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The Type 1 Insulin-Like Growth Factor Receptor Pathway

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Abstract Research conducted over the past two decades has shown the importance of the type 1 insulin-like growth factor receptor (IGF1R) in tumorigenesis, metastasis, and resistance to existing forms of cancer therapy. The IGF1R itself has only recently been accepted as a credible treatment target, however, perhaps reflecting the potential problems for drug design posed by normal tissue IGF1R expression, and close homology with the insulin receptor. Currently ~12 anti-IGF1R therapeutics are undergoing clinical evaluation, including blocking antibodies and tyrosine kinase inhibitors. This review will summarize the principal signaling pathways activated by IGF1R and the preclinical data that validated this receptor as a treatment target. We will review clinical progress in the testing of IGF1R inhibitory drug candidates, the relative benefits and potential toxicities of coinhibition of the insulin receptor, and the rationale for combining IGF1R blockade with other cancer treatments. An understanding of IGF1R signaling is important because it will guide the incorporation of appropriate molecular markers into clinical trial design. This will be key to the identification of patients most likely to benefit, and so will influence the ability of IGF1R inhibition to make the transition from experimental intervention to clinical therapy.

Background

The insulin receptor (IR) and the type 1 insulin-like growth factor (IGF) receptor (IGF1R) evolved from a single ancestral receptor involved in the regulation of metabolism, organismal size, and longevity. The two receptors have acquired distinct functions, while retaining a highly conserved structure. Both IGF and insulin receptors consist of two half-receptors, each comprising one extracellular α-subunit and one transmembrane β-subunit that possesses tyrosine kinase activity (1, 2). The IR is activated by insulin, which is secreted by the pancreas after food intake. The IGF1R is activated by its ligands IGF-I and IGF-II, which are produced by the liver and also by many extrahepatic sites including tumor cells and stromal fibroblasts. In cells that express both receptors, IGF1R/IR hybrids form by random association, when an insulin half-receptor associates with an IGF half-receptor (Fig. 1). Like IGF1Rs, these are activated by IGF-I and IGF-II; their affinity for insulin is an active research topic (3). Further complexity arises from the fact that there are two isoforms of the IR, generated by alternative splicing. IR-B is the classic (exon 11+) isoform that regulates glucose uptake, whereas the exon 11- IR-A is a fetal isoform that mediates apoptosis protection in response to IGF-II (3, 4).

Signaling via the IGF1R. Ligand binding to the IGF1R leads to autophosphorylation of tyrosines 1131, 1135, and 1136 in the kinase domain of the receptor. This induces the phosphorylation of juxtamembrane tyrosines and carboxyl-terminal serines that form binding sites for docking proteins including IR substrates 1 to 4 (IRS-1 to IRS-4), and Src homology and collagen domain protein (Shc). Recruitment of these molecules activates signaling via the phosphatidylinositol-3-kinase (PI3K)-AKT and RAS/RAF/mitogen-activated protein kinase (MAPK) pathways (5–7). Figure 1 illustrates key steps in this process and the principal downstream manifestations of IGF1R signaling.

IGF1R activation is tightly regulated at multiple levels. Ligand availability is influenced by the fact that IGF-II expression is subject to genomic imprinting, by the presence of the type 2 IGF receptor (IGF2R) that acts as a trap for IGF-II, and by high-affinity IGF-binding proteins (IGFBP), which broadly function to inhibit IGF bioactivity (8, 9). Inside the cell, IGF1R kinase activity is regulated by Src, integrins, protein phosphatases including PTP-1B, and the RACK1 scaffolding protein (10). Further downstream, several IGF1R effectors, including mammalian target of rapamycin (mTOR) complex 1 (mTORC1), p70 S6 kinase, extracellular signal-regulated kinases (ERK), and c-*Jun* N-terminal kinase (JNK) are involved in feedback suppression of IRS-PI3K-AKT signaling (Fig. 1; refs. 6, 10, 11). IGF signaling plays a critical role in normal growth, and is a well-established mediator of the malignant phenotype.

