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·临床研究·

# 非小细胞肺癌患者外周血有核细胞miR-205-5p水平及其临床意义

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[摘 要] **目的:** 探讨非小细胞肺癌患者外周血有核细胞miR-205-5p的表达水平是否可作为分子标志物。**方法:** 收集昆明医科大学第三附属医院(云南省肿瘤医院)2011年6月至2012年6月非小细胞肺癌首诊患者60例,其中无远处转移患者30例,有远处转移患者30例。另外收集健康志愿者30例作为对照组。q-RTPCR技术检测人支气管上皮细胞BEAS-2B、云南个旧肺鳞癌细胞YTMLC-90、云南宣威肺腺癌细胞XWLC-05以及人外周血有核细胞的表达水平。分析外周血有核细胞miR-205-5p的表达水平与非小细胞肺癌患者血清标志物水平、TNM分期、淋巴结转移、远处转移等临床病理参数的相关性。**结果:** miR-205-5p在BEAS-2B中表达水平低(0.8208±0.2553),而在YTMLC-90(17.5072±1.9063)和XWLC-05(5.7252±1.0120)中表达水平明显升高,差异有统计学意义($P$<0.05);miR-205-p在健康人外周血中的表达水平显著低于无转移的以及转移的非小细胞肺癌患者(1.0730 *vs* 3.6588、19.6324,均$P$<0.01)。外周血有核细胞miR-205-5p的阳性表达率与非小细胞肺癌患者性别、年龄、淋巴结转移、病理类型和血清肿瘤标志物水平(CEA、CA125、CA242)无关($P$>0.05),而与患者远处转移、TNM分期、血清肿瘤标志物CA153水平明显相关($P$<0.01)。**结论:** miR-205-5p表达水平异常升高可能作为非小细胞肺癌患者转移相关的分子标志物。

[关键词] miR-205-5p; 外周血有核细胞; 转移; 液体活检; 非小细胞肺癌
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# miR-205-5p expression in peripheral blood karyocytes from non-small cell lung cancer patients and its clinical value

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**[Abstract] Objective:** To investigate whether miR-205-5p expression in peripheral blood karyocytes from non-small cell lung cancer (NSCLC) patients could be used as a reasonable molecule biomarker. **Methods:** Peripheral blood from 60 patients, who were primarily diagnosed with NSCLC and treated at the Third affiliated Hospital of Kunming Medical University (Yunnan Cancer Hospital) from June, 2011 to June, 2012, was collected; among them, there were 30 cases with distant metastasis while the other 30 without. In addition, 30 healthy subjects were enrolled as controls. The miR-205-5p expressions in collected peripheral blood karyocytes, Human bronchial epithelial BEAS-2B cells, Gejiu squamous cell lung carcinoma YTMLC-90 cells, and Xuanwei lung adenocarcinoma XWLC-05 cells were detected by q-RTPCR. We also analyzed the correlation between miR-205-5p expression in peripheral blood karyocytes and NSCLC serum markers levels, TNM stage, Lymph node metastasis, as well as distant metastasis etc. **Results:** The expressions of miR-205-5p in YTMLC-90 (17.5072±1.9063) and XMLC-05 cells (5.7252±1.0120) were significantly higher than that in BEAS-2B cells (0.8208±0.2553) ($P$<0.05). The miR-205-5p expres-

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sion level in peripheral blood karyocytes from healthy controls was significantly higher than that from NSCLC patients (P<0.01). The positive rate of miR-205-5p in peripheral blood karyocytes from NSCLC patients was not correlated with patients' sex, age, lymph node metastasis, pathologic subtypes and tumor serum markers (CEA, CA125, CA242) (all *P*>0.05), but significantly correlated with distant metastasis, TNM stage and tumor serum marker CA153 (*P*<0.01). **Conclusions:** Abnormal up-regulation of miR-205-5p may play an important role in the progression of NSCLC and can be used as a reasonable biomarker for the metastasis in NSCLC patients.

