalamic/pituitary axis by growth hormone–releasing hormone (*GHRH*) antagonists or growth hormone receptor on the liver by pegvisomant would result in lowered IGF-I levels. Both IGF-I and IGF-II could be neutralized by monoclonal antibodies. IGF1R function may be disrupted by monoclonal antibodies or tyrosine kinase inhibitors. However, multiple receptors may participate in tumor cell biology, and disruption of multiple signals may be necessary.

bone into a xenograft model, the authors showed that this approach could disrupt endocrine and paracrine sources of IGF-I and IGF-II. This method of disrupting IGF action should not affect insulin receptor signaling, which could have an important therapeutic advantage.

Most of the anti-IGF1R strategies have been directed against the receptor itself. A number of monoclonal antibodies have been developed, which block ligand binding and down-regulate receptor levels over time (28–31). Down-regulation of IGF1R may be common to all of the antibodies and may be an important aspect of the observed effects. A single-chain antibody directed against IGF1R acts as a full agonist of the receptor yet retains its ability to down-regulate receptor levels over time and inhibits tumor growth (32, 33). Thus, the ligand blocking effect of the antibodies may be less important than the monoclonal antibodies' ability to down-regulate receptor levels as suggested by Wu et al. (34). None of the antibodies have cross-reactivity with insulin receptor and should not disrupt insulin interaction with its receptor.

Several tyrosine kinase inhibitors have also been developed (35–37). Although these molecules have higher affinity for IGF1R than insulin receptor, there is still some cross-inhibition due to the high degree of homology between the tyrosine kinase domains of the two receptors. In addition, the tyrosine kinase inhibitors have not been reported to down-regulate IGF1R levels.

Thus, both classes of antagonists, monoclonal antibodies and tyrosine kinase inhibitors, disrupt IGF1R signaling via different mechanisms of actions. Because one of the antibodies (CP-751,871) is currently in phase I clinical trial for the treatment of multiple myeloma, we should soon have the initial results from IGF1R signal disruption as a platform to develop strategies in other diseases.

What Should We Expect from Target Inhibition?

Targeted therapies increasingly depend on the measurement of biomarkers that can be used to predict response. Clinical development of tamoxifen and trastuzumab underscore this point; in the absence of the target, these drugs are ineffective. For IGF1R targeting, development of predictive biomarkers may present a problem. First, virtually every tumor studied has some level of IGF1R expression. Defining a minimum number of IGF1Rs required for biological effects has not been defined in preclinical systems. Second, biomarkers for IGF1R action have not been well characterized. In most xenograft model systems, it is difficult to show IGF1R phosphorylation without supplying ligand to the host. Even in humans with well-characterized mutation of IGF1R,

in vitro isolation of fibroblasts was necessary to show defective ligand-dependent signaling (3). Pretreatment biopsies may not be useful to distinguish IGF-driven tumors from IGF-independent tumors. Third, IGF1R may regulate several different cancer cell phenotypes. IGF1R has been linked to tumor cell invasion and metastasis. Blocking IGF1R may result in inhibition of signaling but may have no effect on primary tumor growth. In some model systems, disruption of IGF1R regulates metastatic potential independently of tumor growth (38, 39). Indeed, as cells become more aggressive, levels of IGF1R decline (40, 41), suggesting that the function of IGF1R may differ in early-stage tumors versus late-stage tumors. Although it is possible that suppression of IGF1R levels leads to dedifferentiation and more aggressive tumor biology, there are no preclinical data to show that a decline in IGF1R is the cause of tumor progression. Phase II studies only measure changes in tumor growth; even careful measurement of biomarkers would be unable to show changes in tumor invasion or metastasis.

Most targeted therapies eventually will be combined with conventional cytotoxic chemotherapy. For example, trastuzumab and chemotherapy are clearly synergistic (42). Initial preclinical studies suggest that IGF1R enhances response to chemotherapy (30), but the effects of IGF1R inhibition may differ between tumor types and even between cell lines within a single tumor type (34). Although initial trials of tamoxifen in combination with chemotherapy suggested synergistic benefit (43), it took 20 years to show that inhibition of ERα actually interfered with cytotoxic chemotherapy (44). Careful attention to the clinical trial design of IGF1R combination chemotherapy will be necessary to determine if disruption of IGF1R function will synergize or antagonize the effects of specific cytotoxic drugs.

Perhaps the most concerning aspect of blocking IGF1R is potential toxicity. Because of the ubiquitous nature of IGF1R expression and action, blockade of IGF1R signaling could affect multiple tissues. An increase in the dependence of malignant tissues on IGF1R function could provide a therapeutic window of tolerable IGF1R signal inhibition. However, IGF1R inhibition could preferentially affect tissues with rapid turnover, such as gastrointestinal and hematopoietic cells, similar to other chemotherapy agents.

