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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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.\textsuperscript{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.\textsuperscript{11,12} Similarly, IGFBP3 promoter methylation in tumor cells has been linked to decreased survival in stage I NSCLC patients.\textsuperscript{13} A large case-control study of Whites identified 64 single nucle-
otide polymorphisms associated with lung cancer risk, of which 11 were related to the growth hormone-insulin-like growth factor axis. Preclinically, IGF-1R activation acts as a cofactor for malignant transformation by a number of different stimuli. Transgenic mice engineered to express constitutively active IGF-1R develop malignant tumors, including salivary and mammary adenocarcinomas. Nearly 70% of transgenic mice over-expressing IGF-2 develop lung adenocarcinomas by 18 months of age.

DEVELOPMENT OF IGF-1R INHIBITORS IN LUNG CANCER

There are several strategies being explored to disrupt IGF pathway signaling in cancers (Figure 2). 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. In contrast, the small molecule inhibitors seem to reduce signaling without requiring receptor internalization. Because of direct effects on ERs, 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. Results of studies on cell lines and xenografts suggest synergistic activity of IGF-1R inhibitors with a variety of cytotoxic agents. 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. IGF-1R activation is also involved in protection from ionizing radiation, and IGF-1R inhibitors increase radiation sensitivity of NSCLC cell lines. 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 agents, thrombocytopenia. There have been hints of toxicities, and assays to influence activating within this pathway are currently underway in association with these clinical trials.

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.

REFERENCES


