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硕士学位论文

胰岛素样生长因子2 mRNA结合蛋白2（IGF2BP2）在肺癌发生发展中的作用研究

The role of insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2) in the development of lung cancer

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摘 要

背景：当今世界，癌症成为威胁人类健康的头号杀手，其中肺癌更是最常见的恶性肿瘤之一，由于其早期症状不明显，恶性程度高，发现时往往已是中晚期，其每年发病率和死亡率均位于所有癌症的前列。尽管手术方式和化学药物不断更新，但均不能达到较好的治疗效果，肺癌的发病率和死亡率仍没有降低的趋势。因此，早期发现、早期治疗成为治愈肺癌的关键。随着分子生物学的进展，肿瘤相关抗原（TAA）逐渐成为了现代医学的关注热点，因为它不仅能使肿瘤患者早期得到诊断，而且也为分子靶向治疗提供了分子基础。类胰岛素生长因子2 mRNA结合蛋白（IGF2BP2）是一种细胞质蛋白，被证明和多种肿瘤的发生发展有关，如肝癌、乳腺癌、神经胶质瘤、食管癌等，但与肺癌的关系尚不清楚。

目的：本研究旨在通过对IGF2BP2在肺癌中的表达量及其对肺癌细胞生物学行为的影响进行研究，以便初步认识IGF2BP2与肺癌的关系，并初步阐明IGF2BP2在肺癌发生发展的作用。

方法：本研究分别从组织水平和细胞水平来研究分析IGF2BP2在肺癌中的表达及其临床意义。首先在组织水平上，通过收集临床肺癌组织标本，提取组织蛋白和RNA，利用Western Blot 、RT-PCR 技术统计分析IGF2BP2的表达特点；在细胞水平，通过Western Blot 、RT-PCR、细胞转染等技术研究肺正常细胞与肺癌细胞IGF2BP2的表达差异以及对细胞生物学特征的影响。

结果：结果发现，肺癌组织中的IGF2BP2表达量明显多于癌旁正常肺组织（$P<0.01$），IGF2BP2在肺癌中的表达与患者性别和肿瘤大小有明显统计学关系（$P<0.01$），与年龄和临床分期没有明显的统计学关系（$P>0.05$）；肺癌细胞中IGF2BP2的表达量比肺正常细胞的表达量多（$P<0.01$）；沉默肺癌细胞中IGF2BP2的表达降低了细胞的增殖和迁移侵袭能力（$P<0.01$）。

结论： IGF2BP2促进了肺癌的增殖和侵袭，在肺癌的发生发展中起到促进作用，这为临床肺癌的早期诊断和预后提供一定的科学实验依据。

关键词：肺癌；IGF2BP2；TAA

Abstract

Background: At present, cancer has become the leading threat to the health of mankind. The lung cancer is one of the most common malignant tumors worldwide. For the hidden symptoms and high malignant of initial lung cancer, it is always late when the disease is diagnosed and the morbidity and mortality rates are always at the top. Despite of continuous development of surgery and chemical drugs, the treatment outcome is not satisfied. Early diagnosis and timely treatment become the key to prevent the human's health from lung cancer. With the development of molecular biology, tumor-associated antigen (TAA) has been gradually becoming the hot spot of modern medical attention. Not only could patients be diagnosed in the early stage, but also the TAA can provide the basis of tumor targeted therapy. Insulin -like growth factor 2 mRNA binding protein 2 (IGF2BP2) is a kind of cytoplasmic protein, which has been proved having a tight connection with many tumors, such as hepatocellular carcinoma, breast cancer, glioma, esophageal carcinoma, etc. But the relationship of IGF2BP2 and lung cancer is still not clear.

Objective: This experiment aims to test the expression level of IGF2BP2 in the lung cancer tissues and study the effects of IGF2BP2 on the biological behavior on lung cancer cells. So that we can explore the association of IGF2BP2 and lung cancer, and to clarify the IGF2BP2's effects on the lung cancer.

