[DOI]10.12016/j.issn.2096-1456.2022.02.004

·基础研究·

血清miR-199a-5p、miR-378a-3p水平与婴幼儿增殖期面部血管瘤普萘洛尔停药后复发的关系

郭彦[1]，张凯[2]，范戌辉[3]，李立峰[4]
1. 西安交通大学口腔医院口腔急诊科，陕西 西安(710001)；2. 空军军医大学口腔医院整形外科，陕西 西安(710032)；3. 河北医科大学第二医院口腔颌面外科，河北 石家庄(050000)；4. 西安交通大学口腔医院创伤整形外科，陕西 西安(710001)

【摘要】 目的 探讨血清miR-199a-5p、miR-378a-3p水平与婴幼儿增殖期面部血管瘤普萘洛尔停药后复发的关系。**方法** 增殖期面部血管瘤患儿93例，均接受普萘洛尔治疗，随访治疗后血管瘤复发情况，并将患儿分为复发组(23例)和无复发组(70例)。治疗前、后采集静脉血，qRT-PCR检测血清miR-199a-5p、miR-378a-3p表达，分析血清miR-199a-5p、miR-378a-3p表达与增殖期面部血管瘤婴幼儿普萘洛尔停药后复发的关系。**结果** 无复发组治疗后血清miR-199a-5p、miR-378a-3p表达较治疗前增高($P<0.05$)，复发组治疗后血清miR-199a-5p、miR-378a-3p表达与治疗前比较差异无统计学意义($P>0.05$)。复发组治疗后血清miR-199a-5p、miR-378a-3p表达低于无复发组($P<0.05$)。治疗后瘤体分级Ⅲ～Ⅳ级患儿血清miR-199a-5p、miR-378a-3p表达高于Ⅰ～Ⅱ级患儿($P<0.05$)。Logistic回归分析结果显示miR-199a-5p低表达、miR-378a-3p低表达、治疗后瘤体分级Ⅰ～Ⅱ级是增殖期面部血管瘤婴幼儿普萘洛尔停药后复发的危险因素($P<0.05$)。**结论** 血清miR-199a-5p、miR-378a-3p低表达与增殖期面部血管瘤婴幼儿普萘洛尔停药后血管瘤复发有关。

【关键词】 微小RNA；miR-199a-5p；miR-378a-3p；普萘洛尔；婴幼儿；血管瘤；复发；内皮细胞增殖
【中图分类号】 R78　**【文献标志码】** A　**【文章编号】** 2096-1456(2022)02-0097-06
【引用著录格式】 郭彦, 张凯, 范戌辉, 等. 血清miR-199a-5p、miR-378a-3p水平与婴幼儿增殖期面部血管瘤普萘洛尔停药后复发的关系[J]. 口腔疾病防治, 2022, 30(2): 97-102. doi:10.12016/j.issn.2096-1456.2022.02.004.

微信公众号

Relationship between serum miR-199a-5p and miR-378a-3p levels and recurrence of infants with proliferative facial hemangioma after propranolol withdrawal

GUO Yan[1], ZHANG Kai[2], FAN Xuhui[3], LI Lifeng[4]. 1. Department of Dental Emergency, Xi′an Jiaotong University Hospital of Stomatology, Xi′an 710001, China; 2. Department of Plastic Surgery, Hospital of Stomatology, Air Force Military Medical University, Xi′an 710032, China; 3. Department of Oral and Maxillofacial Surgery, Second Hospital of Hebei Medical University, Shijiazhuang 050000, China; 4. Department of Traumatology and Plastic Surgery, Hospital of Stomatology, Xi′an Jiaotong University, Xi′an 710001, China
Corresponding author: LI Lifeng, Email: lifeng198601@163.com, Tel: 86-29-87215927

