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CircDOCK1通过调控miR-128-3p/HMGB3轴影响胃癌进展

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摘要 该研究目的在于探讨circDOCK1对胃癌细胞功能的影响及其机制。qRT-PCR法与Western blot法检测胃癌组织、癌旁组织、人胃黏膜上皮细胞GES-1、人胃癌细胞HGC-27中circDOCK1、miR-128-3p、HMGB3的表达情况; 再将si-NC、si-circDOCK1、miR-NC、miR-128-3p mimic、si-circDOCK1+miR-NC inhibitor和si-circDOCK1+miR-128-3p inhibitor分别转染至HGC-27细胞, 分为si-NC组、si-circDOCK1组、miR-NC组、miR-128-3p mimic组、si-circDOCK1+miR-NC inhibitor组和si-circDOCK1+miR-128-3p inhibitor组; 双荧光素酶报告实验证实circDOCK1和miR-128-3p的靶向关系; CCK-8法、克隆形成实验、划痕实验、Transwell实验与流式细胞术分析细胞功能。CircDOCK1与HMGB3在胃癌组织和HGC-27细胞中表达上调, 而miR-128-3p表达下调(P<0.05); circDOCK1可靶向miR-128-3p调控HMGB3表达; 转染si-circDOCK1或miR-128-3p mimic均可促进细胞凋亡(P<0.05), 却抑制细胞增殖、迁移和侵袭(P<0.05); 此外, miR-128-3p inhibitor可逆转si-circDOCK1对HGC-27细胞凋亡的促进作用, 以及对细胞增殖、迁移和侵袭的抑制作用。CircDOCK1可通过miR-128-3p/HMGB3轴促进胃癌细胞增殖、迁移、侵袭并诱导凋亡, 表明circDOCK1可能是胃癌治疗的潜在分子靶点。

关键词 胃癌; circDOCK1; miR-128-3p; HMGB3; 细胞增殖; 迁移; 侵袭

CircDOCK1 Affects Gastric Cancer Progression by Regulating the miR-128-3p/HMGB3 Axis

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Abstract This article aims to explore the effect of circDOCK1 on gastric cancer cell functions and its mechanism. The expression levels of circDOCK1, miR-128-3p and HMGB3 in gastric cancer tissues, adjacent tissues, human gastric mucosal epithelial cells GES-1, and human gastric cancer cells HGC-27 were determined by qRT-PCR and Western blot. si-NC, si-circDOCK1, miR-NC, miR-128-3p mimic, si-circDOCK1+miR-NC inhibitor and si-circDOCK1+miR-128-3p inhibitor were transfected into HGC-27 cells, respectively. The HGC-27 cells were divided into si-NC group, si-circDOCK1 group, miR-NC group, miR-128-3p mimic group, si-circDOCK1+miR-NC inhibitor group and si-circDOCK1+miR-128-3p inhibitor group. Targeting relationship of circDOCK1 and miR-128-3p was assessed by dual-luciferase reporter assay. CCK-8 method, clone formation experiment, scratch experiment, Transwell experiment and flow cytometry were used to detect cell functions. CircDOCK1 and HMGB3 levels were upregulated, while miR-128-3p level was downregulated in gastric cancer tissues and HGC-27 cells

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(P<0.05). CircDOCK1 could target miR-128-3p to regulate HMGB3 expression. Transfection of si-circDOCK1 or miR-128-3p mimic promoted cell apoptosis (P<0.05), but inhibited cell proliferation, migration and invasion (P<0.05). In addition, miR-128-3p inhibitor reversed the promoting effect of si-circDOCK1 on HGC-27 cell apoptosis, as well as the inhibitory effect on cell proliferation, migration and invasion. CircDOCK1 promoted gastric cancer cell proliferation, migration, invasion, and induced apoptosis by miR-128-3p/HMGB3 axis, indicating that circDOCK1 might be a potential molecular target for the treatment of gastric cancer.

