·综 述·

miR-17-5p在肿瘤中作用的研究进展*

吴莹莹[①] 高波[②] 丁跃明[②] 综述 潘云[②] 审校

摘要 微小RNA(microRNA,miRNA)作为生物体内一种重要的基因调控分子,其异常表达与人类多种疾病密切相关。近年来,miRNA在多种肿瘤中起着抑癌基因或是致癌基因的作用,因此,miRNA已成为肿瘤学研究的新方向。miR-17-5p作为miR-17~92簇的一员,是近年来疾病研究的热点,多种肿瘤发生发展中均有涉及。本文主要对miR-17-5p的基本特征及其在肿瘤中的作用进行综述。

关键词 miR-17-5p 肿瘤 靶基因
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Research progress on miR-17-5p in tumors

Yingying WU[1], Bo GAO[2], Yueming DING[2], Yun PAN[2]
Correspondence to: Yun PAN; E-mail: panyun09@163.com
[1]College of Clinical Medicine, Dali University, Dali 671000, China; [2]Department of Pathology, Affiliated Hospital of Dali University, Dali 671000, China

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Abstract As an important gene regulatory molecule, microRNA is closely related with various human diseases. Numerous studies have confirmed that microRNAs function as tumor suppressors or oncogenes in various tumor types. Therefore, microRNA investigation has become a new direction in oncology research. As a member of the miR-17 to -92 cluster, miR-17-5p has been the focus of research recently. MicroRNA is involved in many aspects of diseases, such as diabetes mellitus, endometriosis, and a variety of tumors. In this review, the basic characteristics and roles of miR-17-5p in tumors are elaborated.

Keywords: miR-17-5p, tumor, target gene

微小RNA(microRNA,miRNA)是一类由内源基因编码的长度为19~25个核苷酸的非蛋白编码单链RNA分子,在物种之间高度保守。miRNA通常可作用于一个或多个信使RNA(mRNA),并通过降解mRNA或抑制翻译水平而达到负调控基因表达的目的。近年来,miRNA与肿瘤的关系已成为现阶段研究的一个热点。miRNA可作为肿瘤诊断、治疗及预后的标志物。本文对miR-17-5p的特征及在肿瘤中的研究进展进行综述。

1 miR-17-5p的基本特征

miR-17-5p属于miR-17家族,其家族成员还包括miR-20a/b、miR-106a/b和miR-93,该家族已被证实参与生物正常发育以及恶性肿瘤生长及死亡的关键途径[1]。miR-17-5p属于miR-17~92基因簇,该基因簇成员有miR-17、miR-18a、miR-19a、miR-19b、miR-20a、miR-92a,在多种实体及血液系统肿瘤中高表达。miR-17-5p位于人类13q31和啮齿类14qE4染色体上[2],可直接作用于mRNA的3′端的非编码区[3-4]。miR-17-5p是多顺反子C13ORF25的一员,C13ORF25已被证明是由MYC蛋白的启动子结合域上调的,并且在70%弥漫性大B细胞性淋巴瘤(diffuse large B-cell lymphoma,DLBCL)中过表达[5]。

2 miR-17-5p在肿瘤中的表达

miR-17-5p在多种肿瘤中表达,与肿瘤细胞的增殖、凋亡、淋巴转移及化疗耐药性等相关(表1)。不同组织来源或不同类型的肿瘤都具有特异性的microRNA表达谱,但是同一肿瘤的microRNA表达谱在发生发展的不同分期阶段也可能存在差异。miR-17-5p在大多数肿瘤中呈现上调趋势,发挥着癌基因的作用。但对于少部分肿瘤,不同研究中miR-17-5p呈现不同的表达。

3 miR-17-5p的靶基因

作者单位:①大理大学临床医学院(云南省大理市671000);②大理大学附属医院病理科
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通信作者:潘云 panyun09@163.com

miR-17-5p主要是通过靶基因及相关信号通路等在肿瘤中发挥癌基因或抑癌基因的作用(表2),因此鉴别出miR-17-5p的靶基因对研究其功能至关重要。目前有很多预测miRNA靶基因的软件,其中以miRWalk、Targetscan、miRanda等比较常用,并且可以利用GO(gene ontology)和KEGG(kyoto encyclopedia of genes and genomes)数据库分析靶基因功能。miRNA主要通过降解mRNA或抑制翻译水平负调控其靶基因。在大多数肿瘤中,miR-17-5p呈现上调趋势,因此其靶基因缺失或下调。但是在Li等[4]的研究中发现,在卵巢癌中过表达miR-17-5p可通过作用于细胞周期G_1/S期促进肿瘤细胞增殖、抑制凋亡,同时促进靶基因YES1的表达。敲除YES1基因能够抑制细胞增殖、诱导细胞周期阻滞。