【Abstract】 Objective To investigate the relationship between serum miR-199a-5p and miR-378a-3p levels and the recurrence of infants with proliferative facial hemangioma relapsed after propranolol withdrawal in infants. **Methods** Ninety-three infants with proliferative facial hemangioma were selected, all of whom received propranolol treatment. The recurrence of the hemangioma after treatment was followed up, and the children were divided into a recurrence group (23 patients) and a nonrecurrence group (70 patients). Venous blood was collected before and after treatment, and the serum levels of miR-199a-5p and miR-378a-3p were detected by qRT-PCR, and the relationship between the serum levels

【收稿日期】 2021-07-09；**【修回日期】** 2021-08-25
【基金项目】 陕西省社会发展科技攻关项目(2017SF10325)
【作者简介】 郭彦，医师，硕士，Email：gra567@126.com
【通信作者】 李立峰，主治医师，硕士，Email:lifeng198601@163.com，Tel：86-29-87215927

of miR-199a-5p and miR-378a-3p and the recurrence of proliferative facial hemangioma relapsed after propranolol withdrawal in infants was analyzed. **Results** The serum expressions levels of miR-199a-5p and miR-378a-3p in non-relapsed group were increased after treatment compared with before treatment ($P < 0.05$), and there was no significant difference in the levels of miR-199a-5p and miR-378a-3p in the serum of the recurrence group after treatment compared with before treatment ($P > 0.05$). After treatment, the levels of miR-199a-5p and miR-378a-3p in the serum of the recurrence group were lower than those of the nonrecurrence group ($P < 0.05$). After treatment, the serum levels of miR-199a-5p and miR-378a-3p in patients with Ⅲ ~Ⅳ Norm grade hemangioma were higher than those in patients with Ⅰ ~Ⅱ Norm grade hemangioma ($P < 0.05$). Logistic regression analysis showed that the low expression of miR-199a-5p, low expression of miR-378a-3p and tumor grade Ⅰ ~Ⅱ after treatment were risk factors for the recurrence of proliferative facial hemangioma after propranolol withdrawal in infants ($P < 0.05$). **Conclusion** Low serum levels of miR-199a-5p and miR-378a-3p are associated with the recurrence of proliferative facial hemangioma after propranolol withdrawal in infants.

【Key words】 micro ribonucleic acid; miR-199a-5p; miR-378a-3p; propranolol; infant; hemangioma; recurrence; endothelial cell proliferation

J Prev Treat Stomatol Dis, 2022, 30(2): 97-102.

【Competing interests】 The authors declare no competing interests.

This study was supported by the grants from Shaanxi Province Social Development Science and Technology Project (No.2017SF10325).

血管瘤是来源于血管内皮细胞的良性肿瘤，好发于婴幼儿，增殖期血管瘤瘤体生长迅速易发生溃疡，发生于面部的血管瘤严重影响美观，增大瘤体可压迫周围器官导致视力、听力障碍或鼻软骨扩张，影响器官功能[1]。普萘洛尔是治疗增殖期血管瘤的一线用药，起效快，疗效显著，安全性高[2]。普萘洛尔停药后复发是影响血管瘤疗效、困扰临床医师的一大问题，临床研究显示普萘洛尔停药后复发率达25%，其中头颈部血管瘤复发几率较其它部位明显增加[3]。普萘洛尔停药后复发机制尚不清楚，现有研究发现普萘洛尔停药后复发与未复发患者存在显著的微小RNA（microRNA，miRNAs）表达差异[4]。miR-199a-5p可通过靶向低氧诱导因子1a抑制血管瘤细胞增殖和诱导细胞凋亡[5]，miR-378a-3p是恶性肿瘤潜在标志物，体外研究显示上调miR-378a-3p表达可抑制血管瘤内皮细胞增殖以及侵袭[6]。miR-199a-5p、miR-378a-3p与婴幼儿增殖期面部血管瘤普萘洛尔停药后复发是否有关尚不清楚，鉴于此，本研究拟检测增殖期面部血管瘤患儿血清miR-199a-5p、miR-378a-3p表达，分析其与血管瘤复发的关系。