Methods: We explored and analyzed the IGF2BP2 expression and its clinical value through the organization and cell level. Firstly, we collect the lung cancer tissue samples, from which we extracted the total proteins and RNAs. Then we made an analysis through the Western Blot, RT-PCR technology. On the other hand, we explored the influence of expression difference on the biological characteristics of IGF2BP2, using the Western Blot, RT-PCR and cell transfection technique on the cell level.

Results: The result shows that the IGF2BP2 in cancer tissues expresses significantly more than that in para-carcinoma tissues(P0.05). The IGF2BP2 in cancer cells expresses significantly more than that in normal lung cells (P<0.01). Knocking out the IGF2BP2 gene in lung cancer cells could reduce the ability of cell proliferation and migration (P < 0.01)

Conclusion: IGF2BP2 contributes to proliferation and invasion of the lung cancer cells, and plays an important role in the development of lung cancer, which establishes the scientific basic for the clinical early diagnosis and prognosis of lung cancer.

Keywords: Lung cancer; IGF2BP2; TAA

参考资料

[1]Torre L A, Bray F, Siegel R L, et al. Global cancer statistics, 2012 [J]. CA Cancer J Clin, 2015, 65(2): 87-108.
[2]Siegel R L, Miller K D, Jemal A. Cancer Statistics, 2017 [J]. CA Cancer J Clin, 2017, 67(1): 7-30.
[3]Chen W, Zheng R, Baade P D, et al. Cancer statistics in China, 2015 [J]. CA Cancer J Clin, 2016, 66(2): 115-32.
[4]Chen W. Cancer statistics: updated cancer burden in China [J]. Chin J Cancer Res, 2015, 27(1): 1.
[5]Cronin K A, Ries L A, Edwards B K. The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute [J]. Cancer, 2014, 120 Suppl 23(3755-7.
[6]Ferlay J, Shin H R, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008 [J]. International Journal of Cancer Journal International Du Cancer, 2010, 127(12): 2893-917.
[7]Jemal A, Bray F, Center M M, et al. Global cancer statistics [J]. Ca A Cancer Journal for Clinicians, 2011, 65(2): 87.
[8]Jemal A, Travis W D, Tarone R E, et al. Lung cancer rates convergence in young men and women in the United States: Analysis by birth cohort and histologic type [J]. International Journal of Cancer Journal International Du Cancer, 2003, 105(1): 101 – 7.
[9]Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010 [J]. Ca A Cancer Journal for Clinicians, 2010, 60(5): 277-300.
[10]Youlden D R, Cramb S M, Baade P D. The International Epidemiology of Lung Cancer: geographical distribution and secular trends [J]. Journal of Thoracic Oncology, 2008, 3(8): 819-31.
[11]Parkin D M, Bray F, Ferlay J, et al. Global cancer statistics, 2002 [J]. Ca A Cancer Journal for Clinicians, 2005, 55(2): 74 – 108.
[12]曾谊, 梁杰, 沈洪兵. 南京市1996—2005年1128例肺癌住院病例发病特征的动态变化分析 [J]. 中国肺癌杂志, 2008, 11(3): 406-9.
[13]Jemal A, Bray F, Center M M, et al. Global cancer statistics [J]. Ca A Cancer Journal for Clinicians, 2011, 61(2): 69.
[14]邹小农. 中国肺癌流行病学 [J]. 中华肿瘤防治杂志, 2007, 14(12): 881-3.
[15]Jemal A, Bray F, Center M M, et al. Global cancer statistics [J]. CA Cancer J Clin, 2011, 61(2): 69-90.
[16]Alberg A J, Ford J G, Samet J M, et al. Epidemiology of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition) [J]. Chest, 2007, 132(3 Suppl): 29S-55S.
[17]Taylor R, Najafi F, Dobson A. Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent [J]. Int J Epidemiol, 2007, 36(5): 1048-59.
[18]Kligerman S, White C. Epidemiology of Lung Cancer in Women: Risk Factors, Survival, and Screening [J]. American Journal of Roentgenology, 2011, 196(2): 287.
[19]Gu J, Hua F, Zhong D, et al. [Systematic review of the relationship between family history of lung cancer and lung cancer risk] [J]. Zhongguo fei ai za zhi = Chinese journal of lung cancer, 2010, 13(3): 224.
[20]Jin Y T, Xu Y C, Yang R D, et al. Familial aggregation of lung cancer in a high incidence area in China [J]. British Journal of Cancer, 2005, 92(7): 1321.
[21]Yokota J, Shiraishi K, Kohno T. Genetic basis for susceptibility to lung cancer: Recent progress and future directions [J]. Advances in Cancer Research, 2010, 109(51-72.
[22]Yokota J, Shiraishi K, Kohno T. Chapter 2 - Genetic Basis for Susceptibility to Lung Cancer: Recent Progress and Future Directions [M]. Elsevier Science & Technology, 2010.
[23]Katanoda K, Sobue T, Satoh H, et al. An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan [J]. Journal of Epidemiology, 2011, 21(21): 132-43.
[24]Liaw Y P, Ting T F, Ho K K, et al. Cell type specificity of lung cancer associated with air pollution [J]. Science of the Total Environment, 2008, 395(1): 23-7.

