昆明医科大学学报 2014,35(11):4~9
Journal of Kunming Medical University
CN 53-1221/R

hsa-miR-126的靶基因预测及功能分析

陈 波[1)]，者明伟[2)]，廖泽容[2)]，徐天勇[1)]，卢敏南[1)]，赵洪波[3,4)]
(1) 昆明医科大学科研实验中心；2) 现代教育技术中心；3) 临床医学研究院；4) 云南省干细胞和再生医学重点实验室，云南 昆明 650500)

[摘要] **目的** 检测hsa-miR-126在各个组织器官中的表达情况,通过生物信息学预测hsa-miR-126的靶基因,进一步分析其可能功能，为研究hsa-miR-126的功能和机制奠定基础. **方法** 通过miRGator v3.0数据库查看hsa-miR-126在各个组织器官中的表达丰度情况；应用TargetScan、DIANA-microT-CDS及miRanda预测hsa-miR-126的靶基因;将预测所得靶基因和已证实的靶基因交集组成的基因集合分别进行功能富集分析(GO analysis)和信号转导通路富集分析,分析hsa-miR-126的可能功能. **结果** hsa-miR-126在胃肠道,心脏,肾脏,肝胆系统,肺,干细胞,睾丸,胸腺,甲状腺,子宫中表达丰度较高;结合已被证实靶基因得到40个候选靶基因;靶基因主要参与细胞迁移调控以及腺体发育相关生物过程，涉及数个癌症通路和与癌症发生相关的信号通路，以及神经营养因子信号通路，ErbB信号通路,趋化因子信号通路和VEGF信号通路等. **结论** hsa-miR-126预测的靶基因集合富集于多个生物学过程,与肿瘤和血管性疾病密切相关,生物信息预测结果为今后的研究奠定了基础.

[关键词] hsa-miR-126；微小RNA；生物信息学；靶基因；功能
[中图分类号] R318.04 [文献标识码] A [文章编号] 2095-610X (2014) 11-0004-06

Prediction of hsa-miR-126 Target Genes and Its Function Analysis

CHEN Bo[1)], ZHE Ming-wei[2)], LIAO Ze-rong[2)], XU Tian-yong[1)], LU Min-nan[1)], ZHAO Hong-bo[3,4)]
(1)*Scientific Research Experiment Center, Kunming Medical University*; 2)*Modern Education Technology Center of Kunming Medical University*; 3)*Institute of Molecular and Clinical Medicine, Kunming Medical University*; 4)*Yunnan Key Laboratory of Stem Cell and Regenerative Medicine, Kunming Yunnan* 650500, *China*)

[**Abstract**] Objective To investigate hsa-miR-126 expression levels in human organs, then predict the target genes and functions of hsa-miR-126 by bioinformatics analysis for further study. Methods The expression levels of has-niR-126 in human organs were checked by miRGator v3.0 database. TargetScan, DIANA-microT-CDS and miRanda were used to predict the target genes of hsa-miR-126. The functions of the target genes were predicted via Gene ontology (GO) analysis and Pathway analysis. Results Higher expression of hsa-miR-126 was observed in gastrointestinal tract, heart, kidney, liver and biliary system, lung, stem cell, testis, thymus, thyroid and uterus. 40 candidate target genes were collected. The functions of the target genes were enriched in regulation of cell migration, locomotion, cell motion and gland development. Neurotrophin signaling pathway, insulin signaling pathway, ErbB signaling pathway, aldosterone-regulated sodium reabsorption, chemokine signaling pathway, VEGF signaling pathway and many cancer related pathways were significantly enriched. Conclusion The target genes set of hsa-miR-126 was enriched in multiple biological process which was related with many tumors and vascular diseases, and the prediction results can provide a basis for the further research.

