Prognostic Implications of Tumoral Expression of Insulin Like Growth Factors 1 and 2 in Patients With Non–Small-Cell Lung Cancer

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Abstract

The expression levels of IGF-1 and IGF-2 are characterized and evaluated for their association with IGF-1R and phosphorylated IGF-1R expression in non–small-cell lung cancer (NSCLC). The overexpression of IGF-1 predicts poor survival among patients with NSCLC, especially those with adenocarcinoma. These results might serve as a future guide for clinical trials involving IGR-1R-targeting agents.

Introduction: The currently available systemic therapies for non–small-cell lung cancer (NSCLC) have limited efficacy. Previous studies indicated an association of elevated insulinlike growth factor (IGF)-1 receptor (IGF-1R) and insulin receptor expression levels with poor survival in patients with NSCLC. To better understand the molecular biomarkers involved in the IGF signaling pathway in NSCLC, the expression levels of IGF-1 and IGF-2 are characterized and evaluated for their association with IGF-1R and phosphorylated IGF-1R (pIGF-1R) expression in NSCLC. **Materials and Methods:** A total of 352 patients who underwent NSCLC resection with curative intent were studied. The expression patterns of the IGF-1, IGF-2, IGF-1R, and pIGF-1R proteins were assessed immunohistochemically using tissue microarrays. **Results:** The IGF-1 expression was higher in patients with adenocarcinoma (ADC) than in those with squamous cell carcinoma (SCC), whereas the IGF-2 score was higher in patients with SCC than those with ADC. Likewise, the IGF-1 score was higher in patients with mutated epidermal growth factor receptor (mtEGFR) than in those with wild type EGFR (wtEGFR), whereas the IGF-2 score was higher in patients with wtEGFR than in those with mtEGFR. Patients with low levels of IGF-1 expression had longer overall survival (OS) than those with high IGF-1 expression, and subgroup analyses found a significant difference in OS only in patients with ADC. **Conclusion:** The overexpression of IGF-1 predicts poor survival among patients with NSCLC, especially those with ADC. These results might serve as a future guide for clinical trials involving IGF-1R-targeting agents.

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Introduction

Lung cancer accounted for 13% (1.6 million) of all cancer cases and 18% (1.4 million) of the cancer deaths in 2008 worldwide.[1] The 2 major forms of lung cancer are non–small-cell lung cancer (NSCLC) (approximately 85% of all lung cancers) and small-cell lung cancer (approximately 15% of lung cancers). NSCLCs are further divided into 3 major types: squamous cell carcinoma (SCC), adenocarcinoma (ADC), and large-cell carcinoma. Despite recent advances in treatments for the disease, the currently available systemic therapies for NSCLC have limited efficacy, indicating the need for innovative treatment strategies.[2]

The insulinlike growth factor 1 receptor (IGF-1R) signaling pathway has important roles in tumorigenesis, metastasis, and

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resistance to existing forms of anticancer therapy. The main components of the IGF axis include receptors (IGF-1R and insulin receptor [IR]), ligands (IGF-1 and -2), and at least 6 high-affinity IGF-binding proteins (IGFBP-1 to IGFBP-6) that regulate the availability of the IGF-1R ligands. Targeting the IGF signaling pathway is one evolving anticancer therapy with potential efficacy; however, the outcomes of recent phase III clinical trials with a monoclonal antibody against IGF-1R (IGF-1R mAb) have been unsatisfactory.[3] IR has been proposed to induce intrinsic resistance, acquired resistance, or both to IGF-1R-targeted antibodies.[4] In this respect, cotargeting IGF-1R and IR might be more effective in blocking the IGF-1R/IR pathway in patients with NSCLC. Nonetheless, a better understanding of the molecular biomarkers involved in the IGF-1R signaling pathway is necessary to develop effective therapeutic strategies and to identify the target population for anticancer remedies with IGF-1R inhibitors.

A recent study found that elevated IGF-1R and IR expression levels in NSCLC were associated with poor survival.[5] However, the effect of IGFs on lung cancer risk and prognosis remains controversial. Recent prospective studies have suggested that IGF-1 levels are related to the risk of some epithelial cancers.[6] A nested case-control study from the Beta-Carotene and Retinol Efficacy Trial in heavy smokers found a modest association between serum IGF-1 level and lung cancer risk.[7] Conversely, IGF-1 level was not associated with elevated lung cancer risk in the Alpha-Tocopherol/Beta-Carotene Cancer Prevention Study.[8] Serum levels of IGFs were higher in patients with lung cancer than in healthy participants.[9] More recently, high plasma levels of IGFs and IGFBP-3 were associated with good prognosis in patients with advanced NSCLC in a phase II study with chemotherapy.[10]

All of the aforementioned studies have evaluated serum or plasma IGF levels, which fail to reflect the effect of these ligands from autocrine or paracrine production on aggressive cancers.[11] This study was conducted to assess the effect of tumoral expression of IGF-1 on the survival of patients with NSCLC.

Materials and Methods

Patient Characteristics

The baseline characteristics of the patients represented in the tissue microarray (TMA) are described in Table 1. Detailed clinical and pathologic information was available for most of these cases and included patient demographic data, smoking history (never-smokers or ever-smokers, patients who had smoked at least 100 cigarettes in their lifetime), pathologic TNM staging, overall survival (OS) time, and recurrence-free survival (RFS) time. The TMA included similar numbers of samples from men and women, and nearly two-thirds of the samples were from patients with ADC. Most patients had early-stage lung cancer and were former or current smokers. The tissue banking and research conduct protocols were approved by the MD Anderson Cancer Center Institutional Review Board. All patients provided informed consent, and all patient identifying information was removed from the database.

Case Selection and TMA Construction

For this study, the authors obtained archived formalin-fixed and paraffin-embedded samples from previously described tissue banks at the University of Texas MD Anderson Cancer Center (Houston, TX).[12] The tissue specimens had been collected between 1997 and 2005 and had been classified using the 2004 World Health Organization classification system.[13] The TMA comprises NSCLC specimens obtained from patients who underwent surgery at the MD Anderson Cancer Center from 1997 to 2003. Among these patients, only those with available staging information were included in the analysis (n = 352). After a histologic examination of the NSCLC specimens, the NSCLC TMAs were constructed by obtaining 3 cores, each 1 mm in

Table 1 Summary of Clinicopathologic Characteristics of Patients and Tumors

Feature	NSCLC Histologic Type[a]		
	Adenocarcinoma (n = 231)	Squamous Carcinoma (n = 121)	Total (n = 352)
Age (y), Mean (Range)	65 (34-87)	69 (42-90)	66 (34-90)
Sex			
Male	88	72	189
Female	142	47	160
Smoking Status[b]			
Never	57	6	63
Former	105	69	174
Current	70	44	114
Race			
White	203	110	313
Others	28	11	39
EGFR Mutation			
Positive	38	0	38
Negative	159	48	207
K-Ras Mutation			
Positive	32	0	32
Negative	162	46	208
T Category			
1	100	30	130
2	112	73	185
3	6	12	18
4	14	6	20
N Category			
0	172	82	254
1	28	32	60
2	32	7	39
M Category			
0	223	119	342
1	9	2	11
TNM Stage			
I	160	66	226
II	28	37	65
III	36	14	50
IV	10	2	12

Abbreviations: EGFR = epidermal growth factor receptor; K-Ras = Kirsten rat sarcoma (*KRAS*); NSCLC = non–small-cell lung cancer.
[a]Values are number of cases unless otherwise indicated.
[b]Smoking status was not available in 2 patients with SCC.