1　资料和方法

1.1　临床资料

本研究已经获得西安交通大学口腔医院伦理委员会批准（审批号：2017pz06315），选取2017年1月至2020年1月西安交通大学口腔医院门诊收治的增殖期面部血管瘤患儿93例。男性24例，女性69例，年龄21 d ~ 9个月，平均（5.23 ± 1.16）个月；瘤体大小4 ~ 9 cm^2，平均（6.82 ± 2.09）cm^2；血管瘤分型：单发型11例，多发型22例，节段型49例，中间型11例；血管瘤分类：浅表性21例，深在性52例，混合性20例。所有患儿家属均知情同意签署同意书。

纳入标准：①符合2016版《血管瘤和脉管畸形诊断和治疗指南》中诊断标准[7]；②年龄 < 9个月；③接受普萘洛尔治疗，耐受性良好。

排除标准：①患儿生长缓慢、先天性心脏病、支气管痉挛、颅内动脉异常等；②血管内皮瘤、肌纤维瘤、横纹肌肉瘤；③喂养不良、呼吸困难、睡眠紊乱；④服药依从性差，随访失联。

1.2　主要仪器和试剂

TRIzol试剂（批号170305、181006、190116、000209，Invitrogen生命技术公司，美国）；全波长酶标仪（型号Multiskan SkyHigh，赛默飞公司，美国）；miRNeasy试剂盒（批号17DC12、18PK06、19AA03、00GB02，Qiagen公司，德国）；Prime Script RT试剂盒（批号SG1235、5K1342、PO41M2、L35184，Takara生物技术有限公司，中国）；qRT-PCR系统（型号CFX96，BIO-RAD公司，美国）。

1.3　血清miR-199a-5p、miR-378a-3p检测方法

所有患儿治疗前（普萘洛尔治疗前）、后（普

萘洛尔停药后1周内）采集静脉血3 mL注入干燥试管，室温下静置30～60 min后取上层血清离心（3 000 rpm，半径10 cm，时间10 min）后-20 ℃保存备用。取复融血清标本20 μL加入TRIzol试剂提取组织中总RNA，全波长酶标仪选取OD_{260}：OD_{280} 1.8～2.0样本，miRNeasy试剂盒提取miRNA，Prime Script RT试剂盒将miRNA逆转录为cDNA。取2 μL cDNA样品加入反应体系，qRT-PCR系统进行基因表达分析。引物由金斯瑞生物科技公司合成，引物序列：miR-199a-5p，上游：5′-CAATCGCTTTCAAATAG-3′，下游：5′-CAGGAGATGCTGTCATC-3′。miR-378a-3p，上游：5′-TCAACTGGTGTCGTGGAGT-3′，下游：5′-GGGACTGGACTTGGAGTC-3′。U6（内参）上游：5′-GCTTCGGCAGCACATATACTAAAAT-3′，下游：5′-CGCTTCACGAATTTGCGTGTCAT-3′。反应体系包括PrimeScript RT Enzyme Mix 1.0 μL，RTPrimer Mix 1.0 μL，5×PrimeScript Buffer 2 4.0 μL，RNase Free dH_2O 4.0 μL，cDNA模板2 μL，上下游引物各1 μL，加水至20 μL。扩增条件：95 ℃预变性5 min，然后95 ℃变性10 s和60 ℃退火30 s，共40个循环，每个循环延伸时间递增1 s，最后72 ℃延伸7 min，4 ℃保存。$2^{-\Delta\Delta Ct}$法计算血清miR-199a-5p、miR-378a-3p相对表达水平。

1.4　血管瘤治疗

普萘洛尔（批号174219、180243、190242、000147，云鹏制药有限公司，中国）初始剂量，1 mg/kg/d，分2次口服，维持治疗3～7 d后增加剂量至1.5 mg/kg/d，继续治疗3～7 d后增加剂量至2.0 mg/kg/d[8]，治疗期间出现低血糖、低血压、睡眠障碍者可减少至初始剂量，患儿满1岁或无明显瘤灶或瘤体达到最大消退量并维持3个月可停药[9]。浅表性血管瘤采用1%普萘洛尔软膏（西安交通大学口腔医院自制）外涂于瘤体表面，3次/d，持续用药至瘤体颜色完全消退。混合性血管瘤患者普萘洛尔口服联合1%普萘洛尔软膏外用，方法同上。