[**Key words**] hsa-miR-126; miRNA; Bioinformatics; Target genes; Function

[基金项目] 国家自然科学基金资助项目 (81360336)；云南省应用基础研究基金资助项目 (2012FB152)
[作者简介] 陈波 (1981~)，男，云南永胜县人，硕士，助理实验师，主要从事miRNA方面的研究工作. 者明伟与陈波对本文有同等贡献.
[通讯作者] 赵洪波. E-mail: zhao.hongbo@hotmail.com

miRNA （microRNA）是一类约 22 个核苷酸的非编码小分子 RNA，进化上高度保守，由长约 70nt 可形成发夹结构的前体经 dicer 酶剪切而来. 通过与同源靶信使 RNA（mRNA）3' 端非翻译区（UTR）结合，对基因进行转录后的调控. miRNA 参与生命过程的一系列重要进程，在细胞的增殖、分化、凋亡等生理或病理过程中起着重要作用[1-3]. 特别是在肿瘤疾病中，不同条件下，miRNA 可扮演癌基因或抑癌基因的角色，也可通过对癌基因或抑癌基因的调控来发挥其促进或抑制作用. 然而，miRNA 的调控机制非常复杂，在不同病理环境中，只有很少的一部分靶基因验证被一些 miRNA 所调节，miRNA 涉及到的生物学过程和通路还有很大一部分不清楚.

hsa-miR-126 位于染色体 9q34.3，起源于 EGFL7 基因的前体结构，与其宿主基因 EGFL7 一起被转录因子 Ets1 调控[4]，在成熟前血管内皮细胞中与 EGFL7 一致，呈高表达[5]. hsa-miR-126 部分靶标已鉴定，但其具体调控机制和生物学功能还不完全清楚. 本研究综合多种生物信息学工具预测 hsa-miR-126 的靶基因，对其进行表达分析、功能富集分析（GO analysis）和信号转导通路富集分析（Pathway analysis），进一步挖掘数据中的生物学知识，为后续 hsa-miR-126 的功能研究提供理论依据和数据支持.

1　材料与方法

1.1　hsa-miR-126 的表达情况

将 hsa-miR-126 输入 miRGator v3.0[6]数据库，查看 hsa-miR-126 在各个组织器官中的表达情况. miRGator v3.0 汇编了 GEO，SRA，TCGA 等机构发布的 73 个人类 microRNA 深度测序数据集，包含着 41 亿条短序列和 25 亿条匹配过的序列. 使用者可以快速的检索自己感兴趣的 miRNA 的序列和表达情况.

1.2　hsa-miR-126 的靶基因预测

通过 TargetScan 6.2[7]、DIANA-microT-CDS[8]、miRanda[9]三种工具预测 hsa-miR-126 的靶基因，并取三者预测结果的交集. 从 miRTarBase[10]数据库中提取已证实的靶标基因加入交集作为进一步分析的基因集合.

1.3　hsa-miR-126 靶基因的功能注释分析

将 hsa-miR-26b 的靶基因集合用 Gene Ontology[11]和通路信息进行功能富集分类，通过 DAVID[12,13]分析工具对 hsa-miR-126 的靶基因进行基于 GO 的功能富集和基于 KEGG 的生物通路富集分析.

2　结果

2.1　hsa-miR-126 的表达情况

hsa-miR-126 在各个组织器官中的表达情况见图 1，其中在胃肠道，心脏，肾脏，肝胆系统，肺，干细胞，睾丸，胸腺，甲状腺，子宫中表达丰度较高.

