Editorial

The state of the art in the development of a panel of biomarkers for the early detection of lung cancer

Fatemeh Rahimi Jamnani[1,2]

[1]Human Antibody Lab, Innovation Center, [2]Department of Mycobacteriology and Pulmonary Research, Microbiology Research Center, Pasteur Institute of Iran, Tehran, Iran

Correspondence to: Fatemeh Rahimi Jamnani, PharmD, PhD. Human Antibody Lab, Innovation Center, Pasteur Institute of Iran, Tehran, Iran. Email: Rahimi@pasteur.ac.ir.

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Lung cancer is the second most commonly diagnosed cancer in the US, with 222,500 new cases diagnosed in 2017 (1,2). Furthermore, lung cancer is the leading cause of death in both men and women with cancer, accounting for 155,870 deaths in 2017 (1 in 4 cancer deaths) (1,2). The 5-year relative survival rate for lung cancer is 15% and 21% for men and women, respectively, and for only 16% of lung cancer patients diagnosed at a localized stage, the 5-year relative survival rate is 55% (2). Although screening with low-dose spiral computed tomography (LDCT) resulted in decreased lung cancer mortality, high-quality screening programs seem to be obligatory, particularly in current or former smokers (2). Autoantibodies are generated in patients with cancer due to antigen mutation, overexpression, or altered structure (3). Because autoantibodies exist several months to years before the emergence of any clinical signs, they can be used to determine cancer biomarkers and help in the early detection of cancers, such as lung cancer (4,5). In this regard, several studies have been conducted on patients with non-small cell lung cancer (NSCLC), which led to the identification of a group of autoantigens, such as annexins (I and II), c-myc, complement factor H, cyclin A, cyclin B1, cyclin D1, cyclin-dependent kinase 2 (CDK2), cystic fibrosis transmembrane conductance regulator, dickkopf-related protein 1 (DKK1), mucin 1 (MUC1), cancer/testis antigen 1 (NY-ESO-1), p53, protein kinase C beta, protein kinase C delta type, protein-tyrosine kinase 2-beta, rho-associated protein kinase 1, and serine/threonine-protein kinase Chk1, recognized by autoantibodies (3,6-12). Notably, four combined autoantibody biomarkers were also introduced for early detection of NSCLC, which identified a group of antigens, including hyaluronan mediated motility receptor, metastasis-associated lung adenocarcinoma transcription 1, nucleolar and coiled-body phosphoprotein 1, and spermine oxidase (13).

In the article "Evaluation of serum autoantibodies against tumor-associated antigens as biomarkers in lung cancer" recently published in *Tumor Biology*, Li and colleagues evaluated the presence of autoantibodies against a panel of tumor-associated antigens (TAAs) (14). By using enzyme-linked immunosorbent assay (ELISA), nine proteins, including cyclin B1, cyclin E, HCC1, Koc, p16, p53, p62, RalA, and survivin were used to detect autoantibodies in sera from 50 patients with lung cancer and 42 normal controls. Among which, four antigens with positive values were selected and validated in sera from a validation group. They also found higher levels of anti-cyclin B1 and anti-HCC1 autoantibodies in the sera of lung cancer patients with stages I, II, and III, anti-survivin autoantibodies in patients with stages II and III, and anti-p53 autoantibody in patients with stage I, compared with the controls. Remarkably, the levels of anti-cyclin B1 and anti-survivin

autoantibodies increased with disease histological grades II and III. In this study, anti-p53 autoantibodies were positively associated with tumor size. The most significant part of this study was the parallel utilization of cyclin B1, HCC1, p53, and survivin, which led to increased sensitivity at 65.0% and specificity at 100% in lung cancer detection. Therefore, they suggested that autoantibodies targeting four antigens had higher values in lung cancer detection, and anti-cyclin B1 antibody in the sera of lung cancer patients might function as a novel non-invasive biomarker in the detection of early-stage lung cancer.