**[Key words]** miR-205-5p; peripheral blood mononuclear cells; metastasis; liquid biopsy; non-small cell lung cancer

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肺癌已成为发病率和死亡率最高的恶性肿瘤，5年生存率低于18%[1]。虽然近年来在临床诊断和治疗方面取得了新的进展，但该病死亡率并无明显降低[2]。外周血循环肿瘤细胞(circulating tumor cells，CTCs)作为液体活检技术检测主要对象，在肿瘤早期诊断、监测转移、疗效评估等方面具有良好的临床应用价值。然而，由于CTCs数量非常少，目前大多数CTCs检测分析需要分离富集CTCs，不仅使检测分析成本增加，而且会使检测结果存在假阴性[3-5]。MicroRNAs(miRNAs)具有癌基因或抑癌基因的作用，使它们成为了肿瘤诊断和治疗的新靶点[6-7]。miR-205-5p在乳腺癌患者癌组织中低表达，而在乳腺癌干细胞和乳腺癌患者血清中高表达[8-10]；在非小细胞肺癌患者癌组织和血清中高表达[11-13]。然而，在非小细胞肺癌患者外周血CTCs的表达及其临床应用价值仍然不清楚。本研究采用实时荧光定量PCR(Quantitative Real-time PCR, qRT-PCR)技术，探讨检测非小细胞肺癌(non-small-cell lung cancer, NSCLC)患者外周血有核细胞miR-205-5p表达水平及其临床应用价值，为非小细胞肺癌患者液体活检和精准医疗提供实验依据。

## 1　材料与方法

### 1.1　材料来源

选择2011年6月至2012年6月云南省肿瘤医院收治的经病理确诊为NSCLC的首诊患者，其中30例未发生复发转移的病例，30例已发生复发转移的病例。抽取空腹静脉血5 ml。抽取外周血前均未行化疗、放疗等治疗，并经过胸片、CT、骨扫描、MRI、B超等常规病理学、影象学和临床检测明确诊断。选择30例云南省肿瘤医院年龄、性别相当的健康体检志愿者为正常对照组；分析非小细胞肺癌患者外周血有核细胞miR-205-5p表达水平和临床病理参数之间的关系。本研究方案获得了昆明医科大学第三附属医院伦理委员会批准，受试者及家属签署疗知情同意书。人支气管正常上皮细胞BEAS-2B、云南宣威肺腺癌细胞XWLC-05和云南个旧肺鳞癌细胞YTMLC由云南省肿瘤医院肿瘤研究所提供。

### 1.2　主要试剂

胎牛血清、1640培养基及PBS均购自美国HYCLONE公司，0.25%胰蛋白酶购自美国GIBCO公司，二甲基亚砜购自美国SIGMA公司，红细胞裂解液购自北京康为世纪生物科技有限公司，miRNA提取分离试剂盒购自天根生化科技(北京)有限公司，miRNA实时荧光定量PCR检测试剂盒购自上海吉玛制药技术有限公司。

### 1.3　qRT-PCR检测非小细胞肺癌患者外周血有核细胞和细胞株miR-205-5p的表达水平

抽取空腹静脉血5 ml(EDTA抗凝)，严格无菌操作，防止污染。收集血液时，防止皮肤上皮细胞污染。采血后半小时内按康为世纪生物科技有限公司试剂说明书裂解全血中的红细胞，－80 ℃保存细胞沉淀；收集BEAS-2B、XMLC-05和YTMLC细胞，PBS洗涤，1 000×*g*离心5 min，弃上清。按miRNA提取分离试剂盒说明书提取总RNA，核酸蛋白检测仪检测RNA纯度和浓度，RNA琼脂糖凝胶电泳检测RNA完整性。按miRNA qRT-PCR检测试剂盒说明书，取0.5 μg总RNA合成cDNA，反应条件: 25 ℃、30 min，42 ℃、30 min，85 ℃、5 min。以cDNA为模板，加入相关试剂及引物(表1)，以U6为内参照，在ABI7500 qRT-PCR仪上进行扩增。反应条件: 95 ℃、3 min，(95 ℃、12 s，62 ℃、40 s)×40循环。琼脂糖凝胶电泳检测qRT-PCR扩增产物。