Keywords gastric cancer; circDOCK1; miR-128-3p; HMGB3; cell proliferation; migration; invasion

胃癌是我国常见的一种恶性肿瘤，是全球癌症相关死亡的主要原因，严重影响患者生活质量[1]。胃癌的频繁转移使其治疗复杂化，因此迫切需要开发有效的诊断和治疗方法。近年来，随着对非编码RNA研究的深入，越来越多的RNA被发现。环状RNA(circular RNA, circRNA)是一种非编码RNA，充当微小RNA(miRNA)的海绵分子而调控基因表达，进而介导胃癌发展[2-4]。近年来，circRNA已成为胃癌治疗的药物靶点，特别是在肿瘤免疫、肿瘤代谢和肿瘤转移等领域，这证实了circRNA作为预后、诊断和治疗靶点的重要性[5-7]。CircDOCK1在甲状腺癌组织中表达水平升高，并可促进甲状腺癌细胞增殖、迁移及侵袭[8]。此外，circDOCK1在乳腺癌组织中高表达，其通过靶向miR-128-3p介导的NEK2下调来促进乳腺癌的进展[9]。因此，circDOCK1可能是一个介导肿瘤进展的促癌因子。然而，circDOCK1在胃癌进展中的作用及潜在机制尚不清楚。

研究表明，上调miR-128-3p可抑制肺癌细胞增殖、迁移及侵袭[10]。在胃癌中，miR-128-3p的低表达与胃癌患者的总生存率有关，且上调miR-128-3p可抑制胃癌细胞的活力、侵袭和上皮–间质转化，并加速细胞凋亡[11]。已有报道显示，*HMGB3*作为癌基因可调控肿瘤细胞转移、凋亡和增殖等多种生物学行为，进而介导肿瘤生成过程[12-13]。研究表明，HMGB3在胃癌细胞中表达水平升高，沉默HMGB3可诱导细胞周期阻滞及抑制细胞增殖、迁移及侵袭，表明*HMGB3*作为癌基因调控胃癌恶性进展[14]。通过Starbase和Targetscan预测，我们发现circDOCK1靶向miR-128-3p，且miR-128-3p与高迁移率族蛋白B3(high mobility group-box 3, *HMGB3*)存在互补序列。然而，circDOCK1是否调控miR-128-3p/HMGB3轴介导胃癌发展，仍不清楚。

本研究的目的在于解释circDOCK1在胃癌进展中的作用及潜在分子机制。基于以上，我们推测circDOCK1可能通过调控miR-128-3p/HMGB3轴介导胃癌细胞进展，这些发现可能为胃癌的治疗提供潜在分子靶点。

1 材料与方法

1.1 材料与试剂

收集于本院接受治疗的29例胃癌患者的胃癌组织及癌旁组织，置于–80 °C冰箱内保存备用。病人或其亲属均签署了知情同意书，本研究获得了大庆油田总医院伦理委员会的批准(伦理审批号：DQYTZYYLL-202301-002)。

人胃黏膜上皮细胞GES-1、胃癌细胞HGC-27购自北京Biovector质粒载体菌种细胞蛋白抗体基因保藏中心；DMEM(C0891-100 mL)、胎牛血清(C0251)、CCK-8试剂(C0037)、细胞凋亡检测试剂盒(C1062M)购自上海碧云天生物技术有限公司；兔anti-HMGB3(ab75782)、anti-Bax(ab32503)、anti-Bcl-2(ab32124)、anti-GAPDH(ab8245)、山羊抗兔IgG二抗(ab205718)购自美国Abcam公司；Transwell小室(3422)、Matrigel基质胶(354234)购自美国BD公司；Lipofectamine 2000(11668019)、Trizol试剂(15596018CN)、反转录试剂(N8080234)、荧光定量PCR试剂(10572014)购自美国Invitrogen公司；si-circDOCK1、si-NC、miR-128-3p mimic、miR-NC、miR-128-3p inhibitor购自广州锐博生物科技有限公司；荧光素酶报告基因载体、荧光素酶活性检测试剂盒(E1910)购自美国Promega公司。

1.2 方法

1.2.1 *实验分组及细胞转染* GES-1细胞、HGC-27细胞培养于含10%胎牛血清的DMEM培养基中。在细胞达到50%汇合度时，使用Lipofectamine 2000进行细胞转染，根据转染物的不同，记为si-NC(5′-UUC UCC GAA CGU GUC ACG UTT-3′)组、si-circDOCK1(5′-AAC AGC TTT TTA TAA

