Value of circulating insulin-like growth factor–associated proteins for the detection of stage I non–small cell lung cancer

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Objective: Circulating biomarkers related to insulin-like growth factor (IGF) signaling are associated with disease progression in multiple carcinomas, but their potential diagnostic value for lung cancer screening has been inadequately examined. We evaluated 9 circulating IGF-related factors for their ability to assign clinical significance to indeterminate pulmonary nodules identified via computed tomography-based radiologic studies.

Methods: Patients (n = 224 stage I non–small cell lung cancer; n = 123 benign) were enrolled by Rush University and the Mayo Clinic and had pretreatment serum evaluated for levels of IGF-1, IGF-2, and insulin-like growth factor binding proteins (IGFBPs) 1-7. The Mann-Whitney rank-sum test and receiver-operator characteristics curves were used to assess differences in biomarker concentrations relevant to malignant versus benign pathology. These targets were used to help refine our companion blood test for assigning clinical significance to computed tomography-detected solitary nodules (discovery cohort, n = 94) and were validated against an independent cohort from the Mayo Clinic (n = 81).

Results: Patients with benign pulmonary nodules were found to have serum concentrations of IGFBP-3, IGFBP-5, IGF-1, and IGF-2 that were higher ($P = .001$, $P < .001$, $P = .002$, and $P = .011$, respectively) than those with non–small cell lung cancer, with distinct associations with histologic subtypes observed. Refinement of our multianalyte classification algorithm using IGF-related factors provided a new panel consisting of interleukin-6, interleukin-1 receptor antagonist, interleukin-10, stromal cell-derived factor-1($\alpha + \beta$), IGFBP-4, IGFBP-5, and IGF-2 with improved assay performance—achieving a (validated) negative predictive value of 100%.

Conclusions: Our findings suggest a divergent role for IGF signaling in the biology of benign and malignant pulmonary nodules. Upon further validation, these observations may help identify cases of false positives resulting from computed tomography-based screening studies. (J Thorac Cardiovasc Surg 2015;149:727-34)

See related commentary on pages 735-6.

Supplemental material is available online.

Non–small cell lung cancer (NSCLC) has the highest prevalence of all malignancies worldwide and remains the most common cause of cancer-related mortality. In 2012, lung cancer represented 12.9% of newly diagnosed cancer with 1.8 million cases and 19.4% of cancer-related deaths with 1.59 million cases.[1] In the United States alone during 2013 there were an estimated 228,190 cases of newly diagnosed lung cancer and 159,480 lung cancer-related deaths. The overall 5-year survival rate for lung cancer averages 15% depending on the stage at diagnosis, and falls to 2% for advanced disease. Early diagnosis of NSCLC has been proposed to improve 5-year survival rates by 60% to 80%.[2] Recent single-arm prospective uncontrolled studies on low-dose computed tomography (LDCT) of the chest for screening have yielded conflicting results.[3,4] The National Lung Screening Trial demonstrated a 20% relative reduction in lung cancer mortality with computed tomography-based screening relative to chest radiograph.[5] Further advancements in early detection of NSCLC could confer additional benefits.

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Abbreviations and Acronyms

IGF = insulin-like growth factor
IGFBP = insulin-like growth factor binding protein
IL = interleukin
LDCT = low-dose computed tomography
MMP = matrix metalloproteinase
NSCLC = non–small cell lung cancer

Advances in delineating the tumorigenesis cascade and growth factors implicated in lung cancer dissemination have produced novel therapeutic options. Research indicates that insulin-like growth factor 1 (IGF-1) and the IGF-1 receptor play a role in the development of various malignancies, including lung cancer.[6] Binding of IGF-1 to its receptor can lead to insulin receptor phosphorylation, which instigates protein kinase-mediated pathways that promotes cell growth, differentiation, and survival. Insulin-like growth factor binding proteins (IGFBPs), notably IGFBP-3, regulate this pathway by binding IGF in the serum and regulating the amount of free IGF available to bind with its receptor.[7] A disproportionate elevation of IGF-1 relative to IGFBP-3 is theorized to promote the proliferative capacity and the metastatic potential of lung cancer.[8,9] Wang and colleagues[10] demonstrated increased expression of IGF-1 in the setting of NSCLC with the degree of upregulation correlating directly with the extent of disease progression. Cao and colleagues[11] showed that IGFBP-3 levels were inversely associated with lung cancer, noting a precipitous drop during tumoriogenesis. The proposed mechanism for increased cancer cell dissemination involves an IGF-mediated upregulation of urokinase-type plasminogen activator, matrix metalloproteinase (MMP)-2, and MMP-9. IGFBP-5 has been linked with transforming growth factor–β1-induced epithelial-to-mesenchymal transition-driven invasion of breast cancer cultures. A decrease in the IGFBP-5 allows for unregulated transforming growth factor-β1 action and increased cell migration.[12]