采用以下公式计算miRNA相对表达量：$2^{-\Delta\Delta Ct}$。以U6作内参照，用U6拷贝数作为校正基数，再以正常对照组的△Ct值作为校正，得出-ΔΔCt值。

### 1.4　统计学处理

数据采用SPSS15.0收集处理。细胞株miR-205-5p表达水平呈正态分布采用double-sided Student's *t*检验，以$\bar{x}\pm s$表示；非小细胞肺癌患者外周血有核细胞miR-205-5p表达水平呈非正态分布采用秩和检验，以中位数(四分位数间距)表示。比较非小细胞肺癌患者外周血有核细胞miR-205-5p阳性表达率与TNM分期、淋巴结转移等临床病理参数的关系用

Chi-Square检验，比较非小细胞肺癌患者外周血有核细胞miR-205-5p表达水平与血清肿瘤标志物的关系用Spearman检验。以$P<0.05$或$P<0.01$表示差异有统计学意义。

**表1 qRT-PCR扩增引物序列**

**Tab. 1 Primer sequences for qRT-PCR**

| Target | Primer Sequence (5'-3') |
|---|---|
| miR-205-5p-RT[a] | GACGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACCAGACT |
| miR-205-5p -F[b] | AGTCCTTCATTCCACCGGAGT |
| miR-205-5p -R[b] | GTGCAGGGTCCGAGGT |
| U6-RT[a] | GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACAAAAATATG |
| U6-F[b] | GCGCGTCGTGAAGCGTTC |
| U6-R[b] | GTGCAGGGTCCGAGGT |

[a] indicates the primers are used for cDNA synthesis; [b] indicates the primers for quantitative real-time PCR; U6 was used as reference; RT: Reverse transcription; F: Forward strand; R: Reverse strand

## 2 结 果

### 2.1 miR-205-5p在非小细胞肺癌细胞中高表达

XWLC-05（5.7252±1.0120）和YTMLC（17.5072±1.9063）miR-205-5p表达水平均高于BEAS-2B（0.8208±0.2553）($P<0.05$)，说明miR-205-5p在非小细胞肺癌细胞中高表达。YTMLC的miR-205-5p表达水平高于XWLC-05($P<0.05$)，可能是肺鳞癌较为特异的分子标志物。

### 2.2 miR-205-5p在非小细胞肺癌患者外周血有核细胞中高表达

非小细胞肺癌无转移和有转移患者外周血有核细胞miR-205-5p表达水平均高于健康人 ($P<0.01$)，说明miR-205-5p在非小细胞肺癌患者外周血有核细胞中高表达。非小细胞肺癌有转移患者外周血有核细胞miR-205-5p表达水平高于非小细胞肺癌无转移患者($P<0.01$)，可能作为判断患者转移的分子标志物（表2）。

参考文献报道[14]，将miRNA-205-5p表达水平小于4定义为miRNA-205-5p阴性表达，而将miRNA-205-5p表达水平大于等于4定义为miRNA-205-5p阳性表达。非小细胞肺癌无转移和有转移患者外周血有核细胞miR-205-5p阳性表达率分别为46.7%和83.3%，明显高于健康人（6.7%）($P<0.01$，表3）。

### 2.3 非小细胞肺癌患者外周血有核细胞miRNA-205-5p阳性表达率与临床病理参数的相关性

用Chi-Square检验分析非细胞肺癌患者外周血有核细胞miR-205-5p阳性表达率与临床各病理参数相关性，发现外周血有核细胞miR-205-5p阳性表达率与患者性别、年龄、淋巴结转移、病理类型无关（$P>0.05$），而与患者远处转移、TNM分期有相关性（$P<0.0$，表4）。

