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在线全文

·论　著·

circVRK1靶向miR-4428调控急性淋巴细胞白血病KOCL44细胞增殖及凋亡的分子机制研究*

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【摘要】 **目的** 分析circVRK1和miR-4428在急性淋巴细胞白血病（acute lymphoblastic leukemia, ALL）细胞增殖和凋亡中的关系。**方法** 体外培养ALL细胞KOCL44，实验分组为：pcDNA、pcDNA-circVRK1、anti-miR-NC、anti-miR-4428、si-NC、si-circVRK1、pcDNA-circVRK1+miR-NC和pcDNA-circVRK1+miR-4428组。qRT-PCR检测细胞circVRK1和miR-4428的表达水平；CCK-8法、流式细胞术分别检测细胞增殖及凋亡；双荧光素酶报告实验检测circVRK1与miR-4428的靶向关系〔实验分为circVRK1野生型报告质粒（WT-circVRK1）+miR-NC、WT-circVRK1+miR-4428、circVRK1突变报告质粒（MUT-circVRK1）+miR-NC和MUT-circVRK1+ miR-4428组〕；Western blot检测Ki-67、cleaved caspase-3、cleaved caspase-9蛋白表达量。**结果** 相较于pcDNA组，pcDNA-circVRK1组的circVRK1表达上调（P<0.05）；与转染pcDNA或者转染anti-miR-NC相比，转染pcDNA-circVRK1或anti-miR-4428后，KOCL44细胞活力和Ki-67蛋白表达降低（P<0.05），凋亡率和cleaved caspase-3、cleaved caspase-9蛋白水平增加（P<0.05）；circVRK1可负向调控miR-4428的表达，但该作用仅在转染WT-circVRK1的组别中体现；与pcDNA组相比，pcDNA-circVRK1组miR-4428表达降低（P<0.05）；与si-NC组相比，si-circVRK1组miR-4428表达增加（P<0.05）；与共转染pcDNA-circVRK1+miR-NC相比，共转染pcDNA-circVRK1+miR-4428后细胞活力升高（P<0.05），Ki-67蛋白表达增加（P<0.05），凋亡率和cleaved caspase-3、cleaved caspase-9蛋白水平降低（P<0.05）。**结论** circVRK1过表达可通过下调miR-4428表达而减弱ALL细胞增殖能力及诱导细胞凋亡。

【关键词】 急性淋巴细胞白血病　circVRK1　miR-4428　细胞增殖　细胞凋亡

Molecular Mechanism of circVRK1 Regulating the Proliferation and Apoptosis of Acute Lymphoblastic Leukemia KOCL44 Cells by Targeting miR-4428

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【**Abstract**】 **Objective** To elucidate the role of circVRK1 and its interaction with miR-4428 in regulating proliferation and apoptosis in acute lymphoblastic leukemia (ALL) cells. **Methods** KOCL44 ALL cells were cultured *in vitro*, and experimental groups included pcDNA, pcDNA-circVRK1, anti-miR-NC, anti-miR-4428, si-NC, si-circVRK1, pcDNA-circVRK1+miR-NC, and pcDNA-circVRK1+miR-4428. The expression levels of circVRK1 and miR-4428 were detected using qRT-PCR. CCK-8 assays and flow cytometry were used to assess cell proliferation and apoptosis, respectively. The dual luciferase reporter assays were employed to investigate the interaction between circVRK1 and miR-4428, with groups categorized as WT-circVRK1+miR-NC, WT-circVRK1+miR-4428, MUT-circVRK1+miR-NC, and MUT-circVRK1+ miR-4428. Western blotting was utilized to detect the expression levels of Ki-67, cleaved caspase-3, and cleaved caspase-9 proteins. **Results** Compared to the pcDNA group, circVRK1 expression was up-regulated in the pcDNA-circVRK1 group (P<0.05). Compared to transfection with pcDNA or anti-miR-NC, transfection with pcDNA-circVRK1 or anti-miR-4428 led to decreased cell viability and Ki-67 protein levels in KOCL44 cells (P<0.05), and increased apoptosis rates and levels of cleaved caspase-3 and cleaved caspase-9 (P<0.05). circVRK1 was found to negatively regulate miR-4428 expression, with this effect observed only in the WT-circVRK1 group. miR-4428 levels were lower in the pcDNA-circVRK1 group compared to the pcDNA group (P<0.05) and higher in the si-circVRK1 group compared to the si-NC group (P<0.05). Co-transfection with pcDNA-circVRK1+miR-4428 resulted in increased cell viability (P<0.05) and Ki-67 expression (P<0.05), and decreased apoptosis rates and levels of cleaved caspase-3 and cleaved caspase-9 (P<0.05) compared to co-transfection with pcDNA-circVRK1+miR-NC. **Conclusion** Overexpression of circVRK1 reduces the proliferation ability of acute ALL cells and induces cell apoptosis by downregulating miR-4428 expression.

