Journal of International Translational Medicine 2013; 1(1): 18-22

Review Open Access

Advance on Insulin-like Growth Factor Binding Protein 2 in Lung Cancer and Other Solid Tumors

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ABSTRACT

Increasing evidence has revealed that IGF signalling plays a key role in cellular proliferation, survival, differentiation and senescence. Dysregulation of this signalling pathway is related to the development and progression of many human diseases, including cancer, diabetes and atherosclerosis. Insulin-like growth factor binding protein-2 (IGFBP-2) is reported to be a modulator of the action of insulin-like growth factors (IGFs), whereas IGF-independent effects of IGFBP-2 on cellular proliferation, apoptosis, and mobility have been revealed not only during the embryonic state but also in the pathological state of cancer. IGFBP-2 is involved in the genesis and progress of various malignancies including lung cancer. Recent findings show in many pre-clinical trials that IGFBP-2 may contribute to the transformation and progression of lung cancer. These studies suggest that IGFBP-2 may be a potential therapeutic target for lung cancer.

In this review, we provide an overview on IGFBP-2, review corresponding studies investigating the role of IGFBP-2 as a cancer target in multiple tumors and discuss its possible mechanism in lung cancer.

Key words: Insulin-like growth factor binding protein 2; Lung cancer; Insulin-like growth factor

Introduction

IGF system[1] is composed of two peptide ligands (IGF-1 and IGF-2), two IGF receptors (IGF-1R and IGF-2R) and six high-affinity IGF-binding proteins (IGFBP-1 to IGFBP-6). Its biologic effects are mediated by IGF-1 receptor (IGF-1R). IGFs play the central roles in cell growth, differentiation and survival under physiological conditions. A deregulated IGF axis has been associated with tumor initiation and progression[2]. IGFs influence carcinogenesis, tumorigenesis, metastasis as well as resistance to chemotherapeutics and molecular drugs. According to juicy pre-clinical and clinical evidence, IGF-1R activation increases the tumorigenic potential of breast, prostate, lung, colon and head and neck squamous cell carcinoma (HNSCC).

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When IGFs bind to their receptors, they activate the downstream signaling cascades via the phosphorylation of tyrosine kinase. Activated IGF-1R transmits signals to the major distinct pathways phosphatidyl insitol 3-kinase(PI3K) and mitogen-activated protein kinase(MAPK), which are highly implicated in the development and progression of neoplasia[3]. Agents targeting the IGF axis have been successfully developed, primarily employing mAb and TKI approaches. To date[4], as many as 30 different agents targeting the IGF1R are in preclinical or clinical development and over 60 active clinical trials evaluating the anti-IGF1R targeting are ongoing.

The IGF-binding proteins (IGFBPs) represent the third component of IGF system consisting of a class of six soluble

secretory proteins. They represent a unique class of naturally occurring IGF-antagonists that bind to and sequester IGF-1 and IGF-2, inhibiting their access to the IGF-1R. The actions of IGFs can be modulated by the IGFBPs in either a positive or negative way, depending on tissue type and physiological/pathological status. Furthermore, IGF-independent effects of IGFBPs have been described. Due to their targeting of the IGFs without affecting insulin action, the IGFBPs are a novel class of IGF-1R inhibitors. Therefore, it may provide a new and effective therapy target for the diagnosis and treatment of lung cancer and other solid tumors to study further on the genesis mechanism. The latest research of IGFBP-2 in lung cancer and other solid tumors are outlined in this review.

IGFBPs as a New Therapeutic Method

Characteristics in common

IGFBPs consist of conserved N- and C-terminal domains (33-46% identity) connected by a non-conserved linker region (L-domain),whose distribution has tissue specific[5]. Both the N- and C-domains of IGFBPs are involved in high affinity IGF binding[6], but the three-dimensional (3D) structure of a full-length IGFBP has not been determined. The development of anti-cancer drugs based on the modulation of individual IGFBPs activity depends on gaining a detailed knowledge of their mechanism of action.