CTA TGA dTdT-3′)组、miR-NC(5′-UUC UCC GAA CGU GUC ACG UTT-3′)组、miR-128-3p mimic(5′-UCA CAG UGA ACC GGU CUC UUU-3′)组、si-circDOCK1+miR-NC inhibitor(5′-CAG UAC UUU UGU GUA GUA CAA-3′)组、si-circDOCK1+miR-128-3p inhibitor(5′-AAA GAG ACC GGU UCA CUG UGA-3′)组。正常培养的细胞记为control组。转染48 h后, 使用0.25%胰蛋白酶于37 ℃消化30 s收集细胞, 进行qRT-PCR、CCK-8、克隆形成实验、划痕实验、Transwell实验、流式细胞术或Western blot等实验。

1.2.2 qRT-PCR 取胃癌组织、癌旁组织、GES-1细胞与HGC-27细胞, 加入Trizol试剂提取RNA, 随后利用反转录试剂盒将总RNA反转录合成cDNA, 用荧光定量试剂进行PCR扩增反应, 采用$2^{-\Delta\Delta Ct}$法计算相对表达量。PCR序列如下。CircDOCK1: F 5′-CTG GAA CTC TGC CTC AGG AT-3′, R 5′-CCT CGG TAC CAC CCT TCA TA-3′; *GAPDH*: F 5′-TCG GAG TCA ACG GAT TTG GT-3′, R 5′-TTC CCG TTC TCA GCC TTG AC-3′; miR-128-3p: F 5′-CGC GTC ACA GTG AAC CGG T-3′, R 5′-AGT GCA GGG TCC GAG GTA TT-3′; *U6*: F 5′-ATT GGA ACG ATA CAG AGA AGA TT-3′, R 5′-GGA ACG CTT CAC GAA TTT G-3′。

1.2.3 双荧光素酶报告实验 将circDOCK1或*HMGB3*与miR-128-3p的结合位点(WT-circDOCK1: 272 bp, WT-HMGB3: 170 bp)及其突变序列(MUT-circDOCK1: 238 bp, MUT-HMGB3: 146 bp)分别克隆至pmirGLO载体上, 得到野生型和突变型载体(WT/MUT-circDOCK1或WT/MUT-HMGB3)。将WT/MUT-circDOCK1或WT/MUT-HMGB3载体分别与miR-NC/miR-128-3p mimic共转染至HGC-27细胞, 用双荧光素酶检测试剂盒分析荧光素酶活性, 评估miR-128-3p和circDOCK1或*HMGB3*的互作关系。

1.2.4 CCK-8实验 取各组细胞接种于96孔板于37 ℃和5% CO_2培养48 h, 随后加入CCK-8溶液于37 ℃孵育2 h, 应用酶标仪检测波长为450 nm时的*D*值, 分析细胞增殖抑制率。

1.2.5 克隆形成实验 收集各组细胞接种于6孔板于37 ℃和5% CO_2培养14天, 形成的菌落于室温下用4%多聚甲醛固定15 min和0.5%结晶紫染色10 min, 最后在显微镜下分析克隆形成数。

1.2.6 划痕实验 收集各组细胞接种于6孔板, 待细胞长至90%融合时, 用200 μL无菌移液管在细胞单层划线, 在显微镜下拍照记为0 h, 用无血清培养基室温培养24 h后, 用ImageJ软件分析迁移距离并计算划痕愈合率。

1.2.7 Transwell实验 取各组细胞接种于铺满Matrigel基质胶的Transwell上室, 下室加入完全培养液, 室温培养48 h后, 下室的细胞于室温下用4%多聚甲醛固定15 min和0.5%结晶紫染色10 min。显微镜下分析穿膜细胞数。

1.2.8 流式细胞术 收集各组细胞, 用结合缓冲液重悬, 与Annexin V-FITC和PI于室温下避光孵育10 min, 用流式细胞仪分析细胞凋亡率。

1.2.9 Western blot 取胃癌组织、癌旁组织、GES-1细胞与HGC-27细胞, 用RIPA提取总蛋白, 进行电泳和转膜。膜于室温下经过脱脂牛奶封闭2 h后, 与anti-HMGB3(1:1 000)、anti-Bax(1:1 000)、anti-Bcl-2(1:1 000)或anti-GAPDH(1:2 500)于4 ℃孵育过夜, 随后加入二抗稀释液(1:50 000)于室温孵育1 h, 曝光显影, 用ImageJ软件分析灰度值。

1.3 统计学分析

采用SPSS 21.0统计学软件分析数据, 计量资料以($\bar{x}\pm s$)表示, 组间比较采用独立样本*t*检验或单因素方差分析, 以$P<0.05$为差异具有统计学意义。