**表2 健康人、非小细胞肺癌患者外周血有核细胞的miR-205-5p表达水平**

**Tab. 2 The miR-205-5p expression level in peripheral blood mononuclear cells from healthy control and non-small cell lung cancer patients**

| Group | miR-205-5p expression | *P* |
|---|---|---|
| Healthy control | 1.0730（0.5579−1.9100） | 0.000 |
| NSCLC without distant metastases | 3.6588（1.6309−10.6471） | |
| NSCLC with distant metastases | 19.6324（6.0235−43.9682） | |

*P<0.01 vs* Healthy control

**表3 健康人、非小细胞肺癌患者外周血有核细胞miR-205-5p阳性表达率($n$=30)**

**Tab. 3 The positive rate of miR-205-5p in peripheral blood mononuclear cells from healthy control and non-small cell lung cancer patients($n$=30)**

| Group | miR-205-5p | | *P* |
|---|---|---|---|
| | + | -* | |
| Healthy control | 2%（6.7） | 28%（93.3） | 0.000 |
| NSCLC without distant metastases | 14%（46.7） | 16%（53.3） | |
| NSCLC with distant metastases | 25%（83.3） | 5%（16.7） | |

[*] As described in the literature[14], miRNA-205-5p expression lower than 4 (an cut-off point with maximal septicity) was manually defined as miRNA-205 expression-negative. *P<0.01 vs* Healthy control

将非小细胞肺癌患者外周血有核细胞miR-205-5p表达水平与血清肿瘤标志物进行Spearman检验分析，发现外周血有核细胞miR-205-5p表达水平与血清CA153水平存在相关关系（$P<0.01$)(表5）。

## 3 讨 论

现阶段常用于肺癌临床诊疗的血清肿瘤标志物有CEA、CA125、CA153、NSE、CYFRA-21、SCC等，但其特异性及敏感性均不佳，急需新型分子标志物来提高目前肺癌临床诊疗水平。miR-205-5p与多种肿瘤的发生发展密切相关，发挥癌基因或抑癌基因的作用。

**表4 非小细胞肺癌患者外周血有核细胞miRNA-205-5p阳性表达率与临床病理参数之间的关系**

**Tab. 4 Relationship between the positive rate of miR-205-5p in peripheral blood mononuclear cells from patients with non-small cell lung cancer and clinicopathological parameters**

| Characteristic | *n* | miR-205-5p | | *P* |
|---|---|---|---|---|
| | | + | -* | |
| Gender | | | | |
| Female | 24 | 17(28.3%) | 7(11.7%) | 0.437 |
| Male | 36 | 22(36.7%) | 14(23.3%) | |
| Age | | | | |
| ＜60 | 34 | 20(33.3%) | 14(13.3%) | 0.248 |
| ≥60 | 26 | 19(31.7%) | 7(11.7%) | |
| Lymphatic metastasis | | | | |
| Yes | 48 | 32(53.3%) | 16(26.7%) | 0.592 |
| No | 12 | 7(11.7%) | 5(8.3%) | |
| Distant metastasis | | | | |
| Yes | 30 | 25(41.7%) | 5(8.3%) | 0.002 |
| No | 30 | 14(23.3%) | 16(26.7%) | |
| Pathologic subtypes | | | | |
| Adenocarcinoma | 25 | 15(25.0%) | 10(16.7%) | 0.315 |
| Squamous carcinoma | 16 | 7(11.7%) | 9 (15.0%) | |
| Other | 19 | 8(13.3%) | 11(18.3%) | |
| TNM stage | | | | |
| StageI | 9 | 6(10%) | 3(5%) | |
| StageII | 5 | 1(1.7%) | 4(6.7%) | 0.007 |
| StageIII | 16 | 7(11.7%) | 9(15%) | |
| StageIV | 30 | 25(41.7%) | 5(8.3%) | |

* As described in the literature [14], miRNA-205 expression lower than 4 (an cut-off point with maximal septicity) was manually defined as miRNA-205 expression-negative.