Effects of IGF1R signaling in normal physiology. Studies in knockout mice confirmed the importance of IGFs and the IGF1R in prenatal and postnatal growth (12). In muscle, cartilage, and bone, IGF signaling via PI3K-AKT and/or ERKs mediates differentiation, and IGFs are also required for the maintenance of the myocardium and brain (13, 14). More recently, IGF1R has been shown to be involved in the

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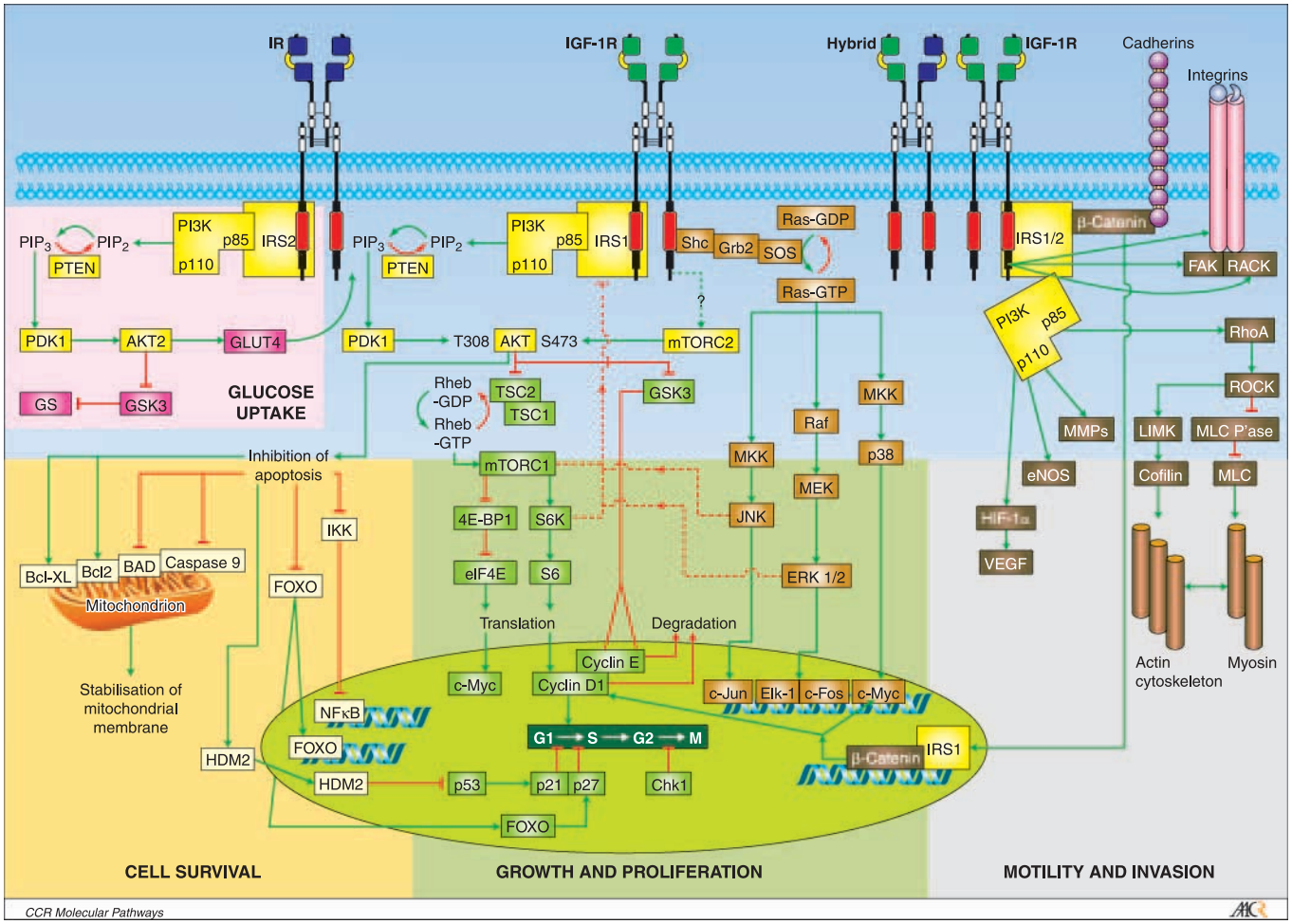