IGFBPs and IGF have higher affinity than IGF-1R and IGF. IGFBPs participate in regulating the bioavailability and biological activity of IGF. By combing with IGF, IGFBPs form a stable complex, which blocks the downstream signal pathways of IGF-1R. However, the complex can be cracked by proteinase[7]. The slowly released IGF then combines with IGF-1R to promote the downstream IGF-1R signal pathways. Therefore, in different conditions, IGFBPs may decrease or enhance the biological effects of IGF.

New therapeutic target

Nowadays, the prevalence of toxicities to IGF-1R directed mAbs and TKIs begs the question[4] whether targeting the ligands, IGF-1 and IGF-2 might be a viable alternative with the potential of reduced toxicities other than hyperglycemia.

When IGFBPs are present in excess, the release of IGFs from IGFBPs is markedly reduced and consequently IGF signals are decreased. It provides feasibility for IGFBPs therapy to the IGF-1R targeting. Besides, IGFBPs selectively bind IGFs and do not influence insulin, which is relatively safe compared to mAbs and TKIs. The efficacy of IGFBPs remains unclear so far. It needs more animal models in vivo and preclinical trials to test and verify.

IGFBP-2 in Lung Cancer

Fundamental information of IGFBP-2

IGFBP-2 mRNA expression is at high levels in many tissues during embryonic and fetal development[8]. In the postnatal period, IGFBP-2 is the second most abundant IGFBP in the circulation. IGFBP-2 is abundant in human cerebrospinal fluid, which depends on the insulin expression and metabolism condition[9]. IGFBP-2 is also present in other biological fluids and tissues of many vertebrate species. IGFBP-2 expression increases after fasting in a variety of pathological conditions. IGFBP-2 is over-expressed in many malignancies and is often correlated with an increasingly malignant status of the tumor, pointing to a potential involvement of IGFBP-2 in tumorigenesis.

In 1999, Dr Fuller first reported in his research that IGFBP-2 was highly expressed in more than 80% of the glioma patients. After that, more researches have been published about its high expression in gastric carcinoma, prostate cancer, lung cancer and other tumors. IGFBP-2 has been proposed as a possible target for the development of novel anti-cancer therapeutics[10].

Research of IGFBP-2 in lung cancer

In lung cancer, IGFBP-2 exerts various biological functions by virtue of IGF-dependent or –independent mechanisms[11]: a. Soluble IGFBP-2 binds to IGFs and consequently inhibits IGF signaling in various human cancers; b. Membrane-associated IGFBP-2 stimulates or inhibits cell proliferation and migration through a direct binding to serum and extracellular matrix molecules.

IGFBP-2 is over-expressed in peripheral blood[12], multiple lung cancer cell lines and tumor tissue[11, 13]. According to relevance reports[11], IGFBP-2 was highly expressed in A549, NCI-H460 cells, but expressed at very low levels in HOP62 and COR-L105 cells. A higher amount of IGFBP-2 protein was also frequently observed in tumor tissue (lung adenocarcinoma and SCLC) compared with paired normal tissue[11, 14].

The expression of IGFBP-2 is sclosely related to the clinical stages metastasis of lymph nodes in lung cancer, and this implies

the role of IGFBP-2 in the development and progression of lung cancer. Yu *et al*[15] showed in their report: IGFBP-2 level increased in patients with malignant pleural effusion (MPE) in the lung, compared with that in benign diseases. This data support the function of IGFBP-2 in migration in lung cancer cells and implies possible application of IGFBP-2 as a potential maker of malignant effusions[16].

However, there also exists a report differing from above data[17], more questions are still in need of studying about the action mechanism of diagnosis, treatment and prognosis in lung cancer: a. Whether IGFBP-2 is associated with pathological types, smoking history, gender and race; b. The specific mechanism between IGF-1R expression and IGFBP-2; c. The molecular mechanism of IGFBP-2 in promoting metastasis and progression. With emergency of new technology in gene expression and gene function, it will make greater achievements in near future about whether IGFBP-2 can be considered as an independence diagnostic and prognostic factor. Researches on IGFBP-2 in PCa, breast cancer and other solid tumors are relatively mature, which is worth of study in the lung cancer research for reference.