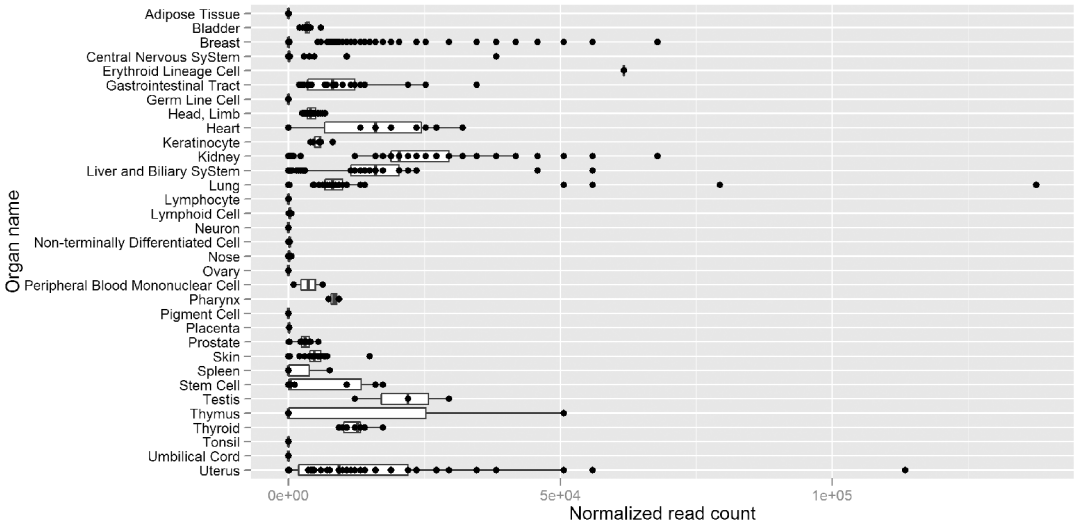

图 1　hsa-miR-126 在各个组织器官中的表达情况

Fig. 1 Expression abundance of hsa-miR-126 in organs

2.2 hsa-miR-126的靶基因预测

Targetscan、DIANA-microT-CDS及miRanda预测的hsa-miR-126靶基因数量分别为25、20、815个，3种预测方法结果的交集并结合miRTarBase数据库中已证实的32个靶标共获得40个候选靶基因（见表1）.

表1 hsa-miR-126候选靶基因

Tab. 1 Candidate target genes of hsa-miR-126

基因名	基因号	基因描述
ADAM9	8 754	ADAM metallopeptidase domain 9 (meltrin gamma)
CAMSAP1	157 922	calmodulin regulated spectrin-associated protein 1
CCNE2	9 134	cyclin E2
CRK	1 398	v-crk sarcoma virus CT10 oncogene homolog (avian)
CRKL	1 399	v-crk sarcoma virus CT10 oncogene homolog (avian)-like
CXCL12	6 387	chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1)
DIP2C	22 982	DIP2 disco-interacting protein 2 homolog C (Drosophila)
DNMT1	1 786	DNA (cytosine-5-)-methyltransferase 1
E2F1	1 869	E2F transcription factor 1
EFHD2	79 180	EF-hand domain family, member D2
EGFL7	51 162	EGF-like-domain, multiple 7
FBXO33	254 170	F-box protein 33
HOXA9	3 205	homeobox A9
IGFBP2	3 485	insulin-like growth factor binding protein 2, 36kDa
IRS1	3 667	insulin receptor substrate 1
KANK2	25 959	KN motif and ankyrin repeat domains 2
KRAS	3 845	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
MERTK	10 461	c-mer proto-oncogene tyrosine kinase
MMP7	4 316	matrix metallopeptidase 7 (matrilysin, uterine)
PGR	5 241	progesterone receptor
PIK3CG	5 294	phosphoinositide-3-kinase, catalytic, gamma polypeptide
PIK3R2	5 296	phosphoinositide-3-kinase, regulatory subunit 2 (beta)
PITPNC1	26 207	phosphatidylinositol transfer protein, cytoplasmic 1
PLK2	10 769	polo-like kinase 2 (Drosophila)
PLXNB2	23 654	plexin B2
PTPN7	5 778	protein tyrosine phosphatase, non-receptor type 7
PTPN9	5 780	protein tyrosine phosphatase, non-receptor type 9
RBMX	27 316	RBMX RNA binding motif protein, X-linked
RGS3	5 998	regulator of G-protein signaling 3
SLC45A3	85 414	solute carrier family 45, member 3
SLC7A5	8 140	solute carrier family 7 (amino acid transporter light chain, L system), member 5
SOX2	6 657	SRY (sex determining region Y)-box 2
SPRED1	161 742	sprouty-related, EVH1 domain containing 1
TEK	7 010	TEK tyrosine kinase, endothelial
TOM1	10 043	hypothetical LOC100128526; target of myb1 (chicken)
TWF1	5 756	twinfilin, actin-binding protein, homolog 1 (Drosophila)
TWF2	11 344	twinfilin, actin-binding protein, homolog 2 (Drosophila)
VCAM1	7 412	vascular cell adhesion molecule 1
VEGFA	7 422	vascular endothelial growth factor A
ZNF219	51 222	zinc finger protein 219

