

Insulin-Like Growth Factor and Lung Cancer

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Lung cancer is the leading cause of cancer-related death in the United States. Despite the availability of several cytotoxic and a few molecularly targeted agents, the outlook for patients with advanced non-small cell lung cancer continues to be dismal. Novel approaches are desperately needed. The insulin-like growth factor (IGF) pathway plays an important role in a number of human malignancies contributing to unregulated cell proliferation. The IGF pathway has several targets for therapeutic intervention. Preclinical studies of IGF inhibitors have demonstrated synergism when combined with chemotherapy agents and radiation. Clinical studies are currently ongoing to investigate the safety and efficacy of IGF inhibitors in combination with chemotherapy agents. In this review, we discuss the biology of the IGF pathway and various potential targets for therapy.

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

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Insulin-like growth factor (IGF) is a polypeptide growth factor with functional homology to insulin.¹ IGF has a wide range of metabolic and developmental functions, including embryogenesis and postnatal organogenesis.² The IGF signaling pathway plays a critical role in regulating cell proliferation and apoptosis. In this review, we discuss the rationale for targeting the IGF pathway in the treatment of non-small cell lung cancer (NSCLC) (Figure 1).

THE IGF PATHWAY

The IGF system involves complex regulatory network comprising IGF-1 and IGF-2 ligands, six specific high-affinity binding proteins (IGFBP-1 to IGFBP-6) and IGFBP proteases (IGFBP-prs), and IGF-1 and IGF-2 cell surface receptors (IGF-1R and IGF-2R).³ The half-life and bioavailability of IGF-1 and IGF-2 in circulation varies depending on the affinity and specificity of the IGFBPs in the serum.⁴ IGFBP-3, the most critical of the binding protein, binds to 70% to 80% of the IGF-1.⁵ Various matrix metalloproteinases (MMPs), often secreted by the tumors, exert proteolytic

action on IGFBPs, particularly IGFBP-3, thus increasing the bioavailability of IGFs for receptor-mediated action.^{6–9} In addition, IGFBP-3 seems to have a non-IGF mediated anti-proliferative and pro-apoptotic action resulting from its association with cell surface proteins or receptors.¹⁰

Most of the actions of IGF-1 and IGF-2 are mediated by high-affinity ligand binding to IGF-1R, although recent evidence suggests that actions of IGF-2 are also mediated through the high-affinity binding with an insulin receptor (IR) isoform-insulin receptor exon 11 isoform (IR-A).¹¹ Upon binding of the IGFs to IGF-1R, the receptor's intrinsic tyrosine kinase is activated, resulting in the phosphorylation of the insulin receptor substrates (IRSs).^{11–13} The tyrosine-phosphorylated IRS activates phosphatidylinositol-3kinase (PI3K), which catalyzes the conversion of phosphatidylinositol biphosphate (PIP2) to phosphatidylinositol triphosphate (PIP3). V-Akt murine thymoma viral oncogene homolog (Akt) is activated by PIP3. Activated Akt results in a cascade of phosphorylation events in the cytosol, resulting in inactivation of key proteins (Bcl-2 antagonist of cell death, caspase 9, and forkhead transcription factor family) involved in apoptosis.¹⁴ The activation of IGF-1R also modulates the voltage-gated calcium channels, causing transient increase in the intracellular Ca₂⁺ level and thereby regulating the nuclear transcription factor, cAMP response element-binding protein (CREB). IGF-2 accentuates the survival and proliferation of lung cancer cells by increasing phosphorylation of CREB via the erk5 pathway.^{15,16}

The insulin growth factor-II receptor (IGF2R) lacks signal transduction capability, and its main role is to act as a sink for IGF II and make less IGF II available for binding with IGF-1R.¹⁷

THE IGF PATHWAY IN LUNG CANCER

Autocrine production of IGF by the tumor cells and high levels of IGF 1 have been reported in the lung tumor tissue.^{18,19} Human lung cancer cells also seem to have a higher expression of IGF-2 compared with normal cells and is associated with poor prognosis.^{16,20} IGF-2 is overexpressed in both the small cell lung cancer (SCLC) and NSCLC cell lines.²¹ Increased expression of IGF-2 in lung cancer results from aberrant regulation of the genomic imprinting mechanism of IGF-2 and mesoderm-specific transcript genes.²² Genetic aberrations of the M6P/IGF2R locus have been reported in lung cancer cell lines.^{23–25} More studies of lung tumor tissue are needed to further elucidate the role of M6P/IGF2R gene in the onset and progression of lung cancer.