表1 miR-17-5p在肿瘤中的表达及作用

Table 1 The expression and functions of miR-17-5p in tumors

Tumor	Expression	Function
Metastatic hepatocellular carcinoma[5-8,9-12]	Upregulation	Associated with the high-grade lesion, lymphatic invasion and poor prognosis, inhibiting apoptosis, promoting the proliferation, growth, invasion and colony formation of tumor
Prostate cancer[13]	Upregulation	Promoting the proliferation, colony formation, cell survival and invasion of tumor
Prostate cancer[14]	Downregulation	Inhibiting the growth of tumor
Breast cancer[15-16]	Upregulation	Diagnostic biomarkers
Breast cancer[17-18]	Downregulation	Inhibiting the proliferation and colony formation of tumor
Pancreatic cancer[19-20]	Upregulation	Promoting the metastasis of tumor, improving chemoresistance and associated with relapse-free survival
Ovarian cancer[4,21]	Upregulation	Promoting the proliferation and inhibiting the apoptosis of tumor, inducing chemoresistance and migration
Endometrial cancer[22]	Upregulation	Promoting the proliferation and inhibiting the apoptosis of tumor
Gastric cancer[23-25]	Upregulation	Promoting the proliferation and inhibiting the apoptosis of tumor, associated with the differentiation of tumor, TNM classification and poor overall survival
Renal cell carcinoma[26]	Upregulation	Promoting the growth and metastasis of tumor
Colorectal cancer[27-29]	Upregulation	Promoting the invasion of tumor, increasing chemoresistance and reducing survival
Lung cancer (lung adenocarcinoma)[30-32]	Upregulation	Associated with poor prognosis and inhibiting apoptosis
Lung cancer (non-small cell lung cancer)[33-34]	Downregulation	Inhibiting the metastasis and invasion of tumor, improving chemosensitivity and inducing apoptosis
Glioblastoma[35]	Upregulation	Promoting cell motility, invasion, and tube-like structure formation
Pituitary carcinoma[36]	Upregulation	Associated with the metastasis of tumor
Oral squamous cell carcinoma[37]	Upregulation	Reducing the sensitivity to radiation
Bladder cancer[38]	Upregulation	—
Anaplastic thyroid cancer[39]	Upregulation	Promoting the growth of tumor and inhibiting the apoptosis
Neuroblastoma[40]	Upregulation	—
Esophageal adenocarcinoma[41]	Upregulation	—
Ependymoma[42]	Upregulation	—
Synovial sarcoma[43]	Upregulation	Promoting the growth of tumor
Pleural mesothelioma[44]	Upregulation	—
Cervical cancer[45]	Downregulation	Inhibiting the proliferation and promoting the apoptosis of tumor

表2 miR-17-5p的靶基因

Table 2 The target genes of miR-17-5p

Target gene	Function
pten (phosphatase and tensin homolog)[3,21,28,35-36,46]	Inhibiting the growth and metastasis of tumor and improving chemosensitivity
timp2 (timp metallopeptidase inhibitor 2)[36]	Inhibiting the metastasis of tumor
ints6/ints6p1 (integrator complex subunit 6/integrator complex subunit 6 pseudogene 1)[9]	Inhibiting the metastasis of tumor and promoting apoptosis
yes1 (yes proto-oncogene 1, src family tyrosine kinase)[4]	Promting the proliferation and inhibiting the apoptosis of tumor
p21 (cyclin-dependent kinase inhibitor 1a)[1,22-23,37,43]	Inhibiting the tumor growth, increasing the sensitivity to radiation , inducing the apoptosis
e2f1 (e2f transcription factor 1)[8,47]	Inhibiting the proliferation, growth, colony formation and invasion of tumor
socs6 (suppressor of cytokine signaling 6)[25]	Inhibition the proliferation of tumor
timp3 (timp metallopeptidase inhibitor 3)[13]	Reducing the cell survival and invasion of tumor
c-myc (v-myc avian myelocytomatosis viral oncogene homolog)[1.8]	Inhibiting the proliferation, invasion and colony formation of tumor
tp53inp1 (tumor protein p53 inducible nuclear protein 1)[23,45]	Inhibiting the proliferation and promoting the apoptosis of tumor
vegf-a (vascular endothelial growth factor a) [26]	Related with hypoxia signaling pathways
bim (bcl2 like 11)[19]	Related with chemoresistance
p130 (nucleolar and coiled-body phosphoprotein 1)[27]	Improving the overall survival of patients
egln3 (egl-9 family hypoxia-inducible factor 3)[26]	Related with hypoxia signaling pathways
stat3 (signal transducer and activator of transcription 3)[48]	—
zbtb4 (zinc finger and btb domain containing 4)[16]	Associated with relapse-free survival
pcaf (beta-ketoadipyl coa thiolase)[14]	Promoting the transcription of genes as a histone acetyltransferase; related with proliferation
becn1 (beclin 1)[33]	Related with chemoresistance