Fig. 1. Signaling downstream of the IGF1R. The figure shows the IGF1R, IR and hybrid receptors, and their principal effectors. Green arrows, activation; red lines/arrows, inhibition. IRS proteins are tyrosine-phosphorylated by the IGF1R, and recruit the regulatory (p85) and catalytic (p110) subunits of PI3K. PIP_3 production activates PDK-1, which phosphorylates AKT on threonine 308. Serine 473 of AKT is phosphorylated by the mTORC2 complex, activated by an unknown mechanism by the IGF1R. AKT promotes cell survival via multiple effectors (*cream*), which stabilize the mitochondrial membrane, inhibiting apoptosis, and induce the expression of prosurvival genes. AKT effectors that regulate growth (*green*) include mTOR within the mTORC1 complex, which enhances the translation of proteins involved in proliferation. AKT also blocks the expression and function of growth inhibitors, via inhibitory phosphorylation of FOXOs, p21, p27, Chk1, and GSK3. In a parallel pathway (*orange*), linked to the IGF1R by IRS or Shc proteins, sequential activation of RAS, RAF, and mitogen-activated protein kinase isoforms ERKs, p38, and JNK, results in the transcription of genes that drive proliferation. This pathway can also mediate differentiation, in the context of unopposed Shc binding to the IGF1R in cells lacking IRS-1. Negative regulation of PI3K-AKT (*dotted red line*) is accomplished by mTORC1, S6K, JNK, and ERKs, which induce IRS-1 serine phosphorylation and degradation. Right, IGF effectors that influence invasion and metastasis (*brown*). IGF1R activation disrupts β-catenin/E-cadherin complexes, disconnecting E-cadherin from the actin cytoskeleton and favoring cell detachment. IRS-1/β-catenin complexes relocate to the nucleus, driving expression of β-catenin target genes. Motility and migration are enhanced by cross-talk between the IGF1R, integrins, FAK, and the RACK1 scaffolding protein, and by Rho-A activation, leading to actin reorganization and actin/myosin contractility. IGFs induce the expression of matrix metalloproteinases, required for invasion, and stimulate angiogenesis by activating endothelial nitric oxide synthase and inducing expression of hypoxia-inducible factor-1α and vascular endothelial growth factor. Top left, pathways activated by the IR to promote glucose uptake (*pink*). Signaling via IRS-2 and AKT2 promotes GLUT4 translocation to the plasma membrane, and inhibits GSK3, leading to the activation of glycogen synthase. There is a degree of overlap in receptor functions: the IGF1R can induce glucose uptake in brain and skeletal muscle, and conversely, insulin can activate hybrid receptors to induce proliferation. Note that this diagram incorporates information from multiple studies, and is not intended to imply that each of these pathways operates in every cell.

regulation of life span. Paradoxically, given the importance of IGFs as survival factors at the cellular level, it is the attenuation of IGF signaling that confers longevity at the level of the whole organism, by relieving inhibition of the FOXO family of transcription factors. Key FOXO target genes have been identified in *Caenorhabditis elegans*, and, intriguingly, some of these FOXO targets are also involved in the suppression of tumorigenesis (15).

Aberrant expression of IGF axis components in cancer. Many tumors show altered expression of the IGF1R, its ligands (especially IGF-II) and/or the IGFBPs, and recent work indicates that tumors can also express the IR-A and hybrid receptors (3, 16). Alterations in IGF axis components can occasionally be early, possibly initiating, events in tumorigenesis; examples include loss of imprinting for IGF-II expression, and inactivation of the antiproliferative IGF2R (17, 18). Furthermore, individuals with high-normal circulating IGF-I levels are at an increased risk of later development of common solid tumors, possibly because IGFs favor the neoplastic progression of small lesions that would otherwise remain occult. Consistent with this, tumor growth in experimental models is influenced by circulating IGF levels (reviewed in ref. 9).

In many tumors, altered expression of the IGF1R follows an earlier molecular event, such as loss of function of

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Table 1. IGF1R TKIs and antibodies

