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Molecular Pathways

Clinical Cancer Research

Targeting the Insulin-like Growth Factor Receptor-1R Pathway for Cancer Therapy

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Abstract

Signaling through the insulin-like growth factor receptor (IGF-1R) is required for neoplastic transformation by a number of oncogenes, and preclinical validation studies have suggested IGF-1R is an attractive target for anticancer therapy. A number of small molecules and antibodies targeting IGF-1R have entered clinical development, and early results have suggested that these agents have generally acceptable safety profiles as single agents. Some evidence of antitumor activity has also been reported. This review highlights key aspects of the IGF-1R signaling pathway that implicate it as an attractive therapeutic target in the management of cancer, as well as some key lessons that have emerged from early clinical development of anti-IGF-1R targeting agents. In addition, we consider the importance of selecting indications characterized by pathological alterations in the signaling pathway, rational selection of combinations based on signaling pathway interactions, and strategies for patient selection based on analysis of predictive biomarkers. *Clin Cancer Res; 16(9); 2512–7. ©2010 AACR.*

Background

The signaling pathway controlled by the insulin-like growth factor receptor (IGF-1R) plays an important role in normal cell growth and differentiation, as well as key aspects of neoplasia such as transformation and anti-apoptotic signaling. The importance of IGF-1R in various aspects of cancer biology has made it an attractive target for therapeutic intervention (1). The IGF-1R signaling axis is comprised of two receptors (IGF-1R and IGF-2R), the ligands IGF-1 and IGF-2, and a system of at least six binding proteins and attendant proteases that modulate ligand availability (Fig. 1). Circulating IGF-1 is predominantly produced by the liver in response to growth hormone stimulation (2). IGF-2 is a major fetal growth factor produced in a variety of tissues, which is also found to circulate in adults and in some cases may be overexpressed by neoplastic cells (2). The bioavailability of both ligands is also modulated by the IGF binding proteins (IGFBP), which are bound to ligand in circulation and thus prevent degradation and thereby increase the half-life of circulating ligand. Ligand can be liberated from this complex by a family of IGFBP proteases. IGF-1R is a heterotetrameric receptor tyrosine kinase (RTK) composed of two alpha and two beta subunits (Fig. 1). Both IGF-1 and IGF-2 are capable of inducing IGF-1R clustering and autophosphorylation, leading to activation of downstream signaling. In contrast, the IGF-2R (also know as mannose 6-phosphate receptor) does not seem to be capable of mediating signaling, but is thought, rather, to regulate extracellular IGF-2 levels through receptor-mediated endocytosis followed by IGF-2 degradation in lysosomes (3). Once activated, phosphorylated IGF-1R recruits and activates signaling adaptor proteins, including IRS-1, IRS-2, and Shc. Elegant studies have suggested that IRS-1 recruitment is primarily required for mitogenic signaling, whereas IRS-2, in contrast, plays a key role in cellular motility responses (4). Once activated by IGF-1R, phosphorylated IRS-1 binds the regulatory subunit of phosphoinositide 3-kinase (PI3K), stimulating PI3K activity and leading to increased levels of membrane bound phosphatidylinositol 3,4,5-triphosphate (PIP_3). This event serves to recruit AKT to the membrane, where it can be phosphorylated and activated by PDK1 and the mammalian target of rapamycin (mTORC2) complex (5). AKT activation exerts anti-apoptotic effects through inhibitory phosphorylation of pro-apoptotic factors such as BAD and members of the Foxo family of transcription factors, as well as increased expression of anti-apoptotic proteins such as BCL-2, BCL-XL, and nuclear factor kappa-B (NF-κB; ref. 6). AKT signaling also impacts glucose metabolism through regulation of GSK-3β activity, and plays a key role in protein synthesis and cell growth by regulating the activity of the TORC1 complex through a series of intermediate signaling events (7). In contrast, activated Shc stimulates activation of the RAS/MAP kinase pathway and transduction of mitogenic signals through nuclear ELK1 activation (8). It should also be noted that IGF-1R is 84% identical to the insulin receptor in the kinase

