The new kid on the block(ade) of the IGF-1 receptor

The insulin-like growth factors (IGF) system, and particularly the IGF-1 receptor, has recently become the subject of major interest in the arena of cancer research. Its involvement in cancer cell growth and survival makes the system an excellent target as potential adjunct therapy to standard chemotherapy.

Most cancer cells in culture express increased levels of components of the insulin-like growth factor (IGF) system, especially IGF-2, and the type 1 IGF receptor (IGF-1R), a receptor tyrosine kinase that mediates both mitogenic and antiapoptotic pathways (Figure 1). Investigators have therefore surmised that the IGF system, and perhaps the IGF-1R in particular, may be an appropriate target for inhibition of cancer cell growth (LeRoith et al., 1995). Further evidence suggesting the importance of the IGF-1R pathway in cancer includes the finding that a variety of oncogenes require an intact IGF-1R for transforming activity (Sell et al., 1994; Toretsky et al., 1997). The link between cancer and IGF signaling is also consistent with recent epidemiological studies showing an increased relative risk for the development of colon, prostate, breast, lung, and bladder cancers in individuals with circulating IGF-1 levels in the upper tertile of the normal range (Chan et al., 1998). These findings were confirmed in animal models, where reduced circulating IGF-1 levels result in significant reductions in cancer development, growth, and metastases, whereas increased circulating IGF-1 levels are associated with enhanced tumor growth (Wu et al., 2003). It is also notable that while no specific mutations in IGF receptors or ligands have been identified in cancers, there is clear evidence of epigenetic alterations—i.e., loss of imprinting (LOI) of IGF-2 in a variety of human tumors (Rainier et al., 1993; Zhan et al., 1994). Taken together, the data provide strong evidence for a critical link between IGF signaling and human cancer.

Various attempts have been made to inhibit the IGF system, which is comprised of two ligands, IGF-1 and IGF-2, six IGF binding proteins (IGFBPs-1 through -6), and the IGF-1R, which mediates most of the cellular signaling functions of this system (Firth and Baxter, 2002). Table 1 lists some of these approaches, including suppression of circulating IGF-1 and monoclonal antibodies that neutralize IGF-1.

Studies in cell culture systems demonstrated that inhibition of IGF-1R expression or activation successfully inhibited cancer cell growth and colony formation, whereas overexpression can transform certain cells, suggesting that similar effects may be reproduced in vivo (Butler et al., 1998). The IGF-1R has been successfully inhibited in rodents using a variety of molecules. When antisense oligonucleotides were injected intraperitoneally, the growth of human cancers was inhibited in nude mice, and similar effects were observed with the mouse monoclonal antibody α IR3 (Table 1). However, these approaches have numerous problems, including lack of specificity, difficulty of drug delivery, etc. Inhibition of IGF-I levels, while useful in mice, probably will not be useful in humans, who also have high circulating levels of IGF-2, which can also activate the IGF-1R.

More recently, investigators have determined that inhibition of the tyrosine kinase domain of a particular receptor may be a better approach, particularly if a small molecule can be found that specifically inhibits a particular kinase. This approach has already been successful, most notably with the development of imatinib mesylate, an inhibitor of the BCR-ABL fusion kinase expressed in CML cells, as well as the c-kit kinase, which is mutated in GIST tumors. This drug exhibited considerable activity in the treatment of these tumors (Heinrich et al., 2003).

In this issue of *Cancer Cell*, two articles describe the inhibition of IGF-1R signaling cascades by a small molecule kinase inhibitor of the pyrrolo[2,3-d]pyrimidine class, discovered by high-throughput screening of molecules that inhibit IGF-1R activity (García-Echeverría et al., 2004; Mitsiades et al., 2004). In the first study (García-Echeverría et al., 2004), NVP-AEW541 exhibited a similar IC50 toward the IGF-1R and insulin receptor (IR) kinase domains in vitro; however, there was a 27-fold higher affinity for the native IGF-1R kinase in assays measuring autophosphorylation of the receptor as the end point. A much lower affinity was demonstrated toward other tyrosine