Agent	Company/Institute	Phase	Comments
IGF1R TKIs			
A-928605	Abbott	Preclinical	Pyrazolopyrimidine TKI
BMS-536924 BMS-554417	Bristol-Myers Squibb	Preclinical	ATP-competitive, equipotent inhibition of IGF1R and IR
INSM-18 (NDGA)	Insmed	Phase I-II	Dual inhibitor of the IGF-I and HER2 receptor kinases Phase I data suggest modest PSA responses in patients with nonmetastatic prostate cancer
PPP	Karolinska Cancer Institute and Biovitrum	Preclinical	Inhibits phosphorylation of Y1136 in the kinase activation loop. Does not inhibit IR Preferentially inhibits PI3K-Akt pathway, blocks growth of a range of tumors *in vitro* and *in vivo* Induces IGF1R down-regulation via involvement of β-arrestin 1/MDM2
NVP-ADW742	Novartis Pharma	Preclinical	ATP-competitive inhibitor, shows ~15-fold selectivity for IGF1R relative to IR in intact cells In SCLC, inhibits PI3K-AKT and induces synergy in combination with chemotherapy
NVP-AEW541	Novartis Pharma	Preclinical	ATP-competitive inhibitor, shows ~27-fold selectivity for IGF1R relative to IR within intact cells Inhibits Akt/mTOR pathway, enhances growth inhibition of MM cells in combination with dexamethasone and bortezomib
OSI-906	OSI Pharmaceuticals	Phase I	Shows ~10-fold selectivity for IGF1R relative to IR. Synergistic antiproliferative effects in combination with erlotinib in CRC cell lines via blockade of AKT and ERK phosphorylation
XL-228	Exelixis	Phase I	Inhibitor of IGF1R, BCR-ABL and Src

tumor suppressor genes, or gain of function mutations in *p53* (19, 20). It should be noted that the degree of IGF1R up-regulation is not of the same order of magnitude as that due to gene amplification, for example of *Her2*, and again unlike Her2, is not accompanied by constitutive receptor activation (21). Nonetheless, in some tumor types, IGF1R overexpression confers adverse prognosis, suggesting that it is biologically significant (22, 23).

The IGF1R mediates key features of malignancy. The IGF1R is not unique in driving tumor cell proliferation. It is required, however, for cellular transformation by most oncogenes and mediates the combination of proliferation and survival signaling required for anchorage-independent growth. This property enables transformed cells to form macroscopic tumors, and to survive the process of detachment required for metastasis (5, 24). Figure 1 shows additional properties of IGF signaling that influence the propensity for local and distant spread. Consistent with these functions, preclinical studies indicate that IGF1R overexpression induces tumor formation and metastasis (25, 26).

Validation of the IGF1R as a Target

Research conducted over the last 15 to 20 years has clarified the effects of inhibiting the expression or function of the IGF1R. In a wide variety of *in vitro* and *in vivo* models, interruption of IGF signaling has been shown to inhibit tumor growth, block metastasis, and enhance the effects of other forms of cancer treatment (reviewed in refs. 5, 27, 28). Notably, the efficacy of IGF1R targeting in preclinical models of Ewing's sarcoma has been predictive of clinical activity (29). Ironically, many of the strategies that served to validate the target are approaches that themselves have little prospect of clinical application. Examples include the use of antisense or small interfering RNA to down-regulate the IGF1R, expression of growth-inhibitory IGFBPs or the IGF2R, and construction of dominant negative IGF1Rs (30–34). Some of these experimental models were specifically designed to be IGF-responsive (33, 35). As outlined previously, however, changes in the expression of IGF axis components are rarely the initiating events in tumorigenesis, and many common solid tumors are characterized by multiple genetic changes (19, 36). A particular concern is the presence of activating mutations downstream of the IGF1R, which could negate the inhibitory effects of IGF1R blockade. Indeed, in colorectal cancer, activation of K-RAS and/or B-RAF confers resistance to epidermal growth factor receptor (EGFR) antibodies (37). Inhibition of IGF signaling, however, seems capable of blocking the growth and survival of tumor cells in which the PI3K-AKT or ERK pathways are activated by loss of functional PTEN or RAS-RAF activation, respectively (31, 38, 39). These findings may reflect the ability of IGF1R targeting to inhibit multiple survival pathways, and provide encouragement for clinical development of this strategy, given the frequency of PTEN, RAS, and RAF mutations in human tumors (36).