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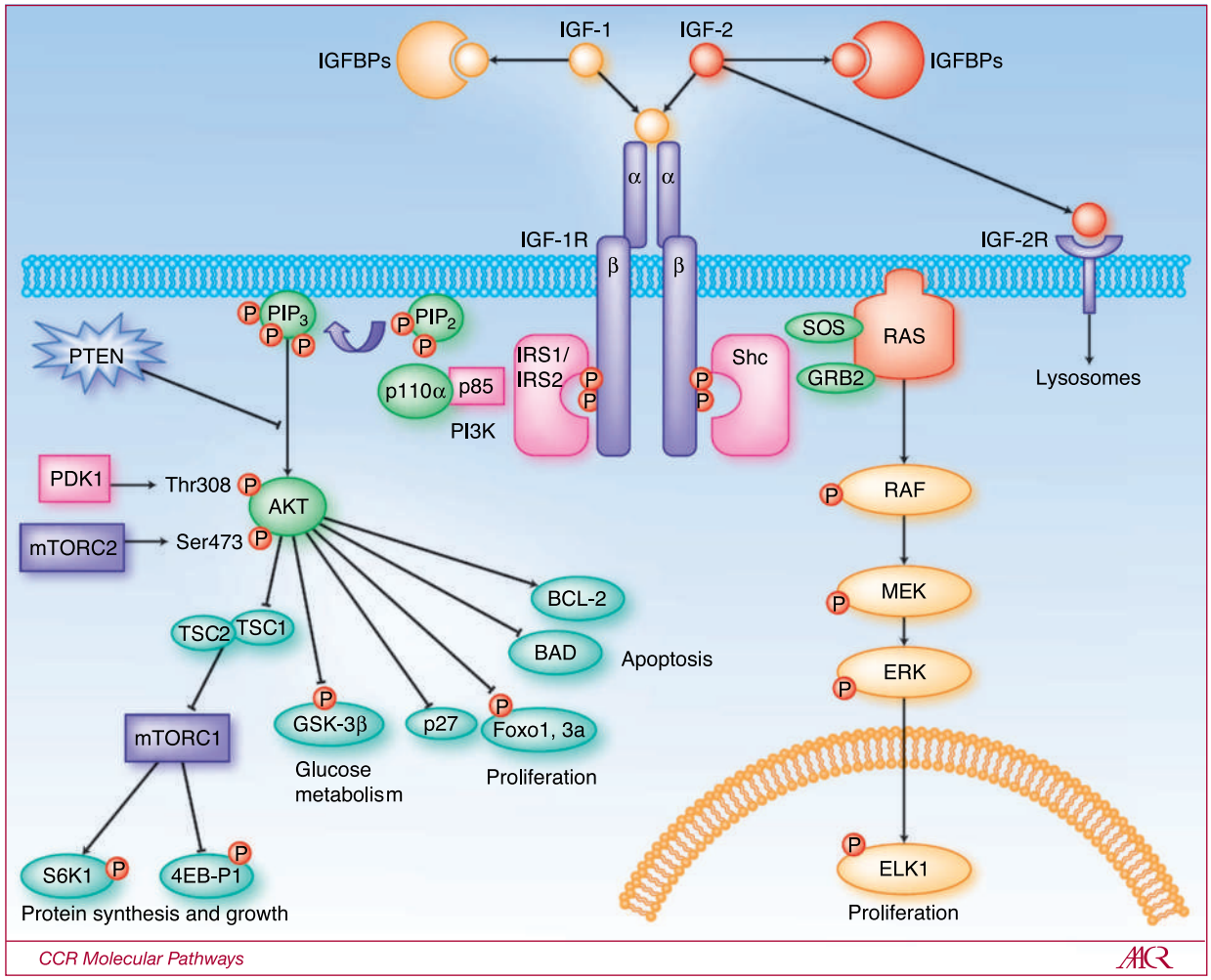