【**Key words**】 Acute lymphocytic leukemia　circVRK1　miR-4428　Cell proliferation　Cell apoptosis

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急性淋巴细胞白血病(acute lymphoblastic leukemia, ALL)是一种恶性疾病, 主要是由于淋巴造血系统中的异常白细胞在骨髓中无法正常发育, 进而在骨髓腔中聚集, 抑制正常的造血功能, ALL患者预后较差[1-3]。环状RNA(circular RNA, circRNA)是一种特殊类型的非编码RNA, 不像线性RNA那样具有5'端和3'端, 它可直接结合特定微小RNA(microRNA, miRNA), 调节其活性, 进而解除miRNA对其靶基因的抑制作用[4]。先前的研究已经表明circRNA的异常表达与疾病的发生和进展密切相关[5]。据报道, circRNA还是某些血液恶性肿瘤病理过程中的关键调控因子[6]。早期的研究表明高表达circVRK1可促进骨肉瘤细胞的增殖和迁移[7]。但circVRK1在ALL进展中的角色还未见报道。本课题组通过StarBase预测发现circVRK1与miR-4428有互补序列, 基于此, 本研究进一步分析了circVRK1和miR-4428在ALL细胞增殖和凋亡中的关系, 现报道如下。

1　材料与方法

1.1　主要材料

ALL细胞KOCL44购自武汉普诺赛; pcDNA、pcDNA-circVRK1购自上海吉满生物; Lipofectamine™ 3000 Transfection Reagent转染试剂购自美国Invitrogen; DMEM培养液与胎牛血清购自美国Gibco; pGL3质粒购自美国Promega; Trizol试剂和反转录与荧光定量PCR试剂盒购自美国Thermo Fisher; 基因定量试剂购自北京天根生化; 一抗购自武汉艾美捷; 二抗购自美国Santa Cruz; miR-4428模拟物(miR-4428 mimics, 记为miR-4428)和抑制剂(anti-miR-4428)、circVRK1小干扰RNA(si-circVRK1)以及相应的对照miR-NC、anti-miR-NC、si-NC购自广州锐博生物; CCK-8试剂、细胞凋亡检测试剂、胰蛋白酶溶液、磷酸缓冲液、蛋白电泳液、双荧光素酶活性检测试剂盒、细胞裂解液、蛋白预制胶、转膜液购自北京索莱宝; BeyoECL Plus化学发光试剂盒购自江苏碧云天生物有限公司。

1.2　研究方法

1.2.1　实验分组

KOCL44细胞放入含有胎牛血清、青霉素和链霉素的DMEM培养基, 于37 ℃、体积分数5%CO_2培养箱内培养, 待细胞生长汇合度达到80%时进行转染, 采用脂质体转染法(参照Lipofectamine™ 3000 Transfection Reagent转染试剂说明书)将pcDNA、pcDNA-circVRK1、anti-miR-NC、anti-miR-4428、si-circVRK1、si-NC分别转染至KOCL44细胞, 分别记为pcDNA组、pcDNA-circVRK1组、anti-miR-NC组、anti-miR-4428组、si-circVRK1组及si-NC组。采用脂质体转染法将pcDNA-circVRK1和miR-NC或miR-4428 mimics共转染至细胞, 分别记为pcDNA-circVRK1+miR-NC组、pcDNA-circVRK1+miR-4428组。