**表5 非小细胞肺癌患者外周血有核细胞miRNA-205-5p表达水平与患者血清肿瘤标志物CEA、CA125、CA153、CA242的相关性**

**Tab.5 The relationship between the miR-205-5p expression level in peripheral blood mononuclear cells from patients with non-small cell lung cancer and serum tumor markers**

| Serum markers | miR-205-5p expression | |
|---|---|---|
| | *R* | *P* |
| CEA | 0.094 | 0.476 |
| CA125 | 0.215 | 0.098 |
| CA153 | 0.369 | 0.004 |
| CA242 | 0.084 | 0.524 |

miR-205-5p在前列腺癌组织中表达水平低，可作为预后判断因子，通过诱导细胞凋亡和阻滞细胞周期抑制肿瘤的生长[15-16]。miR-205-5p在卵巢癌组织中高表达，可作为预后判断因子，通过抑制SMAD4、PTEN促进肿瘤生长和转移[17]。miR-205-5p在非小细胞肺癌患者癌组织和血清中高表达[11-13]，可作为判断预后、化疗疗效评价、鉴别肺腺癌和肺鳞癌的辅助指标[18-20]；miR-205-5p通过抑制PTEN、PHLPP2表达，上调Mcl-1、Survivin表达，促进肺癌生长和转移[21-23]。然而，现有文献关于miR-205-5p在非小细胞肺癌诊疗中的应用价值以及在非小细胞肺癌发生发展中作用机制的结论存在不一致。有学者发现，非小细胞肺癌患者血浆miR-205-5p的表达水平与患者临床病理特征无关[24]，miR-205-5p在非小细胞肺癌患者癌组织的表达水平并不能作为判断预后、鉴别肺腺癌和肺鳞癌的辅助指标，miR-205-5p通过调节integrin α5表达抑制肺癌生长和转移[25-26]。更为重要的是，miR-205-5p在非小细胞肺癌患者外周血有核细胞的表达及其临床应用价值仍然不清楚。本研究结果显示，非小细胞肺癌细胞株miR-205-5p表达水平高于正常支气管细胞株，非小细胞肺癌患者外周血有核细胞miR-205-5p表达水平高于正常对照组，提示miR-205-5p在非小细胞肺癌发生发展中起着癌基因作用。本研究结果还显示，非小细胞肺癌患者外周血有核细胞miR-205-5p表达水平与远处转移密切相关，提示miR-205-5p可能促进非小细胞肺癌的转移。非小细胞肺癌患者外周血有核细胞miR-205-5p表达水平与血清肿瘤标志物CA153密切相关，提示检测外周血有核miR-205-5p表达水平或许可以作为监测非小细胞肺癌患者转移和复发、评价治疗疗效以及评价预后的辅助指标。本课题还发现非小细胞肺癌患者外周血有核细胞miR-205-5p表达水平与TNM分期密切相关，而与淋巴结转移无关。有研究[27]也表明miRNA-205-5p在不同TNM分期食管鳞状细胞癌患者组织中存在差异，且TNM分期越高，miRNA-205-5p表达量越高。此外，有研究证实miR-205-5p在头颈部鳞癌的转移性淋巴结标本中表达水平比良性标本高，可通过检测miR-205-5p的表达水平监测是否存在淋巴结转移[28]。在本研究中miRNA-205-5p的表达水平与非小细胞肺癌患者淋巴结转移无关，可能与样本数量较少有关，也有可能与癌的种类相关，还需要更多的研究来证实。

## [参 考 文 献]

[1] CHEN W, ZHENG R, BAADE P D, et al. Cancer statistics in China, 2015[J]. CA Cancer J Clin, 2016, 66 (2): 115-132. DOI:10.3322/caac.21338.

[2] SIEGEL R L, MILLER K D, JEMAL A. Cancer Statistics, 2017[J]. CA Cancer J Clin, 2017, 67 (1): 7-30. DOI:10.3322/caac.21387.