Fig. 1. Key components of the IGF-1R pathway. The ligands IGF-1 and IGF-2 are both capable of binding and stimulating the catalytic activity of the IGF-1R. Bioavailability of IGF-1 is modulated by a family of IGFBPs, whereas bioavailability of IGF-2 is modulated both by the IGFBPs and by binding to the IGF-2R, an event that leads to receptor-mediated internalization and degradation of IGF-2 in lysosomes. Upon binding by either IGF-1 or IGF-2, the IGF-1R undergoes receptor cross-linking and autophosphorylation, leading to the creation of multiple docking sites for the adaptor proteins IRS-1, IRS-2, and Shc. IRS-1 and IRS-2 binding results in activation of the class I phosphatidyl inositol 3′ kinase, whose catalytic activity is the conversion of PIP_2 to the lipid second messenger PIP_3. This event recruits the AKT family of kinases to the plasma membrane, where they can be phosphorylated and activated by PDK1 and the mTOR-containing complex mTORC2. Activated AKT then mediates a host of cell signaling events, including disinhibition of the mTORC1 complex and increased protein synthesis and cell growth, increased conversion of glucose to glycogen via inhibition of GSK-3β, and increased proliferation and survival by activation or inhibition of key effectors such as the Foxo transcription factors, p27, BAD, and BCL-2. In contrast, Shc binding to activated IGF-1R results in stimulation of the RAS/MAP kinase pathway, which also leads to increased cell proliferation.

domain, and that the insulin receptor A (IR-A) isoform, in particular, is capable of binding IGF-2 with high affinity and mediating mitogenic signaling and survival (9). In addition, IGF-1R is capable of forming heterodimers with insulin receptor that seem to mediate similar signaling events to IGF-1R homodimeric receptors (10).

Several lines of evidence have established a role for the IGF-1R pathway as an important target for cancer therapy. A seminal finding was the observation that expression of IGF-1R is required for neoplastic transformation by a number of cellular and viral oncogenes, including SV40 large T antigen, HRAS, and epidermal growth factor receptor (EGFR), suggesting an obligatory role between expression of this receptor and the acquisition of a transformed phenotype (11, 12). IGF-1R is also highly expressed in a wide variety of human cancers (13), and in rare cases is found to be amplified at the DNA level (14). This overexpression seems to have functional consequences, in particular the ability to block apoptosis induced by a variety of agents or adverse tumor microenvironments (15–17), and can also confer invasive and metastatic capability in a mouse model of pancreatic tumorigenesis (18). Epidemiological and functional studies have also implicated the ligands IGF-1 and IGF-2 in various aspects of cancer biology. In particular, elevated levels of circulating IGF-1 have been associated with increased risk of developing breast, prostate,

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and colorectal cancer (2), whereas increased IGF-2 expression resulting from loss of imprinting occurs in both ovarian (19) and colorectal cancer and has been implicated as a biomarker of colorectal cancer risk (20). IGF-2 loss of imprinting and re-expression has also been shown to occur in the Beckwith-Wiedemann syndrome, characterized by somatic overproliferation, as well as sporadic Wilms' tumor and rhabdosarcomas (21). In addition to being linked to increased cancer risk and certain neoplasias, dysregulation of ligand expression has also been reported to have functional consequences. In particular, IGF-1 overexpression in basal keratinocytes results in increased formation of squamous papillomas (22), whereas forced overexpression of IGF-2 in transgenic mice leads to metastasizing mammary carcinomas (23). Ligand overexpression also seems to be driven by pathological alterations in certain tumor types, notably sarcomas. In particular, the EWS-FLI1 translocation is a defining characteristic of Ewing's sarcoma and has been shown to upregulate expression of IGF-1 and downregulate expression of IGFBP-3, leading to a putative autocrine regulatory loop involving IGF-1 and IGF-1R, which can be blocked by anti-IGF-1R targeting agents (24–27). In addition, synovial sarcomas exhibit characteristic t(X;18) translocations that result in enhanced transcription of the IGF-2 gene and hyperactivation of IGF-1R signaling, which can be blocked with IGF-1R inhibitors (28). Thus, IGF-1R seems to play a general role in neoplastic transformation and metastasis in a number of cancers, and pathological alterations in the pathway may be particularly important in certain cancers.