1.2.2　qRT-PCR检测circVRK1和miR-4428的表达水平

转染48 h后, 采用Trizol试剂分别提取各组KOCL44细胞总RNA, 依据紫外分光光度计测定RNA浓度。随后, 其反转录体系如下: 2 μL 5×gDNA Buffer, 2 μL 10×King RT Buffer, 1 μL FastKing RT Enzyme Mix, 2 μL FQ-RT Primer Mix, 2 μg RNA; 反应条件: 42 ℃ 15 min, 95 ℃ 3 min。然后, 以cDNA为模板, ABI StepOnePlus荧光定量PCR仪进行qRT-PCR扩增, 反应程序: 95 ℃ 2 min, 95 ℃ 15 s, 60 ℃ 1 min, 72 ℃ 30 s(循环40次)。circVRK1和miR-4428的相对表达量通过$2^{-\Delta\Delta Ct}$法计算。

1.2.3　CCK-8实验检测细胞增殖

将KOCL44细胞在96孔板中传代。转染48 h后, 收集各组KOCL44细胞, 按照说明书指南用制备的CCK-8溶液处理细胞4 h, 使用酶标仪测量450 nm处的吸光度值。

1.2.4　流式细胞术检测细胞凋亡率

转染48 h后, 收集各组KOCL44细胞, 调整至所需密度(1×10^6)。根据Annexin Ⅴ-FITC/PI试剂盒说明书, 在黑暗中将细胞凋亡检测试剂添加到每孔中, 然后添加磷酸盐缓冲液。将细胞放至冰上, 流式细胞仪分析早期凋亡率+晚期凋亡率。

1.2.5　双荧光素酶报告实验检测circVRK1与miR-4428的靶向关系

circVRK1的序列中含有与miR-4428互补的核苷酸序列, 见图1。将circVRK1序列中含有miR-4428结合位点的区域通过聚合酶链反应扩增, 扩增的序列由上海擎科生物鉴定。将克隆序列导入pGL3载体, 构建circVRK1野生型报告质粒(WT-circVRK1)。突变circVRK1序列中和miR-4428互补的位点, 将突变的circVRK1序列克隆到pGL3载体, 构建circVRK1突变报告质粒(MUT-circVRK1)。按上述转染方法将WT-circVRK1、MUT-circVRK1分别与miR-4428或miR-NC共转染至KOCL44细胞, 分组: WT-circVRK1+miR-NC、WT-circVRK1+ miR-4428、MUT-circVRK1+miR-NC和MUT-circVRK1+ miR-4428组。然后, 将细胞置于培养箱内培养24 h, 使用双荧光素酶活性

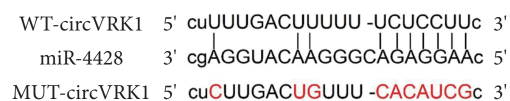

图 1　circVRK1和miR-4428的靶向互补序列

Fig 1　Targeted complementary sequences of circVRK1 and miR-4428

检测试剂盒分析发光情况。

1.2.6 Western blot检测Ki-67、cleaved caspase-3、cleaved caspase-9蛋白表达量

各组细胞转染48 h后，使用预冷的细胞裂解缓冲液制备细胞裂解液，并离心去除颗粒细胞碎片。上清液中的蛋白质样品在高温下变性，并根据其相对分子质量使用聚丙烯酰胺凝胶分离。在使用脱脂牛奶防止非特异性结合之前，将分离的蛋白质转移到硝化纤维素膜上。采用Ki-67（1∶800）、cleaved caspase-3（1∶1 000）、cleaved caspase-9（1∶1 000）一抗与内参GAPDH抗体（1∶3 000）稀释液孵育硝化纤维素膜，去除未结合的一抗后，用酶偶联二抗与膜孵育。通过BeyoECL Plus化学发光试剂盒可视化膜上的蛋白条带。成像的蛋白条带经Image J软件分析灰度值，结果以目的蛋白与内参蛋白GAPDH灰度值的比值表示目的蛋白的相对表达量。

1.3 统计学方法

采用SPSS21.0统计学软件分析数据，计量资料以$\bar{x}\pm s$表示，正态分布的数据两组间比较采用独立样本t检验并使用bonferroni法进行P值校正，多组间比较采用单因素方差分析，两两比较使用Dunnet t法，P<0.05为差异有统计学意义。

2 结果

2.1 circVRK1过表达对KOCL44细胞增殖的影响

相较于pcDNA组，pcDNA-circVRK1组的circVRK1表达上调，KOCL44细胞活力和Ki-67蛋白表达水平降低，差异有统计学意义（P<0.05），见图2。

2.2 circVRK1过表达对KOCL44细胞凋亡的影响

与pcDNA组比较，pcDNA-circVRK1组中KOCL44细胞凋亡率和cleaved caspase-3、cleaved caspase-9蛋白水平升高，差异有统计学意义（P<0.05），见图3。