2.3　hsa-miR-126 靶基因的 GO 分析

将 hsa-miR-126 的靶基因通过 GO 注释描述得到其生物学过程注释信息，功能富集分析显示，主要集中在细胞迁移调控以及腺体发育相关生物过程（表 2）.

2.4　hsa-miR-126 靶基因的生物信号通路分析

对基因集合中的 40 个候选靶基因进行生物通路富集分析. 结果显示，在经典通路数据库 KEGG 中 hsa-miR-126 靶基因预测靶基因集合显著富集于数个癌症通路和与癌症发生相关的信号通路中，以及神经营养因子信号通路（Neurotrophin signaling pathway），ErbB 信号通路（ErbB signaling pathway），趋化因子信号通路（Chemokine signaling pathway），VEGF 信号通路（VEGF signaling pathway），黏着斑（Focal adhesion）通路等，见表3.

表 2　hsa-miR-126 候选靶基因 GO 分析结果

Tab. 2　GO analysis of candidate target genes of hsa-miR-126

收录号	名称	*P*值	校正后 *P*值 a	基因数
GO:0051270	regulation of cell motion	1.12E-04	0.026	6
GO:0040012	regulation of locomotion	1.09E-04	0.038	6
GO:0030334	regulation of cell migration	5.95E-05	0.041	6
GO:0048732	gland development	3.49E-04	0.059	5

表 3　hsa-miR-126 候选靶基因集合的信号转导通路富集分析结果

Tab. 3　Pathway analysis of candidate target genes of hsa-miR-126

收录号	通路	*P*值	校正后 *P*值 a	基因数
hsa05211	Renal cell carcinoma	3.19E-06	1.75E-04	6
hsa05220	Chronic myeloid leukemia	4.50E-06	1.24E-04	6
hsa04722	Neurotrophin signaling pathway	5.28E-05	9.68E-04	6
hsa05200	Pathways in cancer	7.46E-05	0.001	8
hsa04910	Insulin signaling pathway	7.94E-05	8.74E-04	6
hsa05212	Pancreatic cancer	9.73E-05	8.92E-04	5
hsa04012	ErbB signaling pathway	2.04E-04	0.002	5
hsa05215	Prostate cancer	2.22E-04	0.002	5
hsa04960	Aldosterone-regulated sodium reabsorption	3.65E-04	0.002	4
hsa04062	Chemokine signaling pathway	3.70E-04	0.002	6
hsa05223	Non-small cell lung cancer	8.25E-04	0.004	4
hsa05214	Glioma	0.001	0.006	4
hsa05218	Melanoma	0.002	0.008	4
hsa04370	VEGF signaling pathway	0.002	0.008	4
hsa05222	Small cell lung cancer	0.003	0.011	4
hsa04914	Progesterone-mediated oocyte maturation	0.003	0.011	4
hsa04666	Fc gamma R-mediated phagocytosis	0.004	0.014	4
hsa04510	Focal adhesion	0.005	0.014	5
hsa04810	Regulation of actin cytoskeleton	0.006	0.017	5
hsa04670	Leukocyte transendothelial migration	0.008	0.021	4
hsa05219	Bladder cancer	0.009	0.024	3
hsa04360	Axon guidance	0.010	0.024	4
hsa04930	Type II diabetes mellitus	0.012	0.028	3
hsa05213	Endometrial cancer	0.014	0.032	3
hsa04150	mTOR signaling pathway	0.014	0.032	3
hsa05221	Acute myeloid leukemia	0.017	0.038	3