The IGF1R as a mediator of resistance to therapy. IGF1R activation is known to protect tumor cells against apoptosis induced by cytotoxic drugs, and may also influence the repair of DNA damage (40, 41). There is considerable preclinical data to support the view that IGF1R inhibition can modify sensitivity to chemotherapy (reviewed in refs. 27, 28) and biological therapies. For example, IGF-induced PI3K-AKT activation mediates resistance to EGFR blockade in glioblastoma (42). Conversely, in ovarian cancer, activated EGFR or HER2 mediate resistance to IGF1R targeting (43). Consistent with these

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Table 1. IGF1R TKIs and antibodies (Cont'd)

Agent	Company/Institute	Phase	Comments
IGF1R antibodies			
AVE1642	Sanofi-Aventis	Phase I-II	Humanized version of murine EM164 IgG_1 antibody. Phase I single agent in MM, with docetaxel in solid tumors, well-tolerated, no DLT. Planned combination with bortezomib in MM
SCH-717454 (19D12)	Schering-Plough	Phase I-II	Fully human monoclonal antibody Activity against IGF1R/IR hybrid receptors via interaction with the IGF1R component
CP-751,871	Pfizer	Phase I-III	Fully human IgG_2. Phase I: mild hyperglycemia, no DLT, MTD not achieved. At 20 mg/kg, 10 of 15 patients had SD. Phase II in adrenocortical carcinoma, sarcoma: SD in 60% patients. Phase II in NSCLC: RR 51% to CP-751,871 with TC vs. 36% on TC alone. Objective responses to TC with antibody in 72% of squamous tumors, including "striking" responses in bulky disease, and some PR/SD on CP-751,871 after PD on TC alone
IMC-A12	ImClone Systems, Inc.	Phase I-II	Recombinant human monoclonal IgG_1 antibody, binds IGF1R and IGF1R/IR hybrid receptors but not IR alone. Stable disease in 46% of patients with solid tumors in phase I
BIIB022	Biogen Idec	Phase I-II	Fully human nonglycosylated version of IgG4.P antibody lacking Fc-effector function
MK-0646	Merck	Phase I-III	Humanized monoclonal IgG_1. Phase I toxicity hyperglycemia and thrombocytopenia. Current studies: phase II in neuroendocrine tumors and NSCLC; phase II/III in metastatic CRC with cetuximab and irinotecan
R1507	Roche	Phase I-II	Human monoclonal IgG_1 antibody. Phase I showed PR in four of eight patients with sarcoma
AMG 479	Amgen	Phase I-II	Fully human monoclonal IgG_1 antibody. Phase I activity: CR in Ewing's, PR in neuroendocrine tumor. Phase IB with panitumumab or gemcitabine: one DLT (hyperglycemia)

NOTE: A summary of IGF1R small molecule inhibitors and antibodies currently in preclinical and early clinical development. Data from (refs. 27, 57, 58); A. Tolcher (personal communication), and the NIH's ClinicalTrials.gov (http://www.clinicaltrials.gov/) and ClinicalTrialsFeeds.org (http://www.clinicaltrialsfeeds.org/) web sites.
Abbreviations: PSA, prostate-specific antigen; SCLC, small cell lung cancer; NSCLC, non–small cell lung cancer; CRC, colorectal cancer; MM, multiple myeloma; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; TC, taxol/carboplatin; RR, response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

findings, dual inhibition of the IGF1R and EGFR or HER2 is more effective than single receptor blockade at inhibiting the growth of EGFR-overexpressing or HER2-overexpressing tumors *in vitro* and *in vivo* (43–45). Similarly, mTOR inhibitors can activate PI3K-AKT via loss of negative feedback on IRS-1 (see Fig. 1), and this effect can be suppressed by IGF1R blockade (11). There is also evidence that IGF1R inhibition can prolong the response to endocrine therapy in a murine model of prostate cancer (39).

The role of insulin and the IR in tumor biology. Cancers are now known to express IRs, particularly the fetal variant IR-A that mediates proliferation and apoptosis protection in response to IGF-II (3). It is plausible that IR-A and hybrid receptors may also be activated by high levels of insulin, as occur in patients with the "metabolic syndrome", characterized by obesity, type 2 diabetes, and insulin resistance (46). Indeed obesity and insulin resistance are linked to the risk of developing cancers of the esophagus, colon, kidney, and endometrium, and with adverse prognosis in prostate and breast cancer (9, 47). Also consistent with this concept, diet-induced hyperinsulinemia accelerates the growth of prostate cancer xenografts (48), and an antibody that neutralizes both the IGF1R and hybrid receptors shows more potent antitumor activity than antibodies targeting only the IGF1R or receptor hybrids (49).