2.3 circVRK1靶向调控miR-4428的表达

与miR-NC相比，miR-4428模拟物转染抑制了WT-circVRK1组细胞的荧光素酶活性，差异有统计学意义（P<0.05），但不影响MUT-circVRK1组，见表1。此外，circVRK1过表达抑制miR-4428的表达，而circVRK1沉默则促进miR-4428的表达，差异有统计学意义（P<0.05），见表2。

2.4 miR-4428低表达抑制KOCL44细胞增殖、促进细胞凋亡

由图4可见，相对于anti-miR-NC组，anti-miR-4428组的miR-4428的表达减少，KOCL44细胞活力以及Ki-67蛋白水平降低，细胞凋亡率和cleaved caspase-3、cleaved caspase-9蛋白水平升高，差异均有统计学意义（P<0.05）。

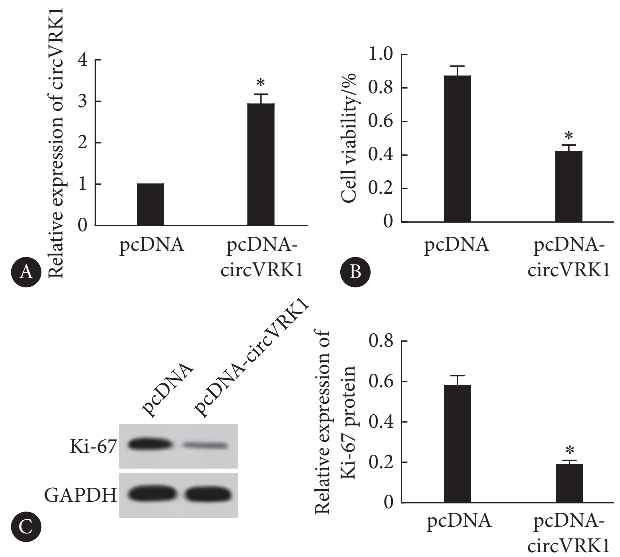

图 2 circVRK1过表达对KOCL44细胞增殖及相关蛋白表达的影响

Fig 2 Effects of circVRK1 overexpression on KOCL44 cell proliferation and related protein expression

A, The expression level of circVRK1 assessed by qRT-PCR (n=9); B, CCK-8 assay performed to evaluate cell viability (n=9); C, Western blot performed to determine Ki-67 protein expression (the relative molecular mass of Ki-67 and GAPDH proteins is 358×10^3 and 37×10^3, respectively. n=3). * P<0.05, vs. pcDNA.

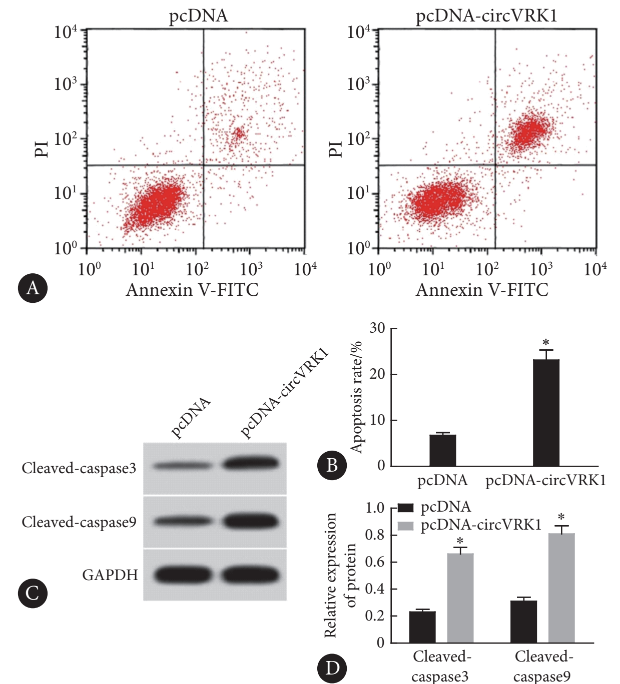

图 3 circVRK1高表达促进KOCL44细胞凋亡

Fig 3 High expression of circVRK1 promoted apoptosis of KOCL44 cells

A, Flow cytometry; B, apoptosis rate determined by flow cytometry (n=9); C, Western blot (the relative molecular mass of cleaved caspase-3, cleaved caspase-9, and GAPDH proteins is 17×10^3, 35×10^3, and 37×10^3, respectively); D, relative expression of proteins assessed by Western blot (n=3). * P<0.05, vs. pcDNA.

