The Insulin-Like Growth Factor Pathway in Lung Cancer

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Abstract: The insulin-like growth factor (IGF) pathway is involved in the normal control of fetal development, tissue growth, and metabolism. Two distinct ligands (insulin-like growth factor-1 [IGF-1] and IGF-2) plus insulin, and two receptors (insulin-like growth factor receptor-1 [IGF-1R] and the insulin receptor) capable of both homo- and heteropolymerization mediate the actions of this pathway. Cellular functions of IGF-regulated signaling are influenced by the expression of a variety of receptor docking proteins, including four different insulin receptor substrate proteins. Downstream signaling is primarily through the phosphatidylinositol-3 kinase-Akt pathway and the mitogen-activated protein kinase pathway, resulting in increased cell proliferation and apoptosis inhibition. Ligand-driven activation is influenced by upstream endocrine factors (particularly for IGF-1), imprinting (for IGF-2), by multiple circulating and tissue-based IGF-binding proteins/proteases, and by the expression of the IGF-2 clearance receptor (IGF-2R). Deregulation of IGF signaling has been described in several cancer types, including both small cell and non-small cell lung cancer. A number of IGF receptor inhibitors, including monoclonal antibodies and small molecule inhibitors are currently undergoing testing in clinical trials as both monotherapy, and in combination with chemotherapy, or with other targeted agents. Preliminary results from a randomized phase II trial of an anti-IGF-1R monoclonal antibody in combination with carboplatin/paclitaxel already suggest a potential efficacy benefit from targeting this pathway in the first line advanced non-small cell lung cancer setting.

Key Words: Insulin-like growth factor, lung cancer.

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The insulin-like growth factor (IGF) pathway involves elements of endocrine, paracrine, and autocrine control in regulating fetal development, growth, and metabolism.[1] Growth hormone stimulates production of insulin-like growth factor-1 (IGF-1) in the liver and peripheral tissues. IGF-1 is also released locally in response to damage, either directly or through the action of other factors associated with tissue responses to damage, including epidermal growth factor, fibroblast growth factor, and platelet-derived growth factor.[1]

The related IGF-2 is present in the circulation at two to three times the levels of IGF-1, and is also produced in the liver and peripheral tissues, but its production is mostly controlled through imprinting-mediated gene dosage regulation.[2] IGF-1 is particularly important in somatic growth, with human mutations in IGF-1 producing severe growth retardation and mental impairment.[3] The role of IGF-2 seems to vary between species. In rodents, IGF-2 has a minor role in embryonic growth development but little role in adult animals, in contrast to in humans, where it is the predominant IGF in adults.[2] Both ligands mediate their effects through activation of the insulin-like growth factor receptor-1 (IGF-1R), which is highly homologous to the insulin receptor (IR). Each ligand also has some activity against IR splice variants (IR-A and IR-B) and/or hybrids of the two receptors (Figure 1). The IGF-1R has a 15- to 20-fold higher affinity for IGF-1 than IGF-2, consistent with its name. Nevertheless, the greater binding potential of IGF-2 across different receptors may give it a broader range of biologic functions than IGF-1. The IGF-2R has no known signal transduction properties and serves as a clearance receptor for IGF-2.[4] The concentration of free ligands and their exposure kinetics are tightly regulated in the circulation and/or periphery by a range of high-affinity binding proteins (IGFBP1–6) and their proteases. All the IGFBPs have a greater affinity than the IGF-receptors for their ligands. In general, it is difficult to ascribe simple roles to the IGFBPs as their effects, modulating the kinetics of free IGF exposure, could in theory, both increase and decrease IGF-related signaling, depending on the time frame considered. IGFBP3 is the dominant circulating binding partner for both IGFs, accounting for 70 to 80% of their blood levels.[1,5]

IGF-1R may also form hybrid multimeric receptors with other membrane receptors, for example, the epidermal growth factor receptor.[6] After ligand binding, conformational changes in the IGF-1R result in activation of its tyrosine kinase domain, phosphorylation of insulin receptor substrate proteins (IRS 1–4), and recruitment of a range of docking proteins The expression of different IRS molecules may be tissue specific, and may also differentiate various aspects of the malignant phenotype associated with this pathway, for example, IRS1 has been associated with proliferation, whereas IRS2 has been associated with metastatic behavior.[7,8] Downstream of the receptors the mitogen-activated