3 讨论

miRNA参与各种各样的调节途径，包括发育、造血过程、器官形成、细胞增殖和凋亡、脂肪代谢等，具有重要的基因表达调控作用. 与多种疾病的发生、发展密切相关，已经有关于其与恶性肿瘤、心脏病、糖尿病、肝炎、帕金森病、唐氏综合征等疾病相关的研究证据. miRNA在人类疾病中的异常表达成为近年来研究的热点之一.

miRNA的表达具有显著的时序性和组织特异性，即在发育、疾病的不同阶段，或在不同的组织、细胞类型中具有特异的表达特征. 功能研究的结果证实miRNA是基因转录后表达的重要调控因子[14-17]，与信号通路和调控因子相互作用形成网络调控系统. Harris等[18]在研究内皮细胞功能时，首次阐述了miR-126的表达，miR-126主要在内皮细胞中表达，在肺脏、心脏和肝脏等血管高度丰富的组织中，miR-126的表达水平也很高[19]. Kane[21]等在miRNA与血管新生的研究中发现，人胚胎干细胞定向分化为内皮细胞，在分化时血管新生相关的线粒体miRNA表达增加，miR-126尤为显著. Jin[22]等在miRNA分级群聚试验中发现造血干细胞中miR-126高度表达. 此外，研究发现miR-126在凋亡小体中含量丰富，miR-126通过调节CXCL12对血管内皮细胞凋亡进行调控[23]. Landgraf等[24]报道has-miR-126对于造血系统、呼吸系统、消化系统、生殖系统及胚胎组织有一定特异性，尤其对于心血管系统特异性最高，与在miRGator数据库中得到的结果一致.

hsa-miR-126在乳腺癌[25]、宫颈癌[26,27]、肺癌[28,29]、慢性淋巴细胞白血病[30]、结直肠肿瘤[31]、酒精相关性肝细胞癌[32]等肿瘤组织中呈低表达，起到类似抑癌基因的作用. 与我们的疾病相关通路分析的部分结果一致. 在非小细胞肺癌的癌细胞中，肺癌细胞株转染miR-126后，其黏附、迁移和侵袭能力降低[33]. Liu等通过实验发现hsa-miR-126可下调肺癌细胞中VEGF的表达，抑制肺癌细胞增殖，进一步证明了其具有抑癌基因的作用[34]，与我们分析的生物学过程吻合. 抑癌作用的机制主要是通过作用于肿瘤细胞本身抑制肿瘤细胞的生长，调节参与细胞信号传导蛋白的合成，抑制细胞周期，减少肿瘤细胞的增殖.

在急性巨核细胞白血病细胞[35]、急性髓性白血病细胞[36,37]、食管腺癌组织[38]、转移性肺肿瘤[39]等肿瘤中hsa-miR-126高表达. 这些类似促癌基因的作用，可能与hsa-miR-126的促进血管生成作用有关，特别是肿瘤血管的生成，促进了肿瘤的生长转移. 已有大量实验表明hsa-miR-126在正常内皮细胞血管生成过程中发挥着重要的调控作用，但是在肿瘤和缺血缺氧引起的新生血管的血管内皮细胞中，hsa-miR-126在基因表达、细胞表型和功能特性上都不同于正常组织的血管内皮细胞[40].

目前，生物信息学已成为研究miRNA最重要的工具之一. 尽管准确预测和鉴定miRNA靶基因的难度都很大，但不同软件预测的结果有可能不一样，采用多个软件进行预测，取其交集部分，可提高预测结果的可靠性，减小假阳性率. 综合三种miRNA作用靶基因的预测结果，采用多种生物信息学方法对hsa-miR-126的表达情况以及靶基因功能富集分析和信号转导通路富集分析，为阐明hsa-miR-126的生物学功能提供了数据支持和理论指导.

[参考文献]

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

[2] BUSHATI N,COHEN S M. microRNA functions[J]. Annu Rev Cell Dev Biol,2007,23(2):175-205.

[3] AMERES S L,ZAMORE P D. Diversifying microRNA sequence and function[J]. Nat Rev Mol Cell Biol,2013,14(8):475-488.