表 1　双荧光素酶报告实验（$\bar{x} \pm s$）

Table 1　Dual luciferase report assay ($\bar{x} \pm s$)

Group	n	Relative luciferase activity		t	P
		miR-NC	miR-4428		
WT-circVRK1	9	0.96±0.06	0.42±0.04	22.465	<0.001
MUT-circVRK1	9	0.99±0.07	0.98±0.05	0.349	0.732

表 2　circVRK1调控miR-4428的表达（$\bar{x} \pm s$）

Table 2　Regulation of miR-4428 expression by circVRK1 ($\bar{x} \pm s$)

Group	n	miR-4428
pcDNA	9	1.00±0.00
pcDNA-circVRK1	9	0.51±0.04*
si-NC	9	1.02±0.07
si-circVRK1	9	3.14±0.26#

* P<0.05, vs. pcDNA group; # P<0.05, vs. si-NC group.

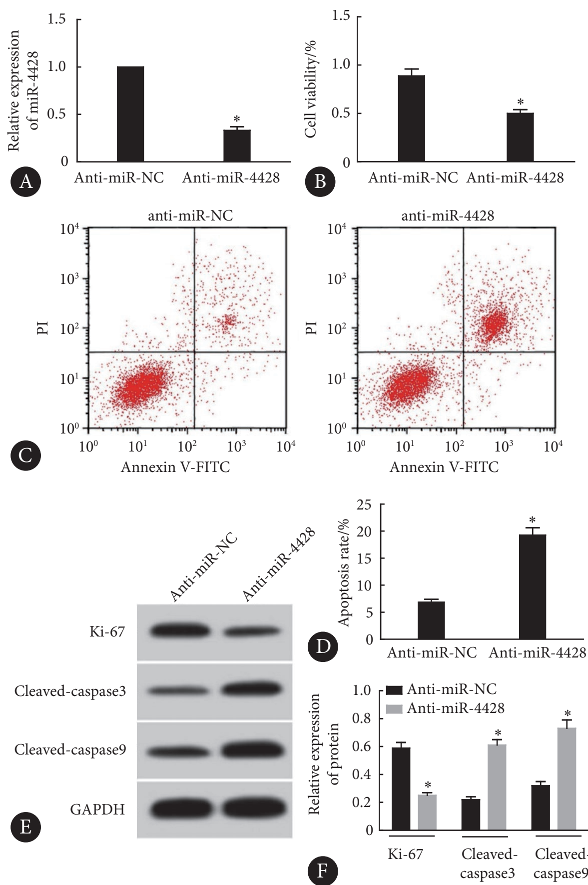

图 4　干扰miR-4428表达对KOCL44细胞增殖和凋亡的影响

Fig 4　Effects of miR-4428 interference on KOCL44 cell proliferation and apoptosis

A, qRT-PCR (n=9); B, CCK-8 (n=9); C, flow cytometry; D, apoptosis rate assessed by flow cytometry (n=9); E, Western blot (the relative molecular mass of Ki-67, cleaved caspase-3, cleaved caspase-9, and GAPDH proteins is 358×10^3, 17×10^3, 35×10^3, and 37×10^3, respectively); F, relative expression of proteins assessed by Western blot (n=3). * P<0.05, vs. anti-miR-NC.

2.5　上调miR-4428表达对circVRK1过表达促进KOCL44细胞增殖和凋亡的逆转作用

由图5可见，与pcDNA-circVRK1+miR-NC组比较，pcDNA-circVRK1+miR-4428组KOCL44细胞活力以及Ki-67蛋白水平增加，细胞凋亡率和cleaved caspase-3、cleaved-caspase9蛋白水平降低，差异均有统计学意义（P<0.05）。