Because of the importance of IGF signaling in many tissues during growth and development (45, 46), children receiving aggressive IGF1R blockade would be expected to have poor growth and may have other developmental delays. The effect of postnatal IGF1R blockade would be expected to have a lesser but age-related effect on neurodevelopment. Throughout life, IGFs play an important role in neuronal survival (47, 48). As such, systemic blockade of IGF signaling could have toxic effects on the central and peripheral nervous systems. IGF1R has also been implicated in cardiac myocyte survival, and signaling in this organ likely plays an important role in maintaining normal cardiac function (49). Disruption of IGF1R action in the heart could have cardiac effects.

Although the importance of expression and function of the IGF1R in the adult is unknown, the effect of aggressive IGF1R blockade in individuals might be clinically similar to the signs and symptoms of severe growth hormone deficiency. Adults with severe growth hormone deficiency who are not receiving supplementation have an increased risk of osteoporosis, hyperlipidemia, visceral adiposity, cardiac events, and impaired physical performance and psychological complaints (50). Whether any of these signs and symptoms are solely due to diminished IGF1R signaling may require an extended period of IGF1R inhibition to discern.

It is expected that disruption of IGF-I feedback at the hypothalamic IGF1R will result in a reflex increase in growth hormone secretion, similar to the reflex increase in serum estradiol seen in premenopausal women receiving tamoxifen (51). The metabolic effect of excessive growth hormone in the absence of IGF-I action has not been determined. One could imagine that IGF-independent effects of growth hormone, such as lipolysis, may be increased under this therapeutic paradigm.

Tissue-specific deletion of the *igf-1*, *igf-1r*, and *irs-2* genes in mice have provided some insight into the potential metabolic effect of IGF1R inhibition (reviewed in ref. 52). Disruption of IGF1R signaling has led to some degree of insulin resistance in most model systems studied. Although this phenotype may be exacerbated by the formation of nonfunctional hybrids of mutant IGF1R and normal insulin receptor, a less severe version of these effects may be expected if a specific IGF-I inhibitor is used. Liver-specific knockout of *igf-I* in mice also results in a phenotype of insulin resistance (53). It is unclear whether the insulin resistance in these experiments is due to growth hormone overproduction or due to an IGF-dependent event. Deletion of the *igf1r*, *irs-1*, and *irs-2* in pancreatic β cells has been shown to reduce β cell mass and increase β cell apoptosis (54–56). The combination of insulin resistance and reduction of β cell mass, perhaps caused by *igf1r* blockade, could result in clinical diabetes. Although temporary induction of insulin resistance could be managed, a permanent effect on pancreatic islet cells would obviously be undesired.

The development of IGF1R antagonists has focused on non–cross-reactivity with insulin receptor. The reason specificity is desired is due to the understanding of the biology and pathology associated with insulin receptor inhibition. The most extreme example of such insulin receptor inhibition is illustrated in individuals with leprechaunism caused by mutations of the insulin receptor (57). Individuals with leprechaunism have severe insulin-resistant diabetes associated with acanthosis nigricans, lipodystrophy, hypertrichosis, and acral hypertrophy (enlarged ears, nose, chin, and fingertips). Again, blockade of insulin signaling by cross-inhibition would be expected to produce a much milder phenotype.

In preclinical model systems, currently published animal data show that short-term inhibition of IGF1R by tyrosine kinase inhibitors (35, 36) or by a monoclonal antibody with significant murine cross-reactivity (34) does not result in substantial weight loss. However, the affinity for these reagents to mouse IGF1R has not been shown, and long-term, more potent inhibition in humans may have other toxicities. There is currently little or no human data regarding the potential short-term and long-term side effects of IGF1R blockade. As therapeutic agents that block IGF1R signaling are developed, special attention needs to be paid to the design of preclinical and clinical trials to collect appropriate safety end points for these therapies alone or in combination with other drugs.

Summary

One perceived disadvantage of targeting IGF1R in cancer is the substantial preclinical understanding of the role this receptor family has in normal physiology. Despite the potential negative side effects of blocking IGF1R signaling, some of which may be

permanent, this class of reagents holds promise for the treatment of a number of different cancer types. The negative effects of these agents will be determined by the potency and duration of IGF1R blockade; their ability to cross-inhibit other tyrosine kinases, particularly the insulin receptor; and the individual properties of each drug. As clinical trial designs move forward, careful attention must be paid to these potential side effects. It is likely that long-term IGF1R inhibition may not be tolerated, but alterations in dose or schedule could potentially ameliorate any observed toxicity. One thing is clear, after many years of hypothesizing a role for IGF1R signaling in cancer, the hypothesis can finally be tested in human clinical trials.

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