[25]何兴舟. 室内燃煤空气污染与肺癌及遗传易感性--宣威肺癌病因学研究22年 [J]. 实用肿瘤杂志, 2001, 16(6): 369-70.
[26]项永兵, 高玉堂. 非吸烟女性肺癌危险因素的多分类logistic模型分析 [J]. 中国卫生统计, 2005, 22(2): 66-70.
[27]De M S, Consonni D, Bertazzi P A. Exposure to occupational carcinogens and lung cancer risk. Evolution of epidemiological estimates of attributable fraction [J]. Acta bio-medica : Atenei Parmensis, 2008, 79 Suppl 1(suppl 1): 34.
[28]Schabath M B, Hernandez L M, Wu X, et al. Dietary Phytoestrogens and Lung Cancer Risk [J]. Jama the Journal of the American Medical Association, 2005, 294(12): 1493.
[29]Peto R, Doll R, Buckley J D, et al. Can dietary beta-carotene materially reduce human cancer rates? [J]. Nature, 1981, 290(290): 201-8.
[30]Bagnardi V, Randi G, Lubin J, et al. Alcohol consumption and lung cancer risk in the Environment and Genetics in Lung Cancer Etiology (EAGLE) study [J]. American Journal of Epidemiology, 2010, 171(1): 36-44.
[31]Schabath M B, Hernandez L M, Wu X, et al. Dietary phytoestrogens and lung cancer risk [J]. Jama the Journal of the American Medical Association, 2005, 294(12): 1493-504.
[32]Bai C, Choi C M, Chu C M, et al. Evaluation of pulmonary nodules: clinical practice consensus guidelines for Asia [J]. Chest, 2016, 150(4): 877-93.
[33]Yau G, Lock M, Rodrigues G. Systematic review of baseline low-dose CT lung cancer screening [J]. Lung Cancer, 2007, 58(2): 161-70.
[34]Zhang W. Introduction and Application of ThinPrep(TCT) [J]. Clinical Medical Engineering, 2008,
[35]Bishop J W, Bigner S H, Colgan T J, et al. Multicenter masked evaluation of AutoCyte PREP thin layers with matched conventional smears. Including initial biopsy results [J]. Acta Cytologica, 1998, 42(1): 189.
[36]Guo X, Song L, Wang G. Clinical evaluation of white light and fluorescence bronchoscopy in the role in early diagnosis of lung cancer [J]. Journal of Clinical Pulmonary Medicine, 2013,
[37]车国卫, 周清华. 肺癌的筛查和早期诊断 [J]. 中国肺癌杂志, 2003, 6(6): 412-7.
[38]Van Rens M T, Schramel F M, Elbers J R, et al. The clinical value of lung imaging fluorescence endoscopy for detecting synchronous lung cancer [J]. Lung Cancer, 2001, 32(1): 13-8.
[39]Hany T F, Steinert H C, Goerres G W, et al. PET diagnostic accuracy: improvement with in-line PET-CT system: initial results [J]. Radiology, 2002, 225(2): 575-81.
[40]Mattes D, Haynor D R, Vesselle H, et al. PET-CT image registration in the chest using free-form deformations [J]. IEEE Transactions on Medical Imaging, 2003, 22(1): 120-8.
[41]Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: proposed definition [J]. Lung Cancer, 2005, 49(1): 25.
[42]De S E, Boffetta P, Ronco A L, et al. Squamous and small cell carcinomas of the lung: similarities and differences concerning the role of tobacco smoking [J]. Lung Cancer, 2005, 47(1): 1-8.
[43]Nicholson S A, Beasley M B, Brambilla E, et al. Small cell lung carcinoma (SCLC): a clinicopathologic study of 100 cases with surgical specimens [J]. American Journal of Surgical Pathology, 2002, 26(9): 1184-97.
[44]Steger V, Walles T, Kosan B, et al. Trimodal therapy for histologically proven N2/3 non-small cell lung cancer: mid-term results and indicators for survival [J]. 2009, 87(6): 1676-83.
[45]Ettinger D S, Akerley W, Borghaei H, et al. Non – Small Cell Lung Cancer [J]. Journal of the National Comprehensive Cancer Network Jnccn, 2012, 8(7): 740.
[46]耿国军, 于修义, 姜杰, et al. 胸腔镜手术3D与2D模式下治疗孤立性肺结节的病例对照研究 [J]. 中国胸心血管外科临床杂志, 2015, 7): 664-7.
[47]Li M. The world's first radical resection for lung cancer using glasses-free 3D thoracoscope was completed in Guangzhou [J]. Journal of Thoracic Disease, 2015, 7(9): E384.
[48]刘伦旭, 梅建东, 蒲强, et al. 全胸腔镜支气管袖式成形肺癌切除的初步探讨 [J]. 中国胸心血管外科临床杂志, 2011, 18(5): 387-9.
[49]Ettinger D S. New drugs for chemotherapy-naive patients with extensive-disease small cell lung cancer [J].