The IGF-1R seem to be overexpressed in both NSCLC and SCLC.^{26–28} Increased metastatic activity was reported in

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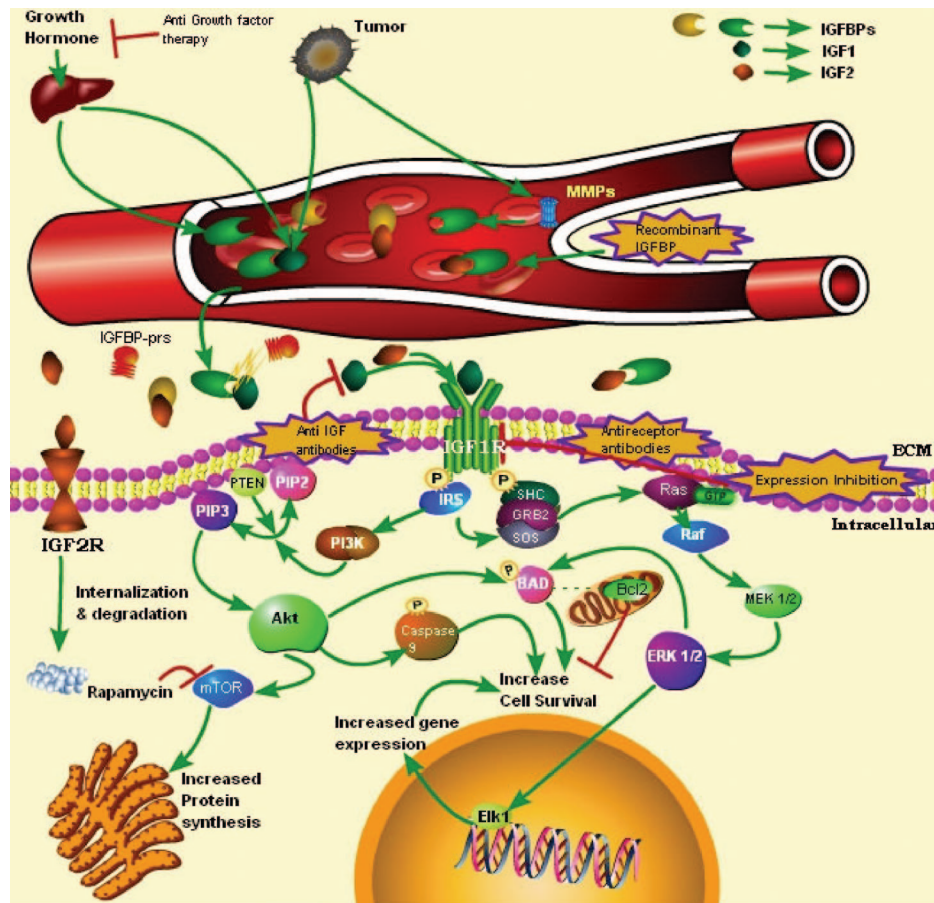


FIGURE 1. The insulin-like growth factor pathway.

mice after intrasplenic injection of lung cancer cell lines transfected with IGF-1R receptors.²⁹