[4] LELIEVRE E,LIONNETON F,SONCIN F,et al. The Ets family contains transcriptional activators and repressors involved in angiogenesis [J]. Int J Biochem Cell Biol,2001,33(4):391-407.

[5] VAN SOLINGEN C,SEGHERS L,BIJKERK R,et al. Antagomir-mediated silencing of endothelial cell specific microRNA-126 impairs ischemia-induced angiogenesis [J]. J Cell Mol Med,2009,13(8A):1 577-1 585.

[6] CHO S,JANG I,JUN Y,et al. MiRGator v3.0: a microRNA portal for deep sequencing, expression profiling and mRNA targeting [J]. Nucleic Acids Res,2013,41 (2): 252-257.

[7] LEWIS B P,BURGE C B,BARTEL D P. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets [J]. Cell,2005,120(1):15-20.

[8] PARASKEVOPOULOU M D,GEORGAKILAS G,KOSTOULAS N,et al. DIANA-microT web server v5.0: service integration into miRNA functional analysis workflows [J]. Nucleic Acids Res,2013,41(3): 169-173.

[9] BETEL D,WILSON M,GABOW A,et al. The microRNA.org resource: targets and expression [J]. Nucleic Acids Res,2008,36(6):149-153.

[10] HSU S D,LIN F M,WU W Y,et al. miRTarBase: adatabase curates experimentally validated microRNA-target inter-