Seminars in Oncology, 2001, 28(2 Suppl 4): 27.
[50]Delbaldo C, Michiels S, Syz N, et al. Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis [J]. Jama the Journal of the American Medical Association, 2004, 292(4): 470-84.
[51]Lynch T J, Bell D W, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib [J]. New England Journal of Medicine, 2004, 350(350): 2129-39.
[52]Okamoto I, Araki J, Suto R, et al. EGFR mutation in gefitinib-responsive small-cell lung cancer [J]. Annals of Oncology, 2006, 17(6): 1028-9.
[53]Pao W, Miller V, Zakowski M, et al. Pao, W. et al. EGF receptor gene mutations are common in lung cancers from 'never smokers' and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc. Natl Acad. Sci. USA 101, 13306-13311 [J]. Proceedings of the National Academy of Sciences, 2004, 101(36): 13306-11.
[54]Tokumo M, Toyooka S, Kiura K, et al. The relationship between epidermal growth factor receptor mutations and clinicopathologic features in non-small cell lung cancers [J]. Clinical Cancer Research, 2005, 49(11): 1167-73.
[55]Soria J C, Mok T S, Cappuzzo F, et al. EGFR-mutated oncogene-addicted non-small cell lung cancer: current trends and future prospects [J]. Cancer Treatment Reviews, 2012, 38(38): 416-30.
[56]Fukuoka M, Yano S, Giaccone G, et al. Multi-Institutional Randomized Phase II Trial of Gefitinib for Previously Treated Patients With Advanced Non – Small-Cell Lung Cancer [J]. Journal of Clinical Oncology, 2003, 21(12): 2237-46.
[57]Kris M G, Natale R B, Herbst R S, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial [J]. Jama the Journal of the American Medical Association, 2003, 290(16): 2149-58.
[58]Shepherd F A, Rodrigues P J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer [J]. New England Journal of Medicine, 2005, 353(2): 123-32.
[59]Kim E S, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial [J]. Lancet, 2008, 372(9652): 1809.
[60]Han J Y, Park K, Kim S W, et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung [J]. Journal of Clinical Oncology, 2012, 30(10): 1122-8.
[61]Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial [J]. Lancet Oncology, 2010, 11(2): 104-5.
[62]Zhou C, Wu Y L, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study [J]. Lancet Oncology, 2011, 12(8): 735-42.
[63]Yang J C, Hirsh V, Schuler M, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations [J]. Journal of Clinical Oncology, 2013, 31(27): 3342-50.
[64]Sun Y, Shi Y, Zhang L, et al. A randomized, double-blind phase III study of icotinib versus gefitinib in patients with advanced non-small cell lung cancer (NSCLC) previously treated with chemotherapy (ICOGEN) [J]. Journal of Thoracic Oncology, 2011, 29(15): -.
[65]Tan F, Shen X, Wang D, et al. Icotinib (BPI-2009H), a novel EGFR tyrosine kinase inhibitor, displays potent efficacy in preclinical studies [J]. Lung Cancer, 2012, 76(2): 177-82.
[66]Lei G, Ming X, Huang Z, et al. Icotinib might be effective for the treatment of leptomeningeal carcinomatosis in non-small cell lung cancer with sensitive EGFR mutations [J]. Lung Cancer, 2015, 89(3): 268.
[67]Mok T S, Wu Y L, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma [J]. New England Journal of Medicine, 2009, 361(10): 947-57.