Research of IGFBP-2 in Other Solid Tumors and Its Implication

Research of IGFBP-2 in prostate cancer

IGFBP-2 has garnered interest as a candidate target for prostate cancer (PCa) development and progression. IGFBP-2 is expressed in invasive PAc, whereas its expression in HG-PIN is low. These findings can be helpful in the correct diagnosis of PAc both in biopsies and in surgical specimens, mainly in untreated patients. IGFBP-2 can serve as an immunohistochemical marker for PCa[20]. Further study confirmes that IGFBP-2 plays a key role in the growth of prostate cancer cells, and silencing IGFBP-2 expression reduces the resistance of these cells to docetaxel. Targeting IGFBP-2 may increase the efficacy of docetaxel[21].

Based on a series of literature, we describe the ability of IGFBP-2 in PCa in three aspects: a. to promote the survival of PCa cells in a castrate environment[20-22]; b. to facilitate the progression to AI[23]; c. to possibly enhance the aggressive behavior of AI PCa cells[24]. IGFBP-2 may be an important driving force in the development of metastatic, hormonally refractive and bone-colonizing PCa.

Currently, studies are needed to determine a. if IGFBP-2 selectively promotes the growth of AI-PCa cells, b. the molecular basis for IGFBP-2 induced migration, metastasis, and invasion, and c. better therapeutic targets for AI PCa and PCa metastasis.

According to these achievements, new research directions in the lung cancer of IGFBP-2 study can be proposed: does IGFBP-2 play a vital role in the chemotherapy resistance of lung cancer? whether IGFBP-2 possesses organ and tissue specificity in invasion and metastasis procedure of lung cancer cells? can treatment directing at IGFBP-2 effectively control progression of lung cancer?

Research of IGFBP-2 in breast cancer

Trastuzumab (Herceptin) is an effective drug against breast cancer. It is known that trastuzumab (an antibody) binds specifically to HER2 to acquire its efficiency. Based on a report, IGFBP-2 stimulates HER2 activation, but rastuzumab reduces IGFBP-2-induced ErbB2 activation to mediate growth inhibition. Changes in secretion profiles of IGFBP-2 may promote the development of IGFBP-2 as a predictive biomarker for trastuzumab resistance.

Recent studies have suggested that not only does IGFBP-2 have a direct proliferative effect on tumor growth but also the protein is a regulator of phosphatidylinositol 3-kinase (PI3K)/Akt activation and may facilitate the malignant transformation (11-13). Stimulating immune eradication of IGFBP-2–overexpressing breast cancer cells may potentially affect cancer progression. Studies[25] on cells in vitro and in transgenic mouse model of breast cancer indicated that T cells specific for IGFBP-2 inhibit tumor growth. For example, over-expression of IGFBP-2 in the MDA-MB-231 ER-negative breast cancer cell line conferred a growth advantage and chemoresistance[26]. Correspondingly, down-regulation of IGFBP-2 using OGX-225, both in IGFBP- 2-overexpressing MDA-MB-231BP-2 cells and in MDA-MB-468 cells that endogenously produces IGFBP-2, abrogates the cytoprotective benefits of IGFBP-2. Besides, OGX-225 may serve as a candidate therapeutics for IGFBP-2-expressing breast cancers.

It was reported[27-28] that IGFBP-2 was an independent and positive predictor of overall survival (hazard ratio, 0.48; 95% confidence interval, 0.24-0.95; P=0.04). These results contrast with abundant experimental evidence showing IGFBP-2 to promote cell proliferation and growth. Given the discordant effects of IGFBP-2 on cell proliferation and tumorigenesis, we need confirmation in larger patient series.