actions [J].Nucleic Acids Res,2011,39(2): 163 – 169.
[11] ASHBURNER M,BALL C A,BLAKE J A,et al. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium [J]. Nat Genet,2000,25(1):25 – 29.
[12] HUANG DA W,SHERMAN B T,AND LEMPICKI R A. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources [J].Nat Protoc,2009,4(1):44 – 57.
[13] HUANG DA W,SHERMAN B T,AND LEMPICKI R A. Bioinformatics enrichment tools: paths toward the comprehensive functional analysis of large gene lists [J]. Nucleic Acids Res,2009,37(1):1 – 13.
[14] POLAJEVA J,SWARTLING F J,JIANG Y,et al. miRNA-21 is developmentally regulated in mouse brain and is co-expressed with SOX2 in glioma [J]. BMC Cancer,2012,12(4):78.
[15] STAUFFER B L,RUSSELL G,NUNLEY K,et al. miRNA expression in pediatric failing human heart [J]. J Mol Cell Cardiol,2013,57(4):43 – 46.
[16] ZHANG Y,WU L,WANG Y,et al. Protective role of estrogen-induced miRNA-29 expression in carbon tetrachloride-induced mouse liver injury [J]. J Biol Chem,2012,287(18):14 851 – 14 862.
[17] BOTCHKAREVA N V. MicroRNA/mRNA regulatory networks in the control of skin development and regeneration [J]. Cell Cycle,2012,11(3):468 – 474.
[18] HARRIS T A,YAMAKUCHI M,FERLITO M,et al. MicroRNA-126 regulates endothelial expression of vascular cell adhesion molecule 1 [J]. Proc Natl Acad Sci U S A,2008,105(5):1 516 – 1 521.
[19] PARKER L H,SCHMIDT M,JIN S W,et al. The endothelial-cell-derived secreted factor Egfl7 regulates vascular tube formation [J]. Nature,2004,428(6 984):754 – 758.
[20] WEI H,WANG C,ZHANG C,et al. Comparative profiling of microRNA expression between neural stem cells and motor neurons in embryonic spinal cord in rat [J]. Int J Dev Neurosci,2010,28(6):545 – 551.
[21] KANE N M,MELONI M,SPENCER H L,et al. Derivation of endothelial cells from human embryonic stem cells by directed differentiation: analysis of microRNA and angiogenesis in vitro and in vivo [J]. Arterioscler Thromb Vasc Biol,2010,30(7):1 389 – 1 397.
[22] JIN P,WANG E,REN J,et al. Differentiation of two types of mobilized peripheral blood stem cells by microRNA and cDNA expression analysis [J]. J Transl Med,2008,6(3):39.
[23] ZERNECKE A,BIDZHEKOV K,NOELS H,et al. Delivery of microRNA-126 by apoptotic bodies induces CXCL12-dependent vascular protection [J]. Sci Signal,2009,2(100):81.
[24] LANDGRAF P,RUSU M,SHERIDAN R,et al. A mammalian microRNA expression atlas based on small RNA library sequencing [J]. Cell,2007,129(7):1 401 – 1 414.
[25] IORIO M V,FERRACIN M,LIU C G,et al. MicroRNA gene expression deregulation in human breast cancer [J]. Cancer Res,2005,65(16):7 065 – 7 070.
[26] WANG X,TANG S,LE S Y,et al. Aberrant expression of oncogenic and tumor-suppressive microRNAs in cervical cancer is required for cancer cell growth [J]. PLoS One,2008,3(7):e2 557.
[27] HUANG T H,CHU T Y. Repression of miR-126 and upregulation of adrenomedullin in the stromal endothelium by cancer-stromal cross talks confers angiogenesis of cervical cancer [J]. Oncogene,2013,33(28):3 636 – 3 647.
[28] YANAIHARA N,CAPLEN N,BOWMAN E,et al. Unique microRNA molecular profiles in lung cancer diagnosis and prognosis [J]. Cancer Cell,2006,9(3):189 – 198.
[29] REN G,KANG Y. A one-two punch of miR-126/126* against metastasis [J]. Nat Cell Biol,2013,15(3): 231 – 233.
[30] CALIN G A,LIU C G,SEVIGNANI C,et al. MicroRNA profiling reveals distinct signatures in B cell chronic lymphocytic leukemias [J]. Proc Natl Acad Sci U S A,2004,101(32):11 755–11 760.
[31] MICHAEL M Z,SM O C,VAN HOLST PELLEKAAN N G,et al. Reduced accumulation of specific microRNAs in colorectal neoplasia [J]. Mol Cancer Res,2003,1(12): 882 – 891.
[32] LADEIRO Y,COUCHY G,BALABAUD C,et al. MicroRNA profiling in hepatocellular tumors is associated with clinical features and oncogene/tumor suppressor gene mutations [J]. Hepatology,2008,47(6):1 955 – 1 963.
[33] CRAWFORD M,BRAWNER E,BATTE K,et al. MicroRNA-126 inhibits invasion in non-small cell lung carcinoma cell lines [J]. Biochem Biophys Res Commun,2008,373(4):607 – 612.
[34] LIU B,PENG X C,ZHENG X L,et al. MiR-126 restoration down-regulate VEGF and inhibit the growth of lung cancer cell lines in vitro and in vivo [J]. Lung Cancer,2009,66(2):169 – 175.
[35] GARZON R,PICHIORRI F,PALUMBO T,et al. MicroRNA fingerprints during human megakaryocytopoiesis [J]. Proc Natl Acad Sci U S A,2006,103(13):5 078 – 5 083.
[36] CAMMARATA G,AUGUGLIARO L,SALEMI D,et al. Differential expression of specific microRNA and their targets in acute myeloid leukemia [J]. Am J Hematol,2010,85(5):331 – 339.
[37] LI Z,LU J,SUN M,et al. Distinct microRNA expression profiles in acute myeloid leukemia with common translocations [J]. Proc Natl Acad Sci U S A,2008,105(40): 15 535 – 15 540.
[38] YANG H,GU J,WANG K K,et al. MicroRNA expression signatures in Barrett's esophagus and esophageal adenocarcinoma [J]. Clin Cancer Res,2009,15 (18): 5 744 – 5 752.
[39] BARSHACK I,LITHWICK-YANAI G,AFEK A,et al. MicroRNA expression differentiates between primary lung tumors and metastases to the lung [J]. Pathol Res Pract,2010,206(8):578 – 584.
[40] BUSSOLATI B,DEAMBROSIS I,RUSSO S,et al. Altered angiogenesis and survival in human tumor-derived endothelial cells [J]. FASEB J,2003,7(9):1 159 – 1 161.

（2014 – 09 – 13 收稿）