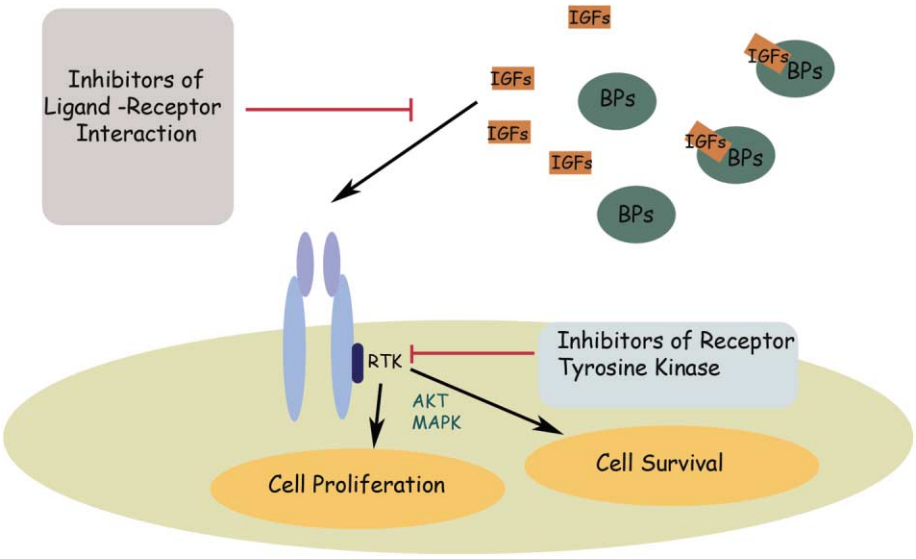

Figure 1. Schematic of the IGF system

Extracellular IGFs bind to the IGF-1R and the activated tyrosine kinase leads to enhanced cell proliferation and cell survival mediated by signaling pathways that include the PI3′ kinase/Akt and the MAPK pathways. Inhibition of the IGF-1R may occur at multiple levels both extracellular and intracellular.

Table 1. Inhibitors of the IGF-1R

1. Blockade of IGF binding
a. Antibody to IGF-1, antibody to the IGF-1R (α IR3)[1]
b. Inhibitors of ligand binding; D amino acid analog of IGF-1[2]
c. Inhibitory IGF binding proteins[3]
2. Reduction of IGF-IR expression
a. Targeting of IGF-1R-expressing cells using IGF-1 fused to pseudomona exotoxin cytotoxic domain[4]
b. Antisense to the IGF-1R, through either oligonucleotides, stable transfections, or siRNAs[5,6]
3. Inhibition of IGF-1R function
a. Dominant negative IGF-1R inhibits receptors of receptor function[7]
b. Small molecule inhibition of the IGF-1R tyrosine kinase activity[8]

[1]J. Clin. Invest. *84*, 1418–1423.
[2]Cancer Res. *53*, 1102–1106.
[3]Endo. Rev. *23*, 824–854.
[4]Cancer Res. *51*, 174–180.
[5]Cancer Res. *55*, 249–255.
[6]Endocr. *136*, 4298–4303.
[7]J. Biol. Chem. *268*, 2655–2661.
[8]Cancer Res. *64*, 236–242.

kinases, suggesting that this is a fairly specific molecule. Inhibition of the IGF-1R tyrosine kinase was also associated with inhibition of both the PI3′K and MAPK signaling pathways, in response to IGF-1 stimulation of cells in culture. Both of these pathways are critical for the anti-apoptotic and mitogenic effects, which were inhibited. Mouse 3T3 fibroblasts overexpressing the human IGF-1R form tumors in nude mice, and subcutaneous injection of NVP-AEW541 inhibited the growth of these tumors.

The second study focuses on the effect of a similar second small molecule (NVP-ADW742) on hematologic malignancies, especially multiple myeloma (Mitsiades et al., 2004). This molecule also demonstrates a >16-fold greater potency against the IGF-1R, as compared to the insulin receptor, and was similarly effective in inhibiting cell growth and survival. When injected intraperitoneally, NVP-ADW742 inhibited multiple myeloma cell growth and enhanced survival of the mice. Importantly, when combined with Melphalan at subtherapeutic doses, the two compounds synergistically reduced tumor burden.

These studies prove that inhibition of the IGF-1R tyrosine kinase activity by small molecules is possible, and suggest that this approach may be useful in the treatment of human cancer. However, many questions remain to be answered:

(1) How should tumors be screened as candidates for treatment using this approach? As noted above, there are no examples of genetic alterations of this pathway in human tumors, so it is unclear how tumors should be selected for treatment. Is activation of the receptor in a tumor likely to predict responsiveness? Are tumors with LOI of IGF-2 likely to respond?

(2) Would small molecule therapy be used together with chemotherapy or between courses? Could this approach be more active if combined with kinase inhibitors targeting downstream molecules of the IGF-1R? Most chemotherapeutic regimens are cytotoxic, and the recurrences are assumed to be due to proliferation of cells that the chemotherapy failed to eradicate. These cells could potentially be killed off by the IGF-1R tyrosine kinase inhibitors.

(3) What effects may the inhibitors have on IGF-1Rs in normal tissues and even on the insulin receptor? While the small molecules described here have a 16- to 27-fold lower affinity for the IGF-1R than the insulin receptor, the relative affinities in patients and on different tissues remain unknown. It is hoped that intermittent therapy with these or similar agents may have minimal effects, perhaps only on tissues that demonstrate a high level of cellular turnover such as the bone marrow and gastrointestinal tract. These side effects may therefore be similar to those seen with chemotherapy and may be limited in extent and duration; clinical trials will be required to establish this. Regarding the insulin receptor, intermittent therapy may worsen insulin resistance and diabetes, which may be limited and easily treatable.

(4) Would these IGF-1R tyrosine kinase inhibitors be useful as chemopreventive agents?

Despite the numerous unanswered questions, the findings in these two studies represent a major advance in this area of research. They strongly support the contention that blockade of the IGF-1R may be an important form of adjunct therapy for cancer patients. It may reduce side effects by lowering the doses of chemotherapeutic agents, and perhaps making chemotherapy more effective, thereby increasing "cures" or remission rates and intervals. Whether the agent used is a humanized antibody, small peptide inhibitor, or small molecule (as described in these studies), it is becoming clear that the IGF system plays a critical role in the development and treatment of cancer.

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Selected reading

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