Similarly, in the lung cancer study, we can easily put forward the following questions: a. Are there any interactions in IGFBP-2 and current targeted therapy? b. What position does IGFBP-2 have in the malignant transformation of cancer cells? c. Does immune eradication of IGFBP-2–overexpressing lung cancer cells have the same treatment significance? d. Can IGFBP-2 take the place of the classic treatment to be a novel way?

Impossible mechanism of IGFBP-2

Reports of domestic and foreign literatures about the mechanism of IGFBP-2 mainly include:

IGF-independent antiapoptotic effect via caspase-3[11]

Several authors have proved that enforced procaspase-3 potentiates sensitivity to chemotherapy and promotes apoptosis. In the lung cancer, decreased caspase-3 expression has been shown as a poorer prognostic factor in non-small-cell lung cancer. In NCI-H522 cells, IGFBP-2 over-expression resulted in the decrease in procaspase-3 expression. Besides, apoptosis induced by camptothecin was significantly inhibited. Conversely, selective knockdown of IGFBP-2 and application of phosphatidyl-inositol 3-kinase LY294002 inhibitor resulted in the increase in procaspase-3 expression and sensitization to camptothecin-induced apoptosis. Immunohistochemistry demonstrated that intracellular IGFBP-2 was highly expressed in lung adenocarcinomas compared with normal epithelium. Intracellular IGFBP-2 and procaspase-3 were expressed in a mutually exclusive manner. These findings suggest that intracellular IGFBP-2 regulates caspase-3 expression and contributes to the inhibitory effect on apoptosis independent of IGF. IGFBP-2 may offer a novel therapeutic target and serve as an antiapoptotic biomarker for lung adenocarcinoma.

The function of p53 gene

The p53 tumor suppressor induces cellular growth arrest and apoptosis in response to DNA damage by transcriptionally activating or repressing target genes and also through protein-protein interactions and direct mitochondrial activities. In 1995, IGFBP-3 was identified as one of the genes transcriptionally activated by p53. Like IGFBP-3, IGFBP-2 secretion is reduced when p53+/+ lung cancer cells are transfected with human papillomavirus E6. IGFBP-2 mRNA is induced by irradiation in vivo in a p53-dependent manner. p53 protein binds IGFBP-2 intronic sequences in an electrophoretic mobility shift assay, and activates transcription in a luciferase assay. Decreasing IGFBP-2 can restrain the function of p53 gene, block regulatory enzyme of IGF-induced mitosis, and promote cell apoptosis[18].

Other mechanisms

IGFBP-2 also exerts effects on activation procession of K-ras[19]. However, it remains lack of systematic research and analytic reports. In neuroendocrine carcinoma, IGFBP-2, differing from NSCLC, is called NeuroD[14], a neuroendocrine specific transcription factor, that affects the downstream signaling pathway. Secreted IGFBP-2 contributes to the slow growth of SCLC in vitro, and the epigenetic alterations in the IGFBP-2 promoter contribute to the striking differences in IGFBP-2 expression between SCLC and NSCLC in vivo.

Conclusion and Prospective

Lung cancer is the leading cause of cancer death in the world. Despite recent progress in the treatment of lung cancer with molecular targeted agents in combination with platinum-based chemotherapy for the first-line treatment, new therapies are still in need for the maximum efficacy. IGF-1R pathway has been implicated in the pathogenesis of lung cancer, and most adverse effects of IGF-1R inhibitors are tolerable and manageable. Hyperglycemia appears to be a typical effect.

IGFBP-2 is a highly sensitive maker of malignant progression in different tumors, including lung cancer. IGFBP-2 models in vivo and in vitro suggested that binding of IGFs by IGFBP-2 has growth-inhibitory consequences. Therefore, it provides a new research direction for solving the problem of chemotherapy resistance in the lung cancer to further study IGFBP-2 mechanism. IGFBP-2 may not only seemed as a biomarker for disease diagnosis and prognosis forecasting, but also a novel target for the treatment of lung cancer. Specific IGFBP-2 pathways and mechanisms in lung cancer have no clear conclusion, so further research is still needed. The applied prospects of IGFBP-2 can be foreseen in terms of current research.

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