Decreased expression of IGFBP-3 is also associated with a higher risk of lung cancer indirectly by increasing the bioavailability of IGF ligands.^{30–32} IGFBP-3 expression levels are low in one of the four SCLC cell lines and all four of the NSCLC cell lines studied.³³ Hypermethylation of the IGFBP-3 promoter is common (>60%) in NSCLC tissue and is strongly associated with poor prognosis in patients with stage 1 NSCLC (5-year overall survival of patients with IGFBP-3 versus patients without IGFBP-3 hypermethylation is 38.9% versus 64.0%).³⁰

A recently published report on a genome wide scan of 1529 patients with lung cancer and 2707 controls in the United Kingdom reported strong evidence that low-penetrance alleles of genes involved in the growth hormone IGF axis are associated with lung cancer susceptibility.³⁴ In a case control study of 204 consecutive patients with primary lung cancer and 218 age-, sex-, race-, and smoking status-matched control subjects, a higher plasma levels of IGF-1 was associated with an increased risk of lung cancer (OR 2.06; CI 95%).³⁵ IGF-mediated signaling mechanisms are essential for the proliferation, survival, and metastases of lung cancer cells. Inhibition of IGF activity is associated with decreased tumor growth in vitro.^{36–38} There are several ongoing studies

exploring the possible therapeutic role of targeting IGF regulation.

THE IGF PATHWAY AS A THERAPEUTIC TARGET

The IGF pathway presents several targets of interest for molecular therapeutics. The possible therapeutic strategies targeting IGF axis-targeted therapies are growth hormone-releasing hormone antagonists, somatostatin analogs, growth hormone (GH) receptor antagonists, IGF-1R antibodies, antibodies directed against IGF ligands, and increasing levels of IGFBP-3.

Clinical trials using somatostatin and other GH receptor antagonists failed to show significant benefit, perhaps because of inadequate reduction in the levels of IGFs. The effect of growth hormone in regulating IGFs of tumor origin is possibly limited; thus, strategies targeting GH may not offer a significant antitumor action.

In vitro studies demonstrated that inhibition of the IGF-1R signaling pathway in human NCLC cells A549 has tumor-inhibiting action and enhances sensitivity to apoptosis-inducing agents.^{39,40} Inhibition of IGF-1 signaling using IGF-1R kinase inhibitor NVP-ADW742 has a synergistic increase in the sensitivity of SCLC cell lines to etoposide and

carboplatin.⁴¹ In vitro studies of dual inhibition of IGF-1R (AG 1024) and c-kit activity (AG 1296) produce synergistic activity in SCLC cell lines.⁴²

In vitro studies on six NSCLC cell lines' blocking of IGF-1R function with anti-IGF-1R monoclonal antibodies potentiated the cytotoxic effects of radiation in a synergistic fashion in one cell line, in an additive fashion in four cell lines, and in a sub-additive fashion in one cell line.⁴³ Complete inhibition of tumor growth has been observed when anti-IGF-1R antibody (h7C10) is combined with vinorelbine or an anti-epidermal growth factor receptor antibody in animal models.⁴⁰ Clinical trials are currently ongoing to assess the safety and efficacy of human monoclonal antibodies specific for IGF-1R, such as CP-751,871 in advanced NSCLC.

Human monoclonal antibodies specific for IGF-2 have been developed (IgG1 m610), and these antibodies showed good inhibitory activity in in vitro models. IGF-1R is widely expressed, has a broad range of physiological actions, and bears a high homology to the insulin receptor; hence, the use of IGF-1R antibodies could possibly result in more toxicities compared with the use of antibodies directed against IGF ligands.⁴⁴

Transfection of IGFBP-3 into lung cancer cell lines seemed to have profound antitumor effect to the tumor cells in vitro and in vivo.^{45,46} Similar results have been found using recombinant human IGFBP-3 in lung carcinoma models using 3LL Lewis lung carcinoma allograft, suggesting a potential therapeutic role of IGFBP-3.^{47,48} Thus, IGBP-3 may also represent a potential target.

In summary, the IGF pathway seems to play a critical role in human neoplasia in general and in lung cancer in particular. Clinical trials with IGF inhibitors just begun in NSCLC hopefully will show promising results.

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