The IGF-1R pathway has also been shown to exhibit cross-talk with a number of other signaling pathways, suggesting a possible role in mediating resistance to therapeutics targeting these other pathways. Several preclinical studies have suggested that anti-IGF-1R-targeting therapies might potentially reverse such resistance. In particular, upregulated IGF-1R expression in response to an EGFR inhibitor results in sustained activation of the PI3K pathway and resistance to the cytotoxic and anti-invasive effects of EGFR inhibition (29). This effect could be reversed by concomitant targeting of EGFR and IGF-1R. In addition, it has been shown that cell lines with an epithelial phenotype and strong dependence on AKT signaling show strongly synergistic effects both *in vitro* and *in vivo* when EGFR and IGF-1R inhibition are combined (30). Similar synergistic effects have been reported when an EGFR inhibitor was combined with the IGF-1R tyrosine kinase inhibitor (TKI) BMS-536924 in a panel of sarcoma cell lines (31). IGF-1R has also been implicated as a resistance mechanism for HER2-targeting agents such as trastuzumab. *In vitro* studies in which cells were selected for trastuzumab resistance identified IGF-1R upregulation as an important resistance mechanism (32), and further analysis showed that HER2 and IGF-1R have a unique heterodimeric interaction in resistant cells that is not seen in sensitive parental cells (33). In contrast to these preclinical studies, a recent report showed that IGF-1R expression determined by immunohistochemistry was not associated with resistance to trastuzumab-based treatment in patients with Her-2/neu-overexpressing metastatic breast cancer (34). A possible explanation for these disparate results would be that it is the ability or propensity of IGF-1R to form heterodimers with HER2 rather than absolute expression levels that underlie resistance, though further study is required to validate this hypothesis clinically. In addition, IGF-1R signaling has been implicated in resistance to endocrine therapies in breast cancer, DNA-damage inducing radiation, and a variety of chemotherapy agents (35).

Clinical-Translational Advances

The IGF-1R pathway has been the subject of intensive drug discovery efforts by a variety of industry and academic groups. Recent estimates suggest that as many as 30 agents targeting IGF-1R are in preclinical or clinical development (36), and currently there are at least 58 active clinical trials evaluating anti-IGF-1R targeting agents alone or in various combinations (www.clinicaltrials.gov). The two main strategies employed to inhibit the pathway are antibodies directed against IGF-1R or small molecule TKIs. Both approaches have inherent strengths and weaknesses, and it remains to be seen which strategy will be more successful clinically. Because IGF-1R is so similar to insulin receptor at the amino acid level and the general conservation of ATP binding sites between RTKs, it has been difficult to identify TKIs selective for IGF-1R (37). Although it can be argued, on the one hand, that this difficulty may result in greater potency because of inhibiting both receptors, it also carries the potential liability of added on- or off-target toxicities that may hinder clinical utility. Antibodies targeting IGF-1R are much more selective for IGF-1R compared to insulin receptor and other RTKs, though some reports have suggested that such antibodies can also downregulate IR/IGF-1R heterodimers and, as such, may interfere with signaling through these heterodimers. The IGF-1R targeting antibodies that have been described all seem to share a common mechanism of drug action, namely to block ligand binding, decrease cell surface receptor expression through receptor internalization, and block intracellular signaling, particularly through the PI3K/AKT pathway (38, 39). A notable difference among the described antibodies is the choice of isotype [immunoglobulin G (IgG1) or IgG2]. Most of the antibodies are fully human or humanized IgG1 antibodies, and as such can mediate antibody-dependent cellular cytotoxicity (ADCC) through recruitment of immune effector cells to antibody-antigen complexes (40). ADCC in some contexts is thought to enhance antitumor activity, though perhaps at the cost of increased lymphocytic toxicity. A notable exception is Pfizer's CP-751,871 (figitumumab), an IgG2 antibody that hence is a poor mediator of ADCC and was purposely designed to have a more favorable hematological toxicity profile (38). Details of early clinical trials with a number of these agents have been extensively described elsewhere in recent reviews (36, 37), so here we will consider some emerging themes and lessons

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from clinical development, as well as our opinion about the outstanding questions that remain in the development of IGF-1R targeting agents.