1.5　随访

停药后随访6个月，其中23例（复发组）停药后再次出现血管瘤病灶或血管瘤病灶体积较治疗结束时明显增大，颜色加深；70例（无复发组）停药后病灶逐渐萎缩，原有病灶未增大或未出现新病灶。

1.6　血管瘤复发危险因素收集

收集患儿性别、年龄、早产、瘤体大小、血管瘤分型、血管瘤分类、停药时年龄、停药时服药疗程、治疗后瘤体分级。根据Achauer等[10]提出的标准评价治疗后瘤体分级，Ⅰ级：瘤体缩小＜25%或瘤体表面颜色略变浅；Ⅱ级：瘤体缩小26%～50%或瘤体表面颜色稍微变浅；Ⅲ级：瘤体缩小51%～75%且瘤体表面颜色明显变浅；Ⅳ级：瘤体缩小＞75%或瘤体表面颜色消退。

1.7　统计学分析

采用SPSS 22.00进行数据分析，miR-199a-5p、miR-378a-3p等计量资料经Kolmogorov-Smirnov检验符合正态分布以均数±标准差表示，采用配对t检验（组内）或独立样本t检验（组间）。性别、血管瘤分型、血管瘤分类、治疗后瘤体分级等计数资料以例（%）表示采用χ^2检验。Logistic回归分析影响婴幼儿增殖期面部血管瘤普萘洛尔停药后复发的危险因素。检验水准$\alpha=0.05$。

2　结　果

2.1　婴幼儿增殖期面部血管瘤复发组和无复发组基线资料

复发组停药时年龄＜1岁、停药时服药疗程＜6个月、治疗后瘤体分级Ⅰ～Ⅱ级患儿比例高于无复发组（$P<0.001$）（表1）。

2.2　婴幼儿增殖期面部血管瘤复发组和无复发组治疗前后血清miR-199a-5p、miR-378a-3p的表达比较

复发组和无复发组治疗前血清miR-199a-5p、miR-378a-3p表达差异无统计学意义（$P>0.05$）。无复发组治疗后血清miR-199a-5p、miR-378a-3p表达较治疗前增高（$P<0.05$），复发组治疗后血清miR-199a-5p、miR-378a-3p表达与治疗前比较差异无统计学意义（$P>0.05$），复发组治疗后血清miR-199a-5p、miR-378a-3p表达低于无复发组（$P<0.05$）（表2）。

2.3　婴幼儿增殖期面部血管瘤治疗后不同瘤体分级患儿血清miR-199a-5p、miR-378a-3p表达比较

治疗后瘤体分级Ⅲ～Ⅳ级患儿血清miR-199a-5p、miR-378a-3p表达高于Ⅰ～Ⅱ级（$P<0.05$）（表3）。

2.4　婴幼儿增殖期面部血管瘤普萘洛尔停药后复发影响因素分析

以婴幼儿增殖期面部血管瘤普萘洛尔停药后是否复发为因变量（赋值：0＝否，1＝是），停药时年龄（赋值：0＝≥1岁，1＝＜1岁）、停药时服药疗

表1　婴幼儿增殖期面部血管瘤复发组和无复发组基线资料

Table 1　Baseline data of infants with proliferative facial hemangioma in the recurrence group and the nonrecurrence group

$\bar{x} \pm s$, n(%)