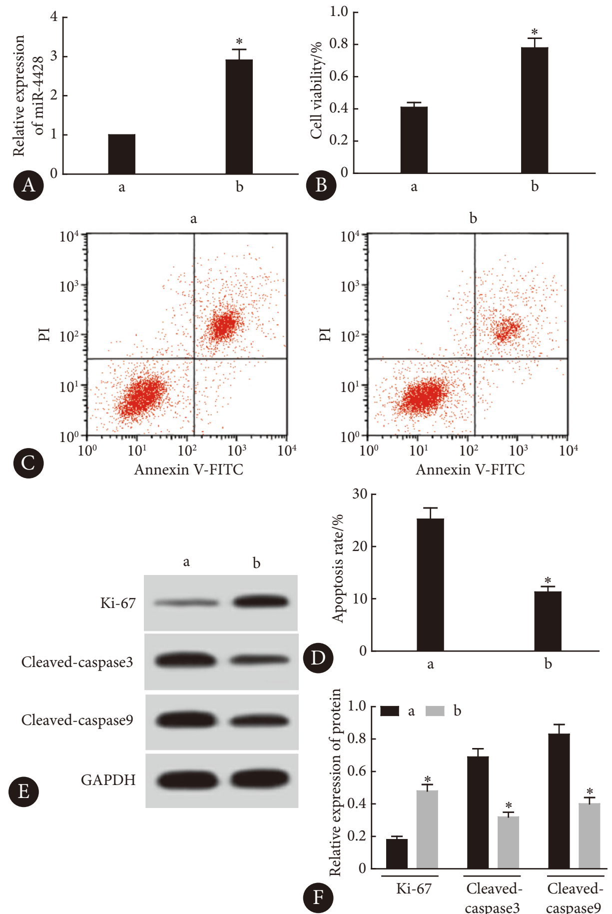

图 5　上调miR-4428表达逆转了circVRK1过表达对KOCL44细胞增殖和凋亡的作用

Fig 5　Upregulation of miR-4428 reversed the effects of circVRK1 overexpression on KOCL44 cell proliferation and apoptosis

A, qRT-PCR (n=9); B, CCK-8 (n=9); C, flow cytometry; D, apoptosis rate assessed by flow cytometry (n=9); E, Western blot (the relative molecular mass of the proteins is as shown in Fig 4); F, relative expression of proteins assessed by Western blot (n=9); a, pcDNA-circVRK1+miR-NC; b, pcDNA-circVRK1+miR-4428. * P<0.05, vs. pcDNA-circVRK1+miR-NC.

3　讨论

circRNA基因序列上富含miRNA的结合位点，并可通过吸附miRNA而负向调控miRNA的表达从而调控细胞增殖、凋亡等生物学过程[8-9]。circRNA中的miRNA结合位点（miRNA响应元件，MRE）能够与miRNA的互补序列结合，形成circRNA-miRNA复合物，ALL发生及发展也涉及此调控机制[10-12]。

敲低circVRK1可减轻氧糖剥夺对 人脑微血管内皮细胞的 迁移、血管生成、死亡、炎症反应和氧化应激的影响[7]。在食管鳞状细胞癌组织和细胞中,circVRK1的表达水平通常较低。然而,当其表达上调时,食管鳞状细胞癌细胞的增殖和迁移能力受到抑制[13]。但circVRK1在ALL进展中的角色还未见报道。本研究结果显示,circVRK1过表达可抑制ALL细胞增殖,同时降低Ki-67的表达水平,而Ki-67表达上调可促进细胞增殖[14],提示circVRK1过表达可减弱ALL细胞增殖能力。caspase9和caspase3被激活标志着细胞发生凋亡[15]。本研究通过分析细胞凋亡率和这两个蛋白的表达发现circVRK1促进ALL细胞凋亡。

干扰miR-4428表达可抑制肺腺癌细胞的增殖、迁移和侵袭,促进细胞凋亡[16]。miR-4428在甲状腺癌中表达上调,并可能作为甲状腺诊断的潜在生物学标志物[17]。本研究证实circVRK1可靶向结合miR-4428,干扰miR-4428表达可抑制ALL细胞增殖及促进细胞凋亡,而miR-4428过表达可减弱circVRK1过表达造成的影响。提示circVRK1可通过靶向结合miR-4428对ALL细胞增殖和凋亡产生影响。

综上所述,circVRK1可通过下调miR-4428抑制ALL细胞增殖及促进细胞凋亡,该结果可能为ALL的治疗提供新的靶向方法。但本研究仅限于体外实验,其在体内的作用还有待研究。随后的研究将用动物模型验证本研究的结论,进一步分析miR-4428调控ALL细胞增殖及凋亡的机制。

* * *

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