A general theme that has emerged from phase I studies is that anti-IGF-1R targeting agents, as a class, are typically well tolerated as single agents and have a favorable toxicity profile with only mild-to-moderate adverse events (41, 42). Endocrine effects such as increases in circulating IGF-1, growth hormone, and insulin are commonly reported in patients treated with these agents, and mild elevations in glucose occur in approximately 25% of the patients in most of the reported studies (36). The reason for glucose increases is not immediately clear, because many of the agents are antibodies that do not inhibit insulin receptor. Possible explanations would be downregulation of IGF-1R/IR heterodimers, though the role of the hybrid receptors in glucose regulation is controversial (43). An alternative explanation proposed by Gualberto and Pollak involves deregulation of a homeostatic mechanism involving IGF-1R regulation of the growth hormone/IGF-1 production and increased liver gluconeogenesis (36). These endocrine and metabolic effects generally have not resulted in serious adverse events and dose limiting toxicities. In fact, for both the IgG1 antibody AMG-479 (Amgen) and the IgG2 antibody figitumumab, a maximum tolerated dose was not reached during the dose escalation phase, but rather escalation was halted at a predetermined dose on the basis of criteria such as reaching drug exposures consistent with preclinical efficacy, receptor occupancy levels in neutrophils, and demonstration of pharmacodynamic target modulation (41, 42). These studies have highlighted the importance of pharmacodynamic endpoints in clinical decision making for therapeutic antibodies. In particular, IGF-1R downregulation on circulating leukocytes was reported by a number of groups (38), and downregulation of IGF-1R on circulating tumor cells has been reported by one group (44). In the case of the IgG1 antibody MK-0646 (Merck), pre- and post-tumor biopsies were collected and used to show tumor downregulation of key pathway components such as IGF-1R, pAKT, pERK, and pS6 (45). One notable clinical differentiation point among the molecules is that antibodies with the IgG1 backbone have been reported to have potentially greater severity of hematological toxicities than IgG2 antibodies, because dose limiting toxicities (DLT) of grade 3 and 4 thrombocytopenia have been described for AMG-479 and MK-0646 in several studies (42, 45, 46). An alternate explanation is that these antibodies may bind to different epitopes, thus contributing to different potency and toxicity. The generally mild safety profile in early studies led to subsequent initiation of phase II and phase III studies. However, a cautionary note must be sounded because of the recently halted phase III study of figitumumab in combination with paclitaxel plus carboplatin in patients with advanced non-small cell lung cancer (NSCLC). The trial was halted because it was deemed unlikely to meet its primary endpoint of superiority to chemotherapy, but had been previously suspended owing to an observed imbalance of serious adverse events between the treatment arms with more events, including fatalities, occurring in patients who were randomized to receive figitumumab (47). A challenge for the field is to determine whether this is a statistical anomaly, a property of this specific combination of agents, or an effect unique to this patient population.

A second theme that has emerged is evidence of potential drug efficacy in particular patient populations, although the studies reported are mostly from early phase trials and thus far underpowered to make strong conclusions. Specifically, complete tumor responses have been observed in one Ewing's sarcoma patient treated with the IgG1 antibody AMG-479 and one Ewing's sarcoma patient treated with the IgG2 antibody figitumumab, and in addition, two partial responses have been documented in Ewing's sarcoma patients treated with the IgG1 antibody R1507 (Roche; refs. 38, 42). Clinically significant activity in patients with Ewing's sarcoma, rhabdomyosarcoma, and osteosarcoma has also been reported from a phase II study of the IgG1 antibody R1507 in sarcoma patients (48). Some activity has also been seen in two chronic myeloid leukemia (both complete responses) and two chronic lymphocytic leukemia patients (both partial responses) treated with the TKI XL-228 (Exelixis; ref. 36). Preliminary signs of single agent activity have also been reported in adrenocortical carcinoma for the TKI OSI-906 (OSI Pharmaceuticals; ref. 49). In addition, preliminary evidence of efficacy was observed in a phase II study of figitumumab in combination with paclitaxel and carboplatin in patients with treatment-naïve NSCLC, specifically an objective response rate of 54% in patients receiving chemotherapy plus figitumumab, compared to a 42% objective response rate in patients receiving chemotherapy alone (38). In addition, prolonged stable disease has been observed in patients with diverse cancer types such as breast, colorectal, liver, prostate, cervical, and pancreatic cancer (36).