Clinical-Translational Advances

IGF1R targeting was first shown to inhibit tumor growth 20 years ago (50). Clinical testing of IGF1R inhibitors began only recently, however, following the precedents provided by targeting EGFR family members. To date, two approaches have progressed to clinical evaluation: small molecule tyrosine kinase inhibitors (TKI) and anti–IGF1R antibodies. The properties of individual agents were discussed in a recent review (27), and are summarized in Table 1.

Sequence homology between the IGF1R and IR has posed problems for the design of IGF1R TKIs (1, 51), which range from the unselective or partially selective competitors of ATP-binding, to the more selective inhibitors of substrate binding or activation loop phosphorylation (Table 1). Unlike IGF1R TKIs, anti–IGF1R antibody drug candidates do not bind to IRs; they

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block ligand binding to IGF1Rs and hybrid receptors, and induce IGF1R down-regulation. Most are IgG_1 antibodies, humanized or fully human to reduce immunogenicity. Therapeutic antibodies of the IgG_1 or IgG_3 class can induce Fc-mediated antibody-directed cellular cytotoxicity, which, as in the case of trastuzumab, may contribute to efficacy (52). However, IGF1R-directed antibody-directed cellular cytotoxicity could also enhance toxicity to normal IGF1R-bearing tissues. Pfizer and Biogen Idec have generated IgG_2 and nonglycosylated IgG4 antibodies, respectively (Table 1); ongoing clinical studies may clarify whether these agents have significantly different properties from anti–IGF1R antibodies of the IgG_1 class. As with any treatment, the variables that will influence the success of this new approach are toxicity, efficacy, and the ability to identify factors that correlate with response.

Toxicity of IGF1R inhibition. The potential for toxicity arises from the expression of IGF1Rs in normal tissues, and homology between the IGF1R and the IR. Long-term IGF1R blockade during childhood and adolescence may cause growth retardation, and at any age, may influence the function of IGF-dependent tissues including the myocardium and brain (13, 14). The possibility of central nervous system toxicity deserves particular attention during treatment with IGF1R TKIs because other molecules in this class have been shown to penetrate the blood-brain barrier in the context of central nervous system malignancy (53).

IGF1R-inhibitory drugs are predicted to influence glucose tolerance, in the case of IGF1R TKIs, by direct inhibition of the IR kinase (35). IGF1R-specific antibodies can induce IR down-regulation via endocytosis of hybrid receptors or IRs within IGF1R-containing lipid rafts (54). Both IGF1R antibodies and TKIs may result in loss of the hypoglycemic effects of IGF-I, and blockade of pituitary IGF1Rs may induce a compensatory increase in circulating growth hormone, which could contribute to insulin resistance (55).

Notwithstanding these theoretical concerns, there have been few major toxicities during early phase trials of anti–IGF1R antibodies, used alone or in combination. Hyperglycemia has been generally mild and reversible, even in patients also treated with dexamethasone or rapamycin, which can impair glucose tolerance (56–59). Clinical studies may soon show whether TKI drug candidates from OSI Pharmaceuticals and Bristol-Myers Squibb interfere with IR signaling when used clinically; whereas IR-B inhibition might be expected to be associated with toxicity, it may be advantageous for clinical efficacy to block both the IGF1R and the IR-A (3).

Efficacy of IGF1R-blocking drugs. The critical issues for clinical utility include the ability of candidate IGF1R inhibitors to block IGF1R in the clinical setting, and the resultant effects on tumor growth and sensitivity to other cancer therapeutics. Pharmacokinetic and pharmacodynamic data from ongoing clinical trials support the concept that IGF1R antibodies can be administered at doses that saturate IGF1R binding, and also induce the elevation of circulating growth hormone, IGF-I and IGFBP-3, consistent with blockade of IGF1Rs, at least in the pituitary (56, 60). Several studies are reporting disease stabilizations and minor responses, including prostate-specific antigen responses in prostate cancer, but there have been no objective responses to single-agent IGF-IR targeting agents in the common cancers (56, 61–64). There is, however, evidence of significant single-agent activity, including apparently durable complete responses, in heavily pretreated patients with Ewing's and other types of sarcoma and neuroendocrine tumors (61, 65, 66).[4]

Even if IGF1R inhibition ultimately proves to have limited single-agent activity in the common cancers, there is a strong rationale for evaluating the effects of IGF1R blockade in combination with other treatment modalities. Early reports indicate that anti–IGF1R antibodies can safely be administered with chemotherapy (57, 58, 64). The CP-751,871 antibody appears to enhance the response to carboplatin and paclitaxel in non–small cell lung cancer, with particularly striking responses in squamous tumors (ref. 57; Table 1). Early data suggest that progression-free survival may also be improved, but longer follow-up from phase II and phase III studies will be needed to determine whether this is clinically meaningful.