2 结果

2.1 胃癌组织中circDOCK1、miR-128-3p和HMGB3表达情况

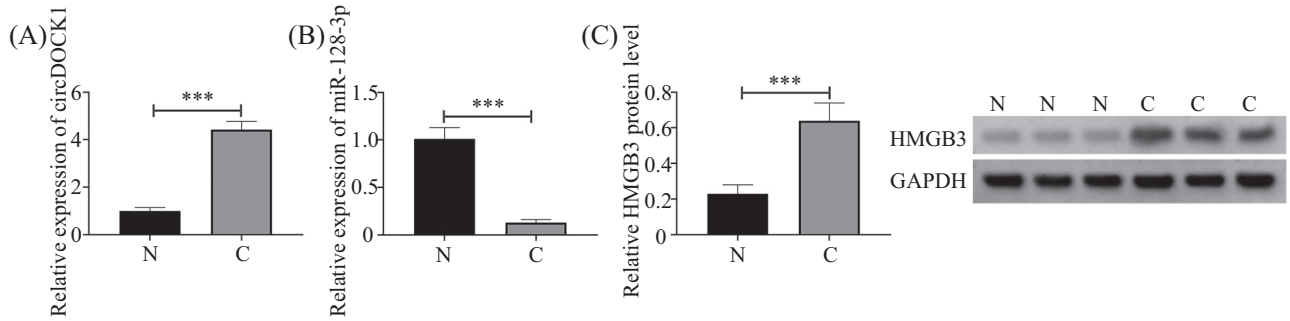
与癌旁组织相比, 胃癌组织中circDOCK1表达水平和HMGB3蛋白水平上调($P<0.05$), 而miR-128-3p表达水平下降($P<0.05$), 见图1。

2.2 胃癌细胞中circDOCK1、miR-128-3p和HMGB3表达情况

与GES-1细胞相比, HGC-27细胞中circDOCK1表达水平和HMGB3蛋白水平上升($P<0.05$), 而miR-128-3p表达水平下降($P<0.05$), 见图2。

2.3 CircDOCK1影响miR-128-3p和HMGB3的表达

与si-circDOCK1+miR-NC inhibitor组相比, si-circDOCK1组circDOCK1表达水平和HMGB3蛋白表达水平下调, 而miR-128-3p表达水平上调($P<0.05$); miR-128-3p mimic组miR-128-3p表达水平上升($P<0.05$), 而HMGB3蛋白表达水平下降($P<0.05$); si-

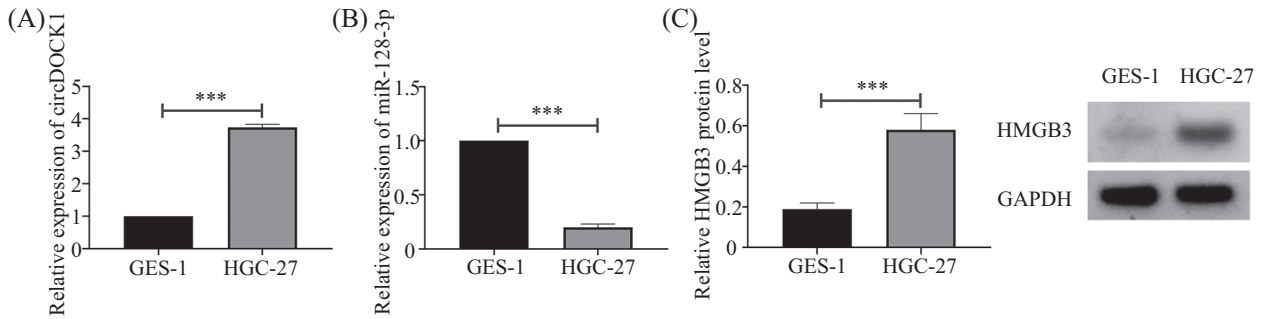


A、B: qRT-PCR检测circDOCK1和miR-128-3p在胃癌组织和癌旁组织中的表达情况; C: Western blot检测HMGB3在胃癌组织和癌旁组织中的表达情况。N: 癌旁组织; C: 胃癌组织。***P<0.001。

A,B: qRT-PCR was used to detect circDOCK1 and miR-128-3p expression in gastric cancer tissues and adjacent normal tissues; C: Western blot was used to measure HMGB3 protein level in gastric cancer tissues and adjacent normal tissues. N: adjacent normal tissues; C: gastric cancer tissues. ***P<0.001.