[3] XU T, SHEN G, CHENG M, et al. Clinicopathological and prognos-

tic significance of circulating tumor cells in patients with lung cancer: a meta-analysis[J]. Oncotarget, 2017, 8(37): 62524-62536. DOI: 10.18632/oncotarget.19122.

[4] CARTER L, ROTHWELL D G, MESQUITA B, et al. Molecular analysis of circulating tumor cells identifies distinct copy-number profiles in patients with chemosensitive and chemorefractory small-cell lung cancer[J]. Nat Med, 2017, 23 (1): 114-119. DOI:10.1038/nm.4239.

[5] CHEN Y, ZOU T N, WU Z P, et al. Detection of cytokeratin 19, human mammaglobin, and carcinoembryonic antigen-positive circulating tumor cells by three-marker reverse transcription-PCR assay and its relation to clinical outcome in early breast cancer[J]. Int J Biol Markers, 2010, 25 (2): 59-68.

[6] CALIN G A, CROCE C M. MicroRNA signatures in human cancers [J]. Nat Rev Cancer, 2006, 6 (11): 857-866. DOI:10.1038/nrc1997.

[7] RUPAIMOOLE R, SLACK F J. MicroRNA therapeutics: towards a new era for the management of cancer and other diseases[J]. Nat Rev Drug Discov, 2017, 16 (3): 203-222. DOI:10.1038/nrd. 2016. 246.

[8] HUO L, WANG Y, GONG Y, et al. MicroRNA expression profiling identifies decreased expression of miR-205 in inflammatory breast cancer [J]. Mod Pathol, 2016, 29 (4): 330-346. DOI:10.1038/modpathol.2016.38.

[9] DE COLA A, VOLPE S, BUDANI M C, et al. miR-205-5p-mediated downregulation of ErbB/HER receptors in breast cancer stem cells results in targeted therapy resistance[J/OL]. Cell Death Dis, 2015, 6: e1823[2017-04-20]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4650737/ . DOI:10.1038/cddis.2015.192.

[10] HUO D, CLAYTON W M, YOSHIMATSU T F, et al. Identification of a circulating microRNA signature to distinguish recurrence in breast cancer patients[J]. Oncotarget, 2016, 7 (34): 55231-55248. DOI:10.18632/oncotarget.10485.

[11] JIANG M, ZHANG P, HU G, et al. Relative expressions of miR-205-5p, miR-205-3p, and miR-21 in tissues and serum of non-small cell lung cancer patients[J]. Mol Cell Biochem, 2013, 383 (1/2): 67-75. DOI:10.1007/s11010-013-1755-y.

[12] LI C, YIN Y, LIU X, et al. Non-small cell lung cancer associated microRNA expression signature: integrated bioinformatics analysis, validation and clinical significance[J]. Oncotarget, 2017, 8(15): 24564-24578. DOI:10.18632/oncotarget.15596.

[13] DUAN B, GUO T, SUN H, et al. miR-205 as a biological marker in non-small cell lung cancer[J/OL]. Biomed Pharmacother, 2017, 91: 823-830 [2017-04-20]. http://www.sciencedirect.com/science/article/pii/S0753332217311241?via%3Dihub. DOI: 10.1016/j.biopha. 2017. 04. 086.

[14] BEGUM S, HAYASHI M, OGAWA T, et al. An integrated genome-wide approach to discover deregulated microRNAs in non-small cell lung cancer: clinical significance of miR-23b-3p deregulation [J/OL]. Sci Rep, 2015, 5: 13236[2017-04-20]. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/26314549/. DOI:10.1038/srep13236.

[15] BOLL K, REICHE K, KASACK K, et al. miR-130a, miR-203 and miR-205 jointly repress key oncogenic pathways and are downregulated in prostate carcinoma[J]. Oncogene, 2013, 32 (3): 277-285. DOI:10.1038/onc.2012.55.