The AMG 479 antibody is undergoing evaluation in combination with gemcitabine or panitumumab, a fully human EGFR antibody, and thus far has achieved disease stabilization in the majority of patients, with evidence of objective activity in colon cancer (58). Numbers are small, however, and this important topic will require further study, in particular to determine which class(es) of cytotoxic drug may be most advantageous to combine with IGF1R inhibitors. The IGF1R is known to play a role in the response to DNA damage (41), but it is also possible that cell cycle arrest induced by IGF1R inhibition (Fig. 1) could attenuate the efficacy of phase-dependent cytotoxic agents.

Factors associated with sensitivity to IGF1R inhibition. The major responses in Ewing's sarcoma are causing considerable interest, and are being followed up in phase I and II trials of anti–IGF1R antibodies in this tumor type (ref. 65; see the ClinicalTrials.gov web site[5]). Most Ewing's tumors are characterized by a reciprocal t(11;22)(q24;q12) translocation that generates an oncogenic fusion protein, EWS/FLI-1, which requires the IGF1R for transformation, and which suppresses the expression of IGFBP-3, a potent inhibitor of IGF bioactivity (67, 68). Ongoing studies will determine whether there is any correlation between the presence of the EWS/FLI-1 fusion protein and sensitivity to IGF1R inhibition.

There are few clues to the identity of specific factors that influence sensitivity to IGF1R blockade in the common cancers, and in particular, no clear evidence of association with anatomic tumor type or IGF1R levels. Neither of these factors should be dismissed at this early stage, however. Receptor levels could be significant in tumors in which IGF1R up-regulation confers adverse prognosis, such as ovarian cancer (23). Furthermore, the observation of striking responses to CP-751,871 plus chemotherapy in squamous non–small cell lung cancer may relate to higher IGF1R expression in squamous tumors than in adenocarcinomas (57, 60). In addition, adenocarcinomas harbor features of epithelial-to-mesenchymal transition, which can be influenced by the IGF axis, and which confers resistance to EGFR inhibition (69, 70). Additional potential mediators of sensitivity to IGF1R inhibition include loss of the IGF2R, or loss of imprinting for IGF-II, which leads to overexpression of ligand and may indicate "addiction" to this growth pathway (16, 17). In designing IGF1R inhibitor

[4] A. Tolcher, personal communication.
[5] http://www.clinicaltrials.gov/

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trials, it will be important to measure the levels and activation of IGF pathway components and effectors, and also to take an unbiased approach to identify hitherto unrecognized molecular features that affect sensitivity. Indeed, IGF1R antibody trials are already beginning to integrate response data with the results of investigations on clinical tumor tissue, in order to distinguish responders from nonresponders (60, 66, 71).

Conclusion

The relevance of the IGF1R to cancer biology was a topic of controversy a decade ago, but now is widely accepted. More than a dozen companies are investigating drug candidates that target the IGF1R, and early clinical data are encouraging. Complete responses are rare during phase I monotherapy trials in heavily pretreated patients, but have been seen with several anti–IGF1R antibody drug candidates.[4] Such anecdotes do not represent formal evidence of efficacy, but they do provide a strong impetus for further research, as do early results of combining IGF1R antibodies with chemotherapy (57, 58, 64).

Although there is considerable enthusiasm for this approach, there are also significant challenges. Because the target is so widely expressed, it will be important to define the most compelling tumor types on which to focus. Trials currently in progress will determine the relative safety and efficacy of IGF1R antibody and TKI strategies, and it will also be important to identify the most rational combination therapies. High priority should be afforded to the identification of molecular markers of sensitivity, related both to the tumor and perhaps also to host metabolic factors, that will allow the selection of patients most likely to benefit from IGF1R inhibition. In addition to measuring standard response variables, well-designed clinical trials will be required to address these important translational research issues.

Disclosure of Potential Conflicts of Interest

V. Macaulay: Pfizer expert panel; trial collaboration: Sanofi-Aventis and OSI-Pharmaceuticals.

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