图1 CircDOCK1、miR-128-3p和HMGB3在胃癌组织中的表达情况

Fig.1 Expression of circDOCK1, miR-128-3p and HMGB3 in gastric cancer tissues



A、B: qRT-PCR检测circDOCK1和miR-128-3p在GES-1和HGC-27细胞中的表达情况; C: Western blot检测HMGB3在GES-1和HGC-27细胞中的表达情况。***P<0.001。

A,B: qRT-PCR was used to detect circDOCK1 and miR-128-3p expression in GES-1 and HGC-27 cells; C: Western blot was used to measure HMGB3 protein level in GES-1 and HGC-27 cells. ***P<0.001.

图2 CircDOCK1、miR-128-3p和HMGB3在HGC-27细胞中的表达情况

Fig.2 Expression of circDOCK1, miR-128-3p and HMGB3 in HGC-27 cells

circDOCK1+miR-128-3p inhibitor组miR-128-3p表达水平降低(P<0.05), HMGB3蛋白表达水平则升高(P<0.05); 见图3。

2.4 CircDOCK1、miR-128-3p和*HMGB3*靶向关系

Starbase预测分析circDOCK1与miR-128-3p互补结合, Targetscan预测分析miR-128-3p与*HMGB3*互补结合, 见图4A。miR-128-3p可降低WT-circDOCK1和WT-HMGB3组细胞荧光素酶活性(P<0.05), 而不影响MUT-circDOCK1和MUT-HMGB3组细胞荧光素酶活性, 见图4B。

2.5 CircDOCK1/miR-128-3p/HMGB3影响HGC-27增殖

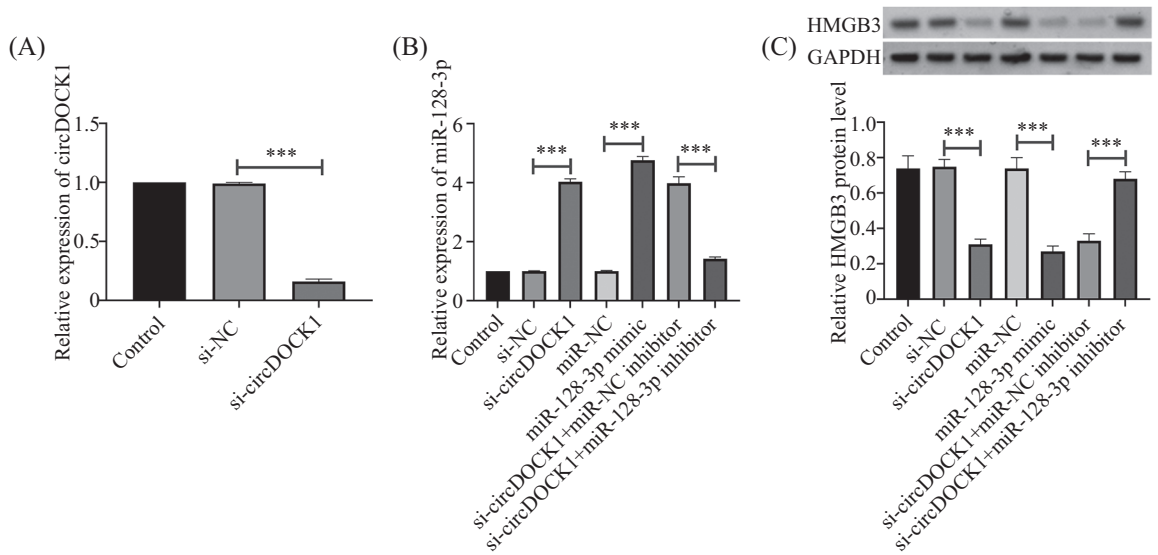
与si-NC组和miR-NC组相比, si-circDOCK1组和miR-128-3p mimic组中的细胞增殖抑制率上升且克隆形成数下降(P<0.05); 与si-circDOCK1+miR-NC inhibitor组相比, si-circDOCK1+miR-128-3p inhibitor组中的细胞增殖抑制率下降且克隆形成数上调(P<0.05); 见图5。

2.6 CircDOCK1/miR-128-3p/HMGB3影响HGC-27迁移、侵袭

与si-NC组和miR-NC组相比, si-circDOCK1组和miR-128-3p mimic组中的划痕愈合率和侵袭细胞数下降(P<0.05); 与si-circDOCK1+miR-NC inhibitor组相比, si-circDOCK1+miR-128-3p inhibitor组中的划痕愈合率和侵袭细胞数上调(P<0.05); 见图6。