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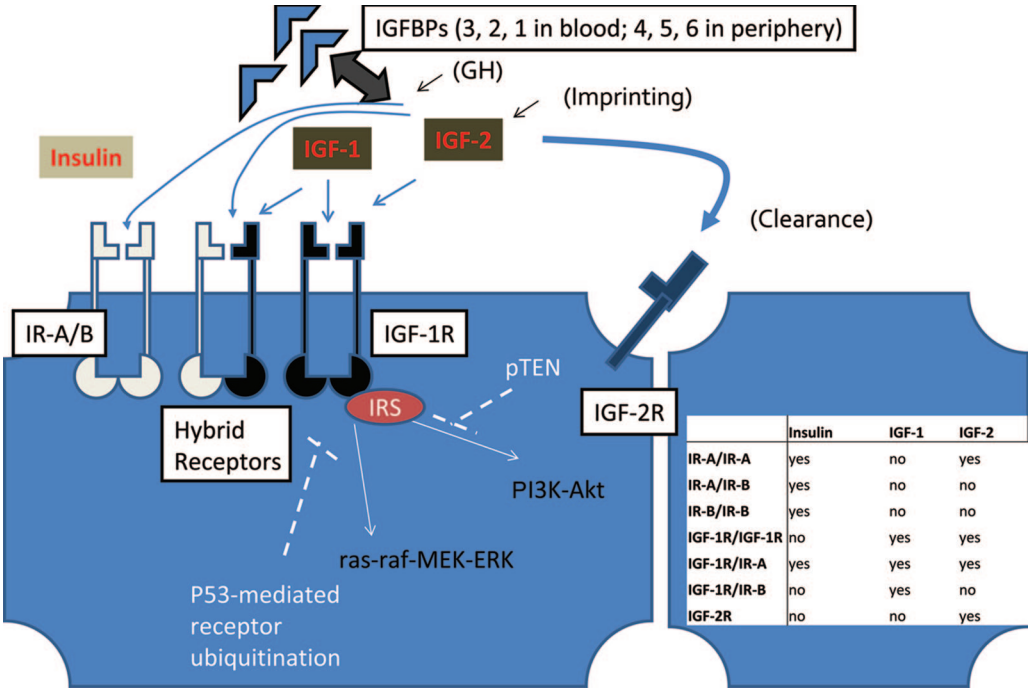

	Insulin	IGF-1	IGF-2
IR-A/IR-A	yes	no	yes
IR-A/IR-B	yes	no	no
IR-B/IR-B	yes	no	no
IGF-1R/IGF-1R	no	yes	yes
IGF-1R/IR-A	yes	yes	yes
IGF-1R/IR-B	no	yes	no
IGF-2R	no	no	yes

FIGURE 1. Schematic representation of the IGF axis at the level of a peripheral tissue. Three different ligands (insulin, IGF-1, IGF-2) affected by upstream elements of hormonal control (prediminatly IGF-1) and imprinting (IGF-2), six different binding proteins, three different receptors, and a range of intracellular substrates and docking proteins influence intracellular signaling. The avidity of the different ligands for the different receptor combinations are shown in the embedded table. Activity in the pathway is also influenced by pTEN inhibition of the PI3K pathway, and p53-mediated receptor down-regulation, and therefore mutations in either/both genes may influence a tumor's dependence on the pathway.

kinase and phosphatidylinositol-3 kinase-Akt (PI3K-Akt) pathways become broadly activated, leading to cell proliferation and inhibition of programmed cell death.

IGF PATHWAY AND LUNG CANCER

Multiple lines of evidence suggest involvement of the IGF pathway across a range of malignancies, including both non-small cell lung cancer (NSCLC) and small cell lung cancer.[9–11] Elevated plasma levels of IGF-1 have been associated with an increased risk of lung cancer, and high plasma levels of IGFBP3 associated with a reduced risk.[11,12] Similarly, IGFBP3 promoter methylation in tumor cells has been linked to decreased survival in stage I NSCLC patients.[13] A large case-control study of Whites identified 64 single nucle-

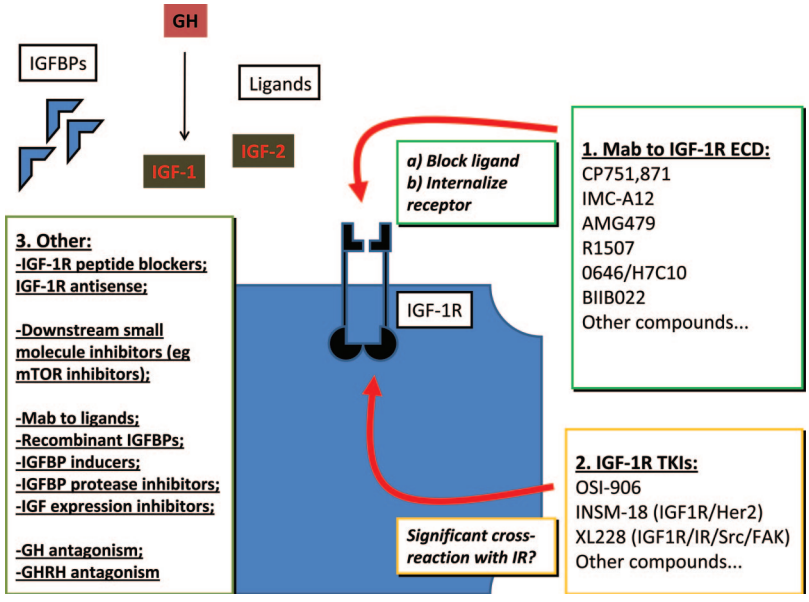

FIGURE 2. Potential therapeutic strategies for reducing IGF pathway signaling. The dominant strategies currently being explored in the clinic are the monoclonal antibodies directed against the extracellular domain of the receptor, and small molecule inhibitors of the IGF-1R tyrosine kinase domain.