[68]Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR [J]. New England Journal of Medicine, 2010, 362(25): 2380-8.
[69]Arcila M E, Oxnard G R, Nafa K, et al. Rebiopsy of Lung Cancer Patients with Acquired Resistance to EGFR Inhibitors and Enhanced Detection of the T790M Mutation Using a Locked Nucleic Acid-Based Assay [J]. Clinical Cancer Research An Official Journal of the American Association for Cancer Research, 2011, 17(5): 1169.
[70]谌茜, 李敏, 马倬, et al. FASN对Erlotinib耐药细胞株生长的影响及其机制 [J]. 中国临床药理学与治疗学, 2014, 19(10): 1120-0.
[71]Jiang T, Zhou C. Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients with EGFR inhibitor-resistant non-small cell lung cancer [J]. 2014, 3(6): 370-2.
[72]Ettinger D S, Akerley W, Borghaei H, et al. Non-small cell lung cancer [J]. Journal of the National Comprehensive Cancer Network Jnccn, 2012, 10(10): 1236.
[73]Soda M, Choi Y L, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer [J]. Nature, 2007, 448(7153): 561-6.
[74]Pender A, Popat S. The efficacy of crizotinib in patients with ALK-positive nonsmall cell lung cancer [J]. Therapeutic Advances in Respiratory Disease, 2015, 9(3): 97.
[75]Choi Y L, Soda M, Yamashita Y, et al. EML4-ALK Mutations in Lung Cancer That Confer Resistance to ALK Inhibitors [J]. New England Journal of Medicine, 2010, 363(18): 1734.
[76]Doebele R C, Pilling A B, Aisner D L, et al. Mechanisms of Resistance to Crizotinib in Patients with ALK Gene Rearranged Non-Small Cell Lung Cancer [J]. Clinical Cancer Research An Official Journal of the American Association for Cancer Research, 2012, 18(18): 1472-82.
[77]Shaw A T, Mehra R, Kim D W, et al. Clinical activity of the ALK inhibitor LDK378 in advanced, ALK-positive NSCLC [J]. Journal of Clinical Oncology, 2013, 37(2): 89-90.
[78]Sakamoto H, Tsukaguchi T, Hiroshima S, et al. CH5424802, a selective ALK inhibitor capable of blocking the resistant gatekeeper mutant [J]. Cancer Cell, 2011, 19(19): 679-90.
[79]Kodama T, Tsukaguchi T, Yoshida M, et al. Selective ALK inhibitor alectinib with potent antitumor activity in models of crizotinib resistance [J]. Cancer Letters, 2014, 351(2): 215-21.
[80]Reck M, Pawel J V, Zatloukal P, et al. Phase III Trial of Cisplatin Plus Gemcitabine With Either Placebo or Bevacizumab As First-Line Therapy for Nonsquamous Non – Small-Cell Lung Cancer: AVAiL [J]. Journal of Clinical Oncology Official Journal of the American Society of Clinical Oncology, 2009, 27(8): 1227.
[81]Cl M, B C, H D, et al. LKB1/KRAS mutant lung cancers constitute a genetic subset of NSCLC with increased sensitivity to MAPK and mTOR signalling inhibition [J]. British Journal of Cancer, 2009, 100(2): 370-5.
[82]Raymond D E, Faivre S, Armand J P. Epidermal Growth Factor Receptor Tyrosine Kinase as a Target for Anticancer Therapy [J]. Drugs, 2000, 60 Suppl 1(1): 15-23; discussion 41-2.
[83]Soussi T. p53 Antibodies in the sera of patients with various types of cancer: a review [J]. Cancer Research, 2000, 60(7): 1777.
[84]Raedle J, Oremek G, Truschnowitsch M, et al. Clinical evaluation of autoantibodies to p53 protein in patients with chronic liver disease and hepatocellular carcinoma [J]. European journal of cancer (Oxford, England : 1990), 1998, 34(8): 1198-203.
[85]Nielsen F C, Nielsen J, Kristensen M A, et al. Cytoplasmic trafficking of IGF-II mRNA-binding protein by conserved KH domains [J]. Journal of Cell Science, 2002, 115(Pt 10): 2087.
[86]Chao J A, Patskovsky Y, Patel V, et al. ZBP1 recognition of β -actin zipcode induces RNA looping [J]. Genes Dev, 2010, 24(2): 148.
[87]Frayling T M. Genome-wide association studies provide new insights into type 2 diabetes aetiology [J]. Nature Reviews Genetics, 2007, 8(9): 657.
[88]Grarup N, Rose C S, Andersson E A, et al. Studies of association of variants near the HHEX, CDKN2A/B, and IGF2BP2 genes with type 2 diabetes and impaired insulin release in 10,705 Danish subjects: validation and