Item		Recurrence group (n = 23)	Nonrecurrence group (n = 70)	t/χ^2 value	P
Age/year		5.19 ± 1.20	5.24 ± 1.13	0.181	0.857
Gender	Male	5(21.74)	19(27.14)	0.264	0.607
	Female	18(78.26)	51(72.86)		
Hemangioma size/cm^2		6.93 ± 1.96	6.78 ± 2.11	0.301	0.764
Hemangioma typing	Single	3(13.04)	8(11.42)	0.290	0.962
	Multiple	6(26.09)	16(22.86)		
	Segmental	11(47.83)	38(54.29)		
Hemangioma classification	Middle	3(13.04)	8(11.43)	3.360	0.186
	Superficial	5(21.74)	16(22.86)		
	Deep	16(69.57)	36(51.43)		
	Mixed	2(8.71)	18(25.71)		
Preterm birth		8(34.78)	19(27.14)	0.490	0.484
Age of withdrawal	< 1 year	18(78.26)	20(28.57)	17.689	< 0.001
	≥ 1 year	5(21.74)	50(71.43)		
Period of treatment	< 6 months	19(82.61)	22(31.43)	18.396	< 0.001
	≥ 6 months	4(17.39)	48(68.57)		
Hemangioma grading after treatment	Ⅰ-Ⅱ grade	20(86.96)	17(24.29)	28.382	< 0.001
	Ⅲ-Ⅳ grade	3(13.04)	53(75.71)		

表2　婴幼儿增殖期面部血管瘤复发组和无复发组治疗前后血清miR-199a-5p、miR-378a-3p的表达差异

Table 2　Difference in the serum levels of miR-199a-5p and miR-378a-3p in infants with proliferative facial hemangioma of the recurrence group and the nonrecurrence group before and after treatment

$\bar{x} \pm s$

Group	n	Time	miR-199a-5p($2^{-\Delta\Delta Ct}$)	miR-378a-3p($2^{-\Delta\Delta Ct}$)
Recurrence group	23	Prior treatment	1.24 ± 0.31	1.17 ± 0.29
		Post treatment	1.29 ± 0.33	1.20 ± 0.31
Nonrecurrence group	70	Prior treatment	1.25 ± 0.30	1.19 ± 0.28
		Post treatment	2.83 ± 0.62	3.08 ± 0.94
Comparison within the recurrence group at different time points		t/P	0.640/0.524	0.409/0.684
Comparison within the nonrecurrence group at different time points		t/P	11.746/ < 0.001	9.474/ < 0.001
Comparison between groups before treatment		t/P	0.138/0.891	0.295/0.769
Comparison between groups after treatment		t/P	11.366/ < 0.001	9.395/ < 0.001

表3　婴幼儿增殖期面部血管瘤治疗后不同瘤体分级患儿血清miR-199a-5p、miR-378a-3p的表达差异

Table 3　Differences in serum levels of miR-199a-5p and miR-378a-3p in infants with different proliferative facial hemangioma grades after treatment

$\bar{x} \pm s$

Hemangioma grading	n	miR-199a-5p($2^{-\Delta\Delta Ct}$)	miR-378a-3p($2^{-\Delta\Delta Ct}$)
Ⅰ-Ⅱ grade	37	1.67 ± 0.30	1.71 ± 0.25
Ⅲ-Ⅳ grade	56	2.96 ± 0.47	3.21 ± 0.60
t		14.806	14.383
P		< 0.001	< 0.001

程(赋值:0 = ≥6个月,1 = < 6个月)、治疗后瘤体分级(赋值:0 = Ⅲ ~ Ⅳ级,1 = Ⅰ ~ Ⅱ级)、miR-199a-5p(原值代入)、miR-378a-3p(原值代入)为自变量,逐步法排除无关变量,最终miR-199a-5p低表达、miR-378a-3p低表达、治疗后瘤体分级Ⅰ ~ Ⅱ级是婴幼儿增殖期面部血管瘤普萘洛尔停药后复发的危险因素(P < 0.05)(表4)。

3　讨　论

普萘洛尔是非选择性β-阻断剂,可抑制一氧

表4　婴幼儿增殖期面部血管瘤普萘洛尔停药后复发影响因素Logistic回归方程

Table 4　Logistic regression equation of affecting factors for recurrence in infants with proliferating facial hemangioma after propranolol withdrawal