[16] HAGMAN Z, HAFLIDADOTTIR B S, CEDER J A, et al. miR-205 negatively regulates the androgen receptor and is associated with adverse outcome of prostate cancer patients[J]. Br J Cancer, 2013, 108 (8): 1668-1676. DOI:10.1038/bjc.2013.131.

[17] LI J, HU K, GONG G, et al. Upregulation of MiR-205 transcriptionally suppresses SMAD4 and PTEN and contributes to human ovarian cancer progression [J/OL]. Sci Rep, 2017, 7: 41330[2017-04-20]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5286557/. DOI:10.1038/srep41330.

[18] CHARKIEWICZ R, PILZ L, SULEWSKA A, et al. Validation for histology-driven diagnosis in non-small cell lung cancer using hsa-miR-205 and hsa-miR-21 expression by two different normalization strategies[J]. Int J Cancer, 2016, 138 (3): 689-697. DOI:10.1002/ijc.29816.

[19] LU Y, GOVINDAN R, WANG L, et al. MicroRNA profiling and prediction of recurrence/relapse-free survival in stage I lung cancer [J]. Carcinogenesis, 2012, 33 (5): 1046-1054. DOI:10.1093/carcin/bgs100.

[20] ZAROGOULIDIS P, PETANIDIS S, KIOSEOGLOU E, et al. miR-205 and miR-218 expression is associated with carboplatin chemoresistance and regulation of apoptosis via Mcl-1 and Survivin in lung cancer cells[J]. Cell Signal, 2015, 27 (8): 1576-1588. DOI: 10.1016/j.cellsig.2015.04.009.

[21] CAI J, FANG L, HUANG Y, et al. miR-205 targets PTEN and PHLPP2 to augment AKT signaling and drive malignant phenotypes in non-small cell lung cancer[J]. Cancer Res, 2013, 73 (17): 5402-5415. DOI:10.1158/0008-5472.CAN-13-0297.

[22] BAI J, ZHU X, MA J, et al. miR-205 regulates A549 cells proliferation by targeting PTEN[J]. Int J Clin Exp Pathol, 2015, 8 (2): 1175-1183.

[23] LARZABAL L, DE ABERASTURI A L, REDRADO M, et al. TMPRSS4 regulates levels of integrin alpha5 in NSCLC through miR-205 activity to promote metastasis[J]. Br J Cancer, 2014, 110 (3): 764-774. DOI:10.1038/bjc.2013.761.

[24] 王佳佳, 雷伟, 陈成, 等. MicroRNA-205在非小细胞肺癌组织和血浆中的表达及临床意义[J]. 江苏医药, 2015, (10): 1167-1169+1173. DOI:10.19460/j.cnki.0253-3685.2015.10.018.

[25] DEL VESCOVO V, CANTALONI C, CUCINO A, et al. miR-205 Expression levels in nonsmall cell lung cancer do not always distinguish adenocarcinomas from squamous cell carcinomas [J]. Am J Surg Pathol, 2011, 35 (2): 268-275. DOI:10.1097/PAS.0b013e3182068171.

[26] MARKOU A, TSAROUCHA E G, KAKLAMANIS L, et al. Prognostic value of mature microRNA-21 and microRNA-205 overexpression in non-small cell lung cancer by quantitative real-time RT-PCR[J]. Clin Chem, 2008, 54 (10): 1696-1704. DOI:10.1373/clinchem.2007.101741.

[27] 董树岭, 尹惠卿, 吕彦萌, et al. miRNA-205在食管鳞状细胞癌患者组织中的表达及临床意义[J]. 第三军医大学学报, 2016, (01): 85-88. DOI:10.16016/j.1000-5404.201504138.

[28] FLETCHER A M, HEAFORD A C, TRASK D K. Detection of metastatic head and neck squamous cell carcinoma using the relative expression of tissue-specific mir-205[J]. Transl Oncol, 2008, 1 (4): 202-208.

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