In this study, the authors used sera collected from 50 patients with lung cancer with different stages and different grades and 60 patients with lung cancer (without clinical characteristic information) selected as a validation group. Approximately 85% of all new cases of lung cancer are categorized as NSCLC, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (15). However, the authors did not mention whether they assessed only patients with NSCLC or not (16). Although adenocarcinoma, squamous cell, and others, have been shown in Table 1, the data are not well defined. The authors mentioned that the cancer sera were collected at the time of cancer diagnosis. The autoantibody repertoire of patients who were administrated treatment has been shown to differ from the autoantibody repertoire of newly diagnosed patients (17); hence, it seemed good if the data on the treatments administrated for these patients (treatment history) were added. Smoking, as the major risk factor for lung cancer, has been considered in different studies (3,9,18). However, this study lacked any data regarding whether the patients and healthy individuals (as controls) were smokers or non-smokers. Furthermore, the authors used sera from 42 normal healthy controls collected during annual health examinations. Autoantibodies, such as cyclin B1-specific antibody, are also produced in healthy individuals without history of cancer (19). In this regard, healthy controls must be checked through chest radiography and based on factors related to autoimmunity.

Four TAAs, including cyclin B1, HCC1, p53, and survivin, were used in this study to evaluate their potential as cancer biomarkers. As the authors pointed out, the roles of these TAAs in lung cancer have been demonstrated in many studies (9,10,16-18,20-26). Because the diagnostic value of a single marker is relatively low, different combinations of these antigens were also used to simultaneously detect antibodies associated with lung cancer (9,10,20,21,26). Detection of anti-survivin autoantibody combined with carcinoembryonic antigen (CEA) leads to the improvement of the positive detection rate of NSCLC (26). The combination of survivin with antigens, such as CDK2, c-myc, cyclin A, cyclin B1, and cyclin D1 could discriminate patients with lung cancer from smokers and non-smokers (9). Besides, using anti-p53 antibody with markers, such as CEA and cytokeratin 19 fragment, could help in the detection of lung cancer (21). Notably, some studies evaluated the presence of autoantibodies against a panel of autoantigens, such as probable ATP-dependent RNA helicase DDX53 (cancer-associated gene protein; CAGE), GBU4-5, ELAV-like protein 4 (Hu-antigen D; Hu-D), melanoma-associated antigen 4 (MAGEA4), NY-ESO-1, p53, and transcription factor SOX-2 (SOX2) (20) and CAGE, c-myc, GBU4-5, HER2, MUC1, NY-ESO-1, and p53 (10), to increase the sensitivity and specificity for detecting lung cancer. In this regard, to achieve a sensitive and specific blood test that can help in the early detection of lung cancer, the commercial kit, RayBio® Lung Cancer IgG Autoantibody Array G1 (tebu-bio, Peterborough, UK), has been developed, which contains 30 human proteins [14-3-3 theta, annexin A1, annexin A2, CAGE, cathepsin D, CDK2, c-myc, cyclin A, cyclin B1, cyclin D1, DKK1, GBU4-5, stress-70 protein, mitochondrial (HSP70-9B/HSPA9/GRP-75), Hu-D, inosine-5'-monophosphate dehydrogenase 2 (IMDH2), insulin-like growth factor 2 mRNA binding protein 1 (IMP1), IMP2/IGF2BP2/p62, IMP3, 40S ribosomal protein SA (laminin receptor 1; LAMR1), MAGEA4, metastasis associated lung adenocarcinoma transcript 1 (MALAT1), NY-ESO-1, p53, paxillin, phosphoglycerate mutase 1 (PGAM1), ubiquitin carboxyl-terminal hydrolase isozyme L1 (PGP9.5), recoverin, SOX2, survivin, and ubiquilin-1] and can concurrently detect human IgG autoantibodies related to lung cancer.