Factors	*β*	*SE*	*Wald*	*OR* (95%*CI*)	*P*
miR-199a-5p	−0.663	0.203	10.667	0.515(0.346 ~ 0.767)	< 0.001
miR-378a-3p	−0.409	0.135	9.179	0.664(0.510 ~ 0.866)	0.003
Hemangioma grading after treatment	0.395	0.106	13.886	1.484(1.206 ~ 1.827)	< 0.001

化氮释放引起血管收缩，减少瘤体血供抑制瘤体生长，还可通过上调miR-125b的表达抑制血管瘤细胞的生长并诱导细胞凋亡[11]。但是普萘洛尔停药后存在复发现象，尤其是面部血管瘤，较其它血管瘤复发更早、更频繁[12]。miRNAs具有调控血管内皮细胞增殖、血管内皮生长因子表达、血管生成信号转导等作用，与血管瘤进展以及对普萘洛尔治疗反应性均存在密切关系[13-14]。

miR-199a-5p是miR-199家族成员，在恶性肿瘤中可损害癌细胞增殖、侵袭和转移能力，发挥抑癌基因作用，是多种恶性肿瘤的潜在生物标志物[15]。miR-199a-5p在血管内皮细胞中表达，可促使一氧化氮产生并提高一氧化氮生物利用度，调控血管内皮细胞迁移、新生血管形成以及维持血管稳态[16]。miR-199a-5p还参与血管内皮细胞一氧化氮合酶/一氧化氮通路调节血管收缩和舒张，并通过调控血管内皮生长因子表达调节新生血管形成[17]。Wang等[5]研究发现miR-199a-5p在血管瘤中表达降低，miR-199a-5p与增殖细胞核抗原表达呈负相关，提示miR-199a-5p可抑制血管瘤内皮细胞增殖。miR-199a-5p与婴幼儿面部血管瘤普萘洛尔停药后复发是否存在关系尚不清楚，本研究发现面部血管瘤普萘洛尔停药后复发患儿血清miR-199a-5p表达低于无复发患儿，治疗后瘤体分级Ⅲ ~ Ⅳ级患儿血清miR-199a-5p表达高于Ⅰ ~ Ⅱ级，说明miR-199a-5p表达与血管瘤普萘洛尔治疗后瘤体缩小程度以及复发均有关。进一步回归分析结果显示治疗后miR-199a-5p低表达是普萘洛尔停药后血管瘤复发的危险因素，说明miR-199a-5p表达缺失可能导致了增殖期面部血管瘤婴幼儿普萘洛尔治疗后复发。分析原因可能为miR-199a-5p通过下游靶基因Oxidored硝基含有结构域的蛋白1（oxidored nitro domain containing protein 1，NOR1）抑制血管内皮生长因子表达[18]，miR-199a-5p表达缺失则引起NOR1，血管内皮生长因子上调，导致血管瘤细胞增殖和治疗后复发。

miR-378a-3p属于miR-378家族成员，源自过氧化物酶体增殖物激活受体γ共激活因子1-β基因的第一个内含子，参与代谢、细胞生长和血管生成等多种生物学过程，与肿瘤细胞增殖、侵袭和转移，化疗耐药均有关[19]。通过高通量测序发现miR-378a-3p在血管瘤中表达下调，且与血管瘤发生、发展有关[20]。本研究无复发组治疗后血清miR-378a-3p表达较治疗前增高，复发组治疗前后血清miR-378a-3p表达则无明显变化，说明miR-378a-3p表达与血管瘤患儿对普萘洛尔治疗反应有关。分析可能机制如下：首先，miR-378a-3p可通过靶向抑制融合蛋白抑制剂间接调节声波刺猬蛋白信号通路的下游靶基因血管内皮生长因子-A，抑制肿瘤血管形成[21]；其次，miR-378a-3p还可靶向抗增殖蛋白-ErbB2转录因子2，抑制细胞周期蛋白D1表达，促使细胞周期G1/S停滞，抑制内皮细胞增殖，诱导内皮细胞凋亡增殖[22]。由此可见，miR-378a-3p表达缺失可促使血管瘤内皮细胞增殖、迁移以及血管网络形成，可能导致血管瘤进展，引起普萘洛尔停药后复发。本研究结果显示治疗后瘤体分级Ⅲ ~ Ⅳ级血清miR-378a-3p表达高于Ⅰ ~ Ⅱ级，说明miR-378a-3p低表达与血管瘤普萘洛尔治疗低反应有关，回归分析结果证实miR-378a-3p低表达是增殖期面部血管瘤婴幼儿普萘洛尔停药后复发的危险因素，验证miR-378a-3p与普萘洛尔停药后复发的关系。