4 miR-17-5p在肿瘤形成和发展中的作用

4.1 miR-17-5p与肿瘤增殖和凋亡

miR-17-5p在细胞增殖G_1/S期起着重要的作用，并且在此过程中调控20多个mRNA表达，其中有促进增殖的基因，也有抑制增殖的基因[49]。目前发现，miR-17-5p在大多数肿瘤中起到癌基因的作用，促进细胞增殖，抑制细胞凋亡。Wang等[23]利用鼠移植瘤模型，证实miR-17-5p在胃癌组织中高表达，并且负调控靶基因P21和TP53INP1，从而促进肿瘤细胞的增殖，抑制其凋亡。有研究发现，在子宫内膜癌细胞中转染miR-17-5p模拟物或是P21小干扰RNA能够逆转化疗药物硼替佐米对子宫内膜癌细胞的增殖抑制和促进凋亡的作用[22]。

但在少部分关于前列腺癌、宫颈癌、乳腺癌等肿瘤的研究中，miR-17-5p则作为抑癌基因起作用。Gong等[14]研究发现前列腺癌中miR-17-5p明显下调，并且负调控靶基因PCAF，PCAF上调可促进雄激素受体转录活性以及癌细胞的生长。

4.2 miR-17-5p与肿瘤的侵袭及转移

Wei等[36]研究发现，miR-17-5p的表达在转移性垂体腺癌中较原发性垂体腺瘤明显上调，可负调控靶基因PTEN和TIMP2。也有研究通过构建肝细胞癌小鼠模型，证实miR-17-5p的上调可增加肿瘤细胞迁移率，血清中miR-17-5p的表达水平可作为非侵袭性肝细胞癌的生物标记物[6-7]。Tayebi等[8]研究发现，miR-17-5p在转移性肝细胞癌中和非转移性细胞癌中的表达存在差异。miR-17-5p的表达水平在非转移性肝细胞癌活检组织中较正常肝组织中明显下调，而在转移性肝细胞癌中高表达。在肝癌细胞株中过表达miR-17-5p能够通过负调控靶基因E2F1和c-MYC促进肿瘤细胞的增殖、生长、侵袭及集落形成，拮抗miR-17-5p的表达则会出现相反的效果。

Fan等[50]证实在乳腺癌细胞中抑制miR-17-5p能增加细胞转移特性，加速原位异种移植瘤向肺部转移，在瘤内注射miR-17-5p模拟物能明显减轻肿瘤的肺转移。

4.3 miR-17-5p与肿瘤的化疗耐药性及预后

miR-17-5p的表达还与肿瘤细胞的化疗耐药性以及患者的总生存率、预后有关。Yan等[19]在胰腺癌中发现miR-17-5p高表达，并且负调控Bim从而降低吉西他滨的化疗敏感性。Wu等[37]证实抑制miR-17-5p的表达能够通过抑制P21增强口腔鳞癌细胞的辐射敏感度。在结直肠癌中miR-17-5p高表达，并且靶向作用于P130，随后激活Wnt/β-catenin通路，与患者总生存率降低有关[27]。Chen等[30]发现在肺癌患者的血清中miR-17-5p高表达，并且与肺癌患者的预后

差相关。

Chatterjee等[33]发现，miR-17-5p在紫杉醇耐药的肺癌细胞中较紫杉醇敏感的肺癌细胞中明显下调，证实肺癌的紫杉醇耐药性可能与miR-17-5p的低表达引起beclin上调有关。

5 展望

近几年，由于各种原因，多种肿瘤发病率明显增加，很多肿瘤患者直至疾病晚期才确诊，大多数肿瘤现在仍无有效的治疗方法，总体生存率较低[51-53]。miR-17-5p属于miR-17～92基因簇，该基因簇在实体癌以及血液学肿瘤中研究较多[54]，并且有研究发现，在某些癌症中miR-17～92基因簇中的miR-17起主导作用[55]。目前miR-17-5p主要作为癌基因发挥作用。但是miR-17-5p可同时调控多个靶点mRNA，其中既有癌基因，也有抑癌基因[49]，因此miR-17-5p在肿瘤发病机制中的作用及其靶基因功能有待进一步深入研究，其作用机制必将为肿瘤诊断、治疗和预后提供新的突破口。

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作者简介

吴莹莹　专业方向为头颈部肿瘤的基础与临床研究。

E-mail：wuyingying0105@126.com