In conclusion, evaluation of autoantibody repertoires in patients with cancers can help in the identification of particular autoantigens involved in cancer development and can help design screening assays, which in turn can help in the prediction of cancers in susceptible patients.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7-30.
2. American Cancer Society. Cancer Facts & Figures 2017. 2017.
3. Pazhouhandeh M, Samiee F, Boniadi T, et al. Comparative network analysis of patients with non-small cell lung cancer and smokers for representing potential therapeutic targets. Sci Rep 2017;7:13812.
4. Zaenker P, Ziman MR. Serologic autoantibodies as diagnostic cancer biomarkers--a review. Cancer Epidemiol Biomarkers Prev 2013;22:2161-81.
5. Järås K, Anderson K. Autoantibodies in cancer: prognostic biomarkers and immune activation. Expert Rev Proteomics 2011;8:577-89.
6. Hirasawa Y, Kohno N, Yokoyama A, et al. Natural Autoantibody to MUC1 Is a prognostic indicator for non-small cell lung cancer. Am J Respir Crit Care Med 2000;161:589-94.
7. Yao X, Jiang H, Zhang C, et al. Dickkopf-1 autoantibody is a novel serological biomarker for non-small cell lung cancer. Biomarkers 2010;15:128-34.
8. Amornsiripanitch N, Hong S, Campa MJ, et al. Complement Factor H autoantibodies are associated with early stage NSCLC. Clin Cancer Res 2010;16:3226-31.
9. Rom WN, Goldberg JD, Addrizzo-Harris D, et al. Identification of an autoantibody panel to separate lung cancer from smokers and nonsmokers. BMC Cancer 2010;10:234.
10. Chapman CJ, Murray A, McElveen JE, et al. Autoantibodies in lung cancer: possibilities for early detection and subsequent cure. Thorax 2008;63:228-33.
11. Leidinger P, Keller A, Ludwig N, et al. Toward an early diagnosis of lung cancer: An autoantibody signature for squamous cell lung carcinoma. Int J Cancer 2008;123:1631-6.
12. Brichory FM, Misek DE, Yim AM, et al. An immune response manifested by the common occurrence of annexins I and II autoantibodies and high circulating levels of IL-6 in lung cancer. Proc Natl Acad Sci U S A 2001;98:9824-9.
13. Yao Y, Fan Y, Wu J, et al. Potential application of non-small cell lung cancer-associated autoantibodies to early cancer diagnosis. Biochem Biophys Res Commun 2012;423:613-9.
14. Li P, Shi JX, Xing MT, et al. Evaluation of serum autoantibodies against tumor-associated antigens as biomarkers in lung cancer. Tumour Biol 2017;39:1010428317711662.
15. Gridelli C, Rossi A, Carbone DP, et al. Non-small-cell lung cancer. Nat Rev Dis Primers 2015;1:15009.
16. Belyanskaya LL, Hopkins-Donaldson S, Kurtz S, et al. Cisplatin activates Akt in small cell lung cancer cells and attenuates apoptosis by survivin upregulation. Int J Cancer 2005;117:755-63.
17. Karanikas V, Khalil S, Kerenidi T, et al. Anti-survivin antibody responses in lung cancer. Cancer Lett 2009;282:159-66.
18. Broodman I, VanDuijn MM, Stingl C, et al. Survivin autoantibodies are not elevated in lung cancer when assayed controlling for specificity and smoking status. Cancer Immunol Res 2016;4:165-72.
19. Vella LA, Yu M, Fuhrmann SR, et al. Healthy individuals have T-cell and antibody responses to the tumor antigen cyclin B1 that when elicited in mice protect from cancer. Proc Natl Acad Sci U S A 2009;106:14010-5.
20. Tang ZM, Ling ZG, Wang CM, et al. Serum tumor-associated autoantibodies as diagnostic biomarkers for lung cancer: A systematic review and meta-analysis. PLoS One 2017;12:e0182117.
21. Park Y, Kim Y, Lee JH, et al. Usefulness of serum anti-p53 antibody assay for lung cancer diagnosis. Arch Pathol Lab Med 2011;135:1570-5.
22. Mattioni M, Soddu S, Prodosmo A, et al. Prognostic role of serum p53 antibodies in lung cancer. BMC Cancer 2015;15:148.
23. Lubin R, Zalcman G, Bouchet L, et al. Serum p53 antibodies as early markers of lung cancer. Nat Med 1995;1:701-2.
24. Yagihashi A, Asanuma K, Nakamura M, et al. Detection of anti-survivin antibody in gastrointestinal cancer patients. Clin Chem 2001;47:1729-31.
25. Chai Y, Liu X, Dai L, et al. Overexpression of HCC1/CAPERalpha may play a role in lung cancer carcinogenesis. Tumour Biol 2014;35:6311-7.
26. Ma L, Yue W, Zhang L, et al. Clinical significance and diagnostic value of Survivin autoantibody in non-small cell lung cancer patients. Zhongguo Fei Ai Za Zhi 2010;13:706-12.

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