综上，增殖期面部血管瘤普萘洛尔停药后复发患儿血清miR-199a-5p、miR-378a-3p表达均降低，miR-199a-5p、miR-378a-3p低表达与普萘洛尔停药后血管瘤复发有关。miR-199a-5p、miR-378a-3p可作为增殖期面部血管瘤婴幼儿普萘洛尔停药后复发评估的潜在指标。

【Author contributions】 Guo Y designed research plans, implemented the research process, and wrote the article; Li LF proposed research ideas, analyzed experimental data, Zhang K, Fan XH reviewed the papers and conducted statistical analysis. All authors read and approved the final manuscript as submitted.

参考文献

[1] Cheirif-Wolosky O, Novelo-Soto AD, Orozco-Covarrubias L, et al. Infantile hemangioma: an update in the topical and systemic treatments[J]. Bol Med Hosp Infant Mex, 2019, 76(4): 167-175. doi: 10.24875/BMHIM.19000002.

[2] Schwartz T, Faria J, Pawar S, et al. Efficacy and rebound rates in propranolol-treated subglottic hemangioma: a literature review[J]. Laryngoscope, 2017, 127(11): 2665-2672. doi: 10.1002/lary.26818.

[3] Ahogo CK, Ezzedine K, Prey S, et al. Factors associated with the relapse of infantile haemangiomas in children treated with oral propranolol[J]. Br J Dermatol, 2013, 169(6): 1252-1256. doi: 10.1111/bjd.12432.

[4] Chang L, Lv D, Yu Z, et al. Infantile hemangioma: factors causing recurrence after propranolol treatment[J]. Pediatr Res, 2018, 83(1/1): 175-182. doi: 10.1038/pr.2017.220.

[5] Wang Y, Dai YX, Wang SQ, et al. miR-199a-5p inhibits proliferation and induces apoptosis in hemangioma cells through targeting HIF1A[J]. Int J Immunopathol Pharmacol, 2018, 31: 394632017749357. doi: 10.1177/0394632017749357.

[6] 吴卫红, 潘凯, 柯锦, 等. 上调miR-378a-3p对血管瘤内皮细胞生长和侵袭能力的影响[J]. 西部医学, 2020, 32(8): 1128-1131, 1141. doi: 10.3969/j.issn.1672-3511.2020.08.007.
Wu WH, Pan K, Ke J, et al. Effect of up-regulation of miR-378a-3p on proliferation and invasion of endothelial cells of hemangioma[J]. Med J West Chin, 2020, 32(8): 1128-1131, 1141. doi: 10.3969/j.issn.1672-3511.2020.08.007.

[7] 中华医学会整形外科分会血管瘤和脉管畸形学组. 血管瘤和脉管畸形诊断和治疗指南(2016版)[J]. 组织工程与重建外科杂志, 2016, 12(2): 63-93, 97. doi: 10.3969/j.issn.1673-0364.2016.02.001.
Chinese Medical Association Plastic Surgery Division Hemangioma and Vascular Malformation Group. Guidelines for diagnosis and treatment of hemangioma and vascular malformations (2016 edition)[J]. J Tissue Eng Reconstr Surg, 2016, 12(2): 63-93, 97. doi: 10.3969/j.issn.1673-0364.2016.02.001.

[8] Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference[J]. Pediatrics, 2013, 131(1): 128-140. doi: 10.1542/peds.2012-1691.