Our objective in this study was to identify novel biomarkers useful for distinguishing stage I NSCLC from benign disease and apply these to the refinement of our multianalyte classification algorithm. Our previous work in this area demonstrated the prognostic ability of IGFBP-5 and IGFBP-7 to predict disease recurrence and outcomes in patients undergoing an anatomic resection for NSCLC.[13] Here, we investigate the potential value of these IGF-related factors to distinguish early-stage NSCLC from cases of benign disease in high-risk individuals with positive radiography. Further, we also evaluate the value of these biomarkers as a means to improve upon the performance of our multivariate plasma test for this purpose[14] and validated this refined panel against a second, independent cohort from the Mayo Clinic.

PATIENTS AND METHODS

Patient Cohorts

Serum based studies. Between 2004 and 2011, more than 1200 patients who underwent an anatomic resection for suspected lung cancer provided consent for the lung cancer biorepository at Rush University Medical Center; a total of 220 of these patients were enrolled in our study based on possessing nodules $\leq$5 cm with histology relevant to lung cancer screening. None of these patients was previously treated for cancer before the surgical encounter. A second cohort from Rush with benign pathology was also accrued from an internal LDCT screening trial. Enrollment criteria for these individuals include age older than 50 years and a smoking history >20 pack-years. These criteria were more permissive than the National Lung Screening Trial criteria (age $\geq$ 55 years with 30+ pack-year smoking history) and represent a more moderate-to-high risk cohort. All patients in this benign nodule cohort possessed a solitary nodule $\leq$5 cm and were followed with annual LDCT and remained cancer free for a minimum of 2 years. Finally, our collaboration with the Mayo Clinic provided additional patients with either benign disease (n = 52) or with pathologically diagnosed stage I lung cancer (n = 44) who matched the inclusion criteria outlined above. All stage classifications are reported according to the American Joint Committee on Cancer seventh edition criteria and confirmed by pathologic evaluation.[15,16] All patient data were obtained after the patient gave informed consent. The study was conducted in compliance with either the Institutional Review Board at Rush University Medical Center or the Mayo Clinic. These cases were collectively divided into the following groups: high-risk patients with benign disease on pathology (n = 123) and patients with stage I NSCLC (n = 224).

Plasma-based studies. Development of a multianalyte classification algorithm was conducted with (approximately) the identical cohort we previously employed for this purpose.[14] Briefly, this consisted of 30 cases of benign disease and 64 cases of lung cancer from Rush University Medical Center and a unique validation cohort from the Mayo Clinic, consisting of patients with benign disease (n = 61) and those with pathologically diagnosed stage I lung cancer (n = 20). Please note there was no overlap in cases from the discovery to the validation phases of the study and 7 cases from the original Rush cohort were not included in our study due to insufficient evaluable materials available.

Measurement of Serum Biomarker Concentrations

Pretreatment serum or plasma was prepared using standard phlebotomy protocols and archived at −80°C in 100 μL aliquots. All evaluable specimens were subjected to <2 freeze-thaw cycles.[17-20] Nine biomarkers associated with insulin uptake were evaluated in this study.[20] All 9 biomarkers were part of either the Milliplex Map Human IGF or Human IGF Binding Protein Panels (EMD Millipore, Billerica, Mass) and included the following assays: IGF-1, IGF-2, IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-3, IGFBP-4, IGFBP-5, IGFBP-6, and IGFBP-7. All assays were performed in a blinded fashion using a 384-well adaptation of the manufacturer's recommended protocols. All data were collected on a Luminex FlexMAP 3D system (Luminex Corp, Austin, Tex) with concentrations calculated based on 7-point standard curves using a 5-parametric fit algorithm in xPonent version 4.0.3 (Luminex Corp).

Statistical Methods: Cancer Detection and Progression

A primary objective of our study was to evaluate the association of circulating biomarkers of IGF signaling with histology and/or clinical characteristics to permit the development of a blood test potentially capable of assigning clinical significance of indeterminate pulmonary nodules identified during LDCT-based screening studies. The Mann-Whitney *U* test was used to compare each of the 9 candidate biomarkers across the patient cohorts, as defined above. A receiver operator characteristics

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