extension of genome-wide association studies [J]. 2008, 56(12): 3105-11.
[89]M ü ellerpillasch F, Lacher U, Wallrapp C, et al. Cloning of a gene highly overexpressed in cancer coding for a novel KH-domain containing protein [J]. Oncogene, 1997, 14(22): 2729.
[90]J Y Zhang W Z, H Imai, K Kiyosawa, E K L Chan, E M Tan. De-novo humoral immune responses to cancer-associated autoantigens during transition from chronic liver disease to hepatocellular carcinoma [J]. Clinical & Experimental Immunology, 2001, 125(1): 3-9.
[91]Imai H, Nakano Y, Kiyosawa K, et al. Increasing titers and changing specificities of antinuclear antibodies in patients with chronic liver disease who develop hepatocellular carcinoma [J]. Cancer, 1993, 71(1): 26.
[92]Covini G, M ü hlen C a V, Pacchetti S, et al. Diversity of antinucelar antibody responses in hepatocellular carcinoma [J]. Journal of Hepatology, 1997, 26(6): 1255 – 65.
[93]Tan E M. Autoantibodies as reporters identifying aberrant cellular mechanisms in tumorigenesis [J]. Journal of Clinical Investigation, 2001, 108(10): 1411-5.
[94]Liu X, Ye H, Li L, et al. Humoral autoimmune responses to insulin-like growth factor II mRNA-binding proteins IMP1 and p62/IMP2 in ovarian cancer [J]. Research Journal of Immunology, 2013, 2014(7): 326593.
[95]刘桂红. 2型糖尿病易感基因TCF7L2、IGF2BP2多态性与汉族女性乳腺癌发病风险的关联研究 [D]; 河北医科大学, 2014.
[96]Liu G, Zhu T, Cui Y, et al. Correlation between IGF2BP2 gene polymorphism and the risk of breast cancer in Chinese Han women [J]. Biomedicine & Pharmacotherapy, 2015, 69(297-300.
[97]Wen P Y, Kesari S. Malignant gliomas in adults. N Engl J Med [J]. New England Journal of Medicine, 2008, 359(5): 492-507.
[98]Mu Q, Wang L, Yu F, et al. Imp2 regulates GBM progression by activating IGF2/PI3K/Akt pathway [J]. Cancer Biology & Therapy, 2015, 16(4): 623-33.
[99]Barghash A, Golob-Schwarzl N, Helms V, et al. Elevated expression of the IGF2 mRNA binding protein 2 (IGF2BP2/IMP2) is linked to short survival and metastasis in esophageal adenocarcinoma [J]. Oncotarget, 2016, 7(31): 49743-50.
[100] Liu W, Peng B, Lu Y, et al. Autoantibodies to tumor-associated antigens as biomarkers in cancer immunodiagnosis [J]. Autoimmunity Reviews, 2011, 10(6): 331-5.
[101]Mu Q, Wang L, Yu F, et al. Imp2 regulates GBM progression by activating IGF2/PI3K/Akt pathway [J]. Cancer Biology & Therapy, 2015, 16(4): 623-33.