[9] Chang L, Gu Y, Yu Z, et al. When to stop propranolol for infantile hemangioma[J]. Sci Rep, 2017, 7: 43292. doi: 10.1038/srep43292.

[10] Achauer BM, Chang CJ, Vander Kam VM. Management of hemangioma of infancy: review of 245 patients[J]. Plast Reconstruct Surg, 1997, 99(5): 1301-1308. doi: 10.1097/00006534-199704001-00014.

[11] Huang J, Jiang D, Zhao S, et al. Propranolol suppresses infantile hemangioma cell proliferation and promotes apoptosis by upregulating miR-125b expression[J]. Anticancer Drugs, 2019, 30(5): 501-507. doi: 10.1097/CAD.0000000000000762.

[12] Frongia G, Byeon JO, Mehrabi A, et al. Recurrence rate of infantile hemangioma after oral propranolol therapy[J]. Eur J Pediatr, 2021, 180(2): 585-590. doi: 10.1007/s00431-020-03872-5.

[13] Yuan X, Xu Y, Wei Z, et al. CircAP2A2 acts as a ceRNA to participate in infantile hemangiomas progression by sponging miR-382-5p *via* regulating the expression of VEGFA[J]. J Clin Lab Anal, 2020, 34(7): e23258. doi: 10.1002/jcla.23258.

[14] Liu C, Zhao Z, Ji Z, et al. MiR-187-3p enhances propranolol sensitivity of hemangioma stem cells[J]. Cell Struct Funct, 2019, 44(1): 41-50. doi: 10.1247/csf.18041.

[15] Li DJ, Wang X, Yin WH, et al. MiR-199a-5p suppresses proliferation and invasion of human laryngeal cancer cells[J]. Eur Rev Med Pharmacol Sci, 2020, 24(23): 12200-12207. doi: 10.26355/eurrev_202012_24010.

[16] Le NT, Abe JI. MicroRNA 199a and the eNOS (endothelial no synthase)/NO pathway[J]. Arterioscler Thromb Vasc Biol, 2018, 38(10): 2278-2280. doi: 10.1161/ATVBAHA.118.311515.

[17] Joris V, Gomez EL, Menchi L, et al. MicroRNA-199a-3p and microRNA-199a-5p take part to a redundant network of regulation of the NOS (NO synthase)/NO pathway in the endothelium[J]. Arterioscler Thromb Vasc Biol, 2018, 38(10): 2345-2357. doi: 10.1161/ATVBAHA.118.311145.

[18] Gui R, Huang R, Zhang JH, et al. MicroRNA-199a-5p inhibits VEGF-induced tumorigenesis through targeting oxidored-nitro domain-containing protein 1 in human HepG2 cells[J]. Oncol Rep, 2016, 35(4): 2216-2222. doi: 10.3892/or.2016.4550.

[19] Ding N, Sun X, Wang T, et al. miR-378a-3p exerts tumor suppressive function on the tumorigenesis of esophageal squamous cell carcinoma by targeting Rab10[J]. Int J Mol Med, 2018, 42(1): 381-391. doi: 10.3892/ijmm.2018.3639.

[20] 陈耀兵. 血管肉瘤miRNA表达谱分析及其意义[D]. 武汉: 华中科技大学, 2013.
Chen YB. Analysis and significance of miRNA expression profile in hemangiosarcoma[D]. Wuhan: Huazhong Uni Sci Technol, 2013.

[21] Lee DY, Deng Z, Wang CH, et al. MicroRNA-378 promotes cell survival, tumor growth, and angiogenesis by targeting SuFu and Fus-1 expression[J]. Proc Natl Acad Sci USA, 2007, 104(51): 20350-20355. doi: 10.1073/pnas.0706901104.

[22] Feng M, Li Z, Aau M, et al. Myc/miR-378/TOB2/cyclin D1 functional module regulates oncogenic transformation[J]. Oncogene, 2011, 30(19): 2242-2251. doi: 10.1038/onc.2010.602.

（编辑　张琳，刘曙光）

官网