otide polymorphisms associated with lung cancer risk, of which 11 were related to the growth hormone-insulin-like growth factor axis.[14] Preclinically, IGF-1R activation acts as a cofactor for malignant transformation by a number of different stimuli.[15] Transgenic mice engineered to express constitutively active IGF-1R develop malignant tumors, including salivary and mammary adenocarcinomas.[16] Nearly 70% of transgenic mice over-expressing IGF-2 develop lung adenocarcinomas by 18 months of age.[17]

DEVELOPMENT OF IGF-1R INHIBITORS IN LUNG CANCER

There are several strategies being explored to disrupt IGF pathway signaling in cancers (Figure 2).[18,19] The two dominant strategies currently being explored are monoclonal antibodies directed against the extracellular domain of the IGF-1R, and small molecule inhibitors of its intracellular kinase domain. The monoclonal antibodies are further advanced in clinical development at present and seem to act primarily through down-regulation of the IGF-1R.[20] In contrast, the small molecule inhibitors seem to reduce signaling without requiring receptor internalization.[21] Because of direct effects on IRs, and/or complementary signaling between the pathways, hyperglycemia (potentially controllable with oral agents such as metformin) has already been noted and is anticipated to be a class-specific toxicity. IGF-1R activation provides a potential mechanism of cell protection to cytotoxic chemotherapeutics through increased downstream signaling through the prosurvival PI3K-Akt pathway.[22,23] Results of studies on cell lines and xenografts suggest synergistic activity of IGF-1R inhibitors with a variety of cytotoxic agents.[24–26] Prolonged treatment of NSCLC cell lines with low concentrations of erlotinib or gefitinib resulted in acquired resistance mediated by activated IGF-1R with IGF-1R/epidermal growth factor receptor heterodimer formation leading to up-regulation of survivin expression.[6,27] IGF-1R activation is also involved in protection from ionizing radiation, and IGF-1R inhibitors increase radiation sensitivity of NSCLC cell lines.[28,29] These findings support the clinical testing of combinations of IGF-1R inhibitors with both traditional anticancer therapies (cytotoxics, radiotherapy) and targeted agents in lung cancer. Phase I monotherapy study results reported for the monoclonal antibodies CP-751,871, R1507, AMG 479, and IMC-A12 have shown little in the way of toxicities, apart from some hyperglycemia and, for some of the antibodies, thrombocytopenia.[30–33] There have been hints of single agent activity across several different cancer types in these all-comers studies, but noted dramatic single agent activity in Ewing sarcoma patients, fast-tracking a range of subsequent sarcoma-specific phase II studies.[32] To date, in lung cancer, preliminary phase II results of only one anti-IGF-1R agent have been reported. In a randomized first-line advanced NSCLC phase II study of paclitaxel and carboplatin plus/minus CP751,871, 46% of patients in the experimental arm achieved objective responses (22/48 patients) versus 32% (8/25 patients) in the control arm.[31] An unplanned subgroup analysis by histology has suggested a greater benefit in patients with squamous histology within this trial, but the results of additional patient numbers, including planned enrichment for those with squamous histology, are awaited.

CONCLUSIONS

The IGF pathway is implicated in the induction and maintenance of a range of different malignancies. Its activity is influenced by a range of different ligands, upstream hormonal regulation, imprinting, binding protein and protease expression, signaling and clearance receptor expression and hybridization, and intracellular substrate expression. Clinical data already show a favorable toxicity profile and some monotherapy activity signals for several anti-IGF-1R monoclonal antibodies, whereas little data on the tolerability or efficacy of the small molecule inhibitors of the IGF-1R are currently available. Early efficacy signals from a phase II study of CP-751,871 in combination with carboplatin/paclitaxel in advanced NSCLC are promising, however, final reports of this trial are awaited and several other trials of anti-IGF-1R antibodies in combination studies in lung cancer are ongoing. The challenge will inevitably be how to optimally select patients to treat with IGF-1R inhibitors based on the molecular characteristics of their tumors, and several correlative studies looking across the range of factors known to influence activating within this pathway are currently underway in association with these clinical trials.

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