[102]Ye S, Song W, Xu X, et al. IGF2BP2 promotes colorectal cancer cell proliferation and survival through interfering with RAF-1 degradation by miR-195 [J]. Febs Letters, 2016, 590(11):
[103]Zeng H, Zheng R, Guo Y, et al. Cancer survival in China, 2003-2005: A population-based study [J]. International Journal of Cancer, 2015, 136(8): 1921.
[104]Franklin W A. Diagnosis of Lung Cancer : Pathology of Invasive and Preinvasive Neoplasia [J]. Chest, 2000, 117(4): 80S-9S.
[105]Sone S, Kakiuchi S, Yano S. [Molecular targeting in the treatment of lung cancer--toward the development of individualized treatment] [J]. Nihon Naika Gakkai Zasshi the Journal of the Japanese Society of Internal Medicine, 2004, 93(9): 1963-70.
[106]Proctor R N. Tobacco and the global lung cancer epidemic [J]. Nature Reviews Cancer, 2001, 1(1): 82-6.
[107]Feins R H. Surgery for early stage non-small cell lung cancer [J]. Thorax, 2003, 68(10): 419.
[108]S D, D W, M S, et al. Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers [J]. Radiology, 2002, 222(3): 773-81.
[109]Bandman O, Goli S K, Shah P, et al. Tumor-associated antigen [M]. US. 1999: 3063-.
[110]Gu T, Horov á E, Möllsten A, et al. IGF2BP2 and IGF2 genetic effects in diabetes and diabetic nephropathy [J]. Journal of Diabetes & Its Complications, 2012, 26(26): 393-8.
[111]Zhang J, Chan E K. Autoantibodies to IGF-II mRNA binding protein p62 and overexpression of p62 in human hepatocellular carcinoma [J]. Autoimmunity Reviews, 2002, 1(3): 146.
[112]Barghash A, Helms V, Kessler S M. Overexpression of IGF2 mRNA-Binding Protein 2 (IMP2/p62) as a

feature of basal-like breast cancer correlates with short survival [J]. Scandinavian Journal of Immunology, 2015, 82(2): 142 – 3.
[113]Molina R, Filella X, Aug é J M, et al. Tumor markers (CEA, CA 125, CYFRA 21-1, SCC and NSE) in patients with non-small cell lung cancer as an aid in histological diagnosis and prognosis. Comparison with the main clinical and pathological prognostic factors [J]. Tumor Biology, 2003, 24(4): 209-18.
[114]Chen F, Li W M, Wang D M, et al. [Clinical value of combined detection of serum tumor markers in lung cancer diagnosis] [J]. Sichuan da xue xue bao Yi xue ban = Journal of Sichuan University Medical science edition, 2008, 39(5): 832-5.