Future Directions

Clearly, early results have suggested some potential utility of IGF-1R targeting agents in the management of particular cancers, and a wealth of additional data should become available over the next year or two. However, it is already apparent from early studies that these agents do not benefit all patients uniformly, and that potential toxicity in particular combinations may be a liability that must be overcome if the full potential of these agents is to be realized. We suggest several areas of focus that could yet play a role in the successful development of IGF-1R targeting agents. These areas include continued emphasis on selecting appropriate indications in which the pathway may play a critical role, the use of predictive biomarkers to identify likely responders, and rational development in combination with other targeted agents. To the first point, it seems apparent from preclinical and early clinical studies that sarcomas seem to have strong dependence on the pathway on the basis of underlying genetic alterations,

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and it will be intriguing to follow ongoing studies with various inhibitors in these indications. It is also tempting to speculate that other tumor types with dysregulation of the pathway, for instance colorectal and ovarian cancer, which show loss of imprinting at the IGF-2 locus, might also constitute indications with dependence on the pathway and increased likelihood of benefit. Predictive biomarkers of response to IGF-1R targeting agents is a pressing issue (50), and a variety of preclinical studies have suggested that expression or phosphorylation of IGF-1R, levels of the ligands IGF-1 and 2, and levels of the IGFBPs and the adaptor proteins IRS-1 and IRS-2 may have predictive value in identifying responsive patients (4, 51–54). Gene expression signatures predictive of response to some IGF-1R targeting agents have also been described (31, 54). In addition, whereas other components of the pathway such as the IGFBP proteases and InR-A have not been preclinically established as candidate biomarkers, they could also conceivably impact response to these agents on the basis of their role in IGF-1R signaling. Collection of archival or fresh tumor material from patients enrolled in clinical studies and analysis of pathway-focused panels of biomarkers would thus be of great utility in determining if a particular marker or set of markers are associated with clinical benefit, and pave the way for prospective studies in selected or stratified patient populations. Finally, we have already commented on the rationale and promise of combining IGF-1R-directed therapies with EGFR- or HER2-targeting inhibitors, and it will be intriguing to see results from ongoing studies with a variety of these agents in combination with the EGFR TKI erlotinib in NSCLC and pancreatic cancer (36). Studies have also suggested important regulatory links between IGF-1R and estrogen receptor signaling in breast cancer (54, 55), and it is encouraging to note that multiple studies are ongoing in combination with anti-estrogens or hormonal therapies in estrogen receptor-positive breast cancer (36). The extensive knowledge of IGF-1R signaling and impact on downstream pathways gleaned over the past 20 years also suggest other appealing combinations with targeted agents. For instance, the combination of upstream inhibition at the level of IGF-1R with inhibitors targeting downstream nodes such as AKT or mTOR might be predicted to overcome pathway activation and drug resistance owing to feedback loops known to emanate from mTOR back to IGF-1R (56). In a different fashion, the combination of IGF-1R inhibitors with inhibitors acting in the RAS pathway at the level of BRAF or MAPK/ERK kinase (MEK) is also conceptually appealing due to reported upregulation of PI3K pathway signaling in the presence of MEK inhibition (57, 58). With the emerging understanding of crosstalk between the major signaling pathways in cancer, IGF-1R targeting agents may prove to be another useful weapon in our arsenal of cancer therapies.

Disclosure of Potential Conflicts of Interest

J. Zha, M. Lackner, employment, Genentech, Inc.

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