2.7 CircDOCK1/miR-128-3p/HMGB3影响HGC-27凋亡

与si-NC组和miR-NC组相比, si-circDOCK1组

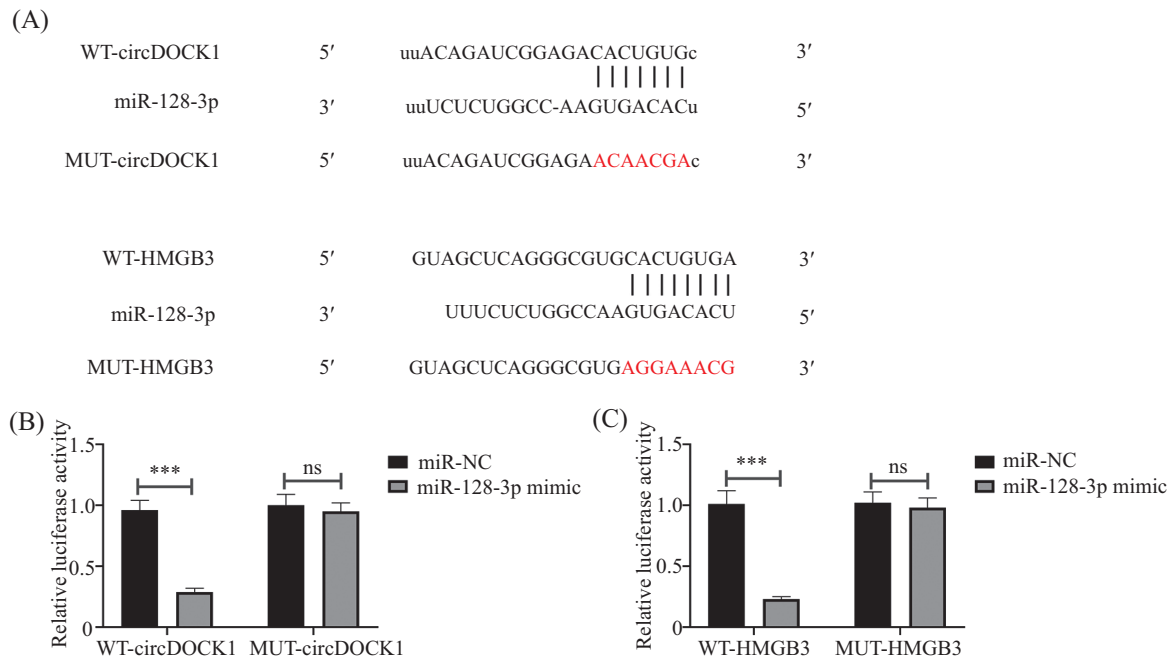


A: qRT-PCR检测circDOCK1在HGC-27细胞中转染si-NC、si-circDOCK1后的表达情况; B: qRT-PCR检测miR-128-3p在HGC-27细胞中转染si-NC、si-circDOCK1、miR-NC、miR-128-3p mimic、si-circDOCK1+miR-NC inhibitor、si-circDOCK1+miR-128-3p inhibitor后的表达情况; C: Western blot检测HMGB3在HGC-27细胞中转染si-NC、si-circDOCK1、miR-NC、miR-128-3p mimic、si-circDOCK1+miR-NC inhibitor、si-circDOCK1+miR-128-3p inhibitor后的蛋白表达情况。***P<0.001。

A: qRT-PCR was used to detect circDOCK1 expression in HGC-27 cells transfected with si-NC, si-circDOCK1; B: qRT-PCR was used to detect miR-128-3p expression in HGC-27 cells transfected with si-NC, si-circDOCK1, miR-NC, miR-128-3p mimic, si-circDOCK1+miR-NC inhibitor, si-circDOCK1+miR-128-3p inhibitor; C: Western blot was used to measure HMGB3 protein level in HGC-27 cells transfected with si-NC, si-circDOCK1, miR-NC, miR-128-3p mimic, si-circDOCK1+miR-NC inhibitor, si-circDOCK1+miR-128-3p inhibitor. ***P<0.001.

图3 各个处理组中circDOCK1、miR-128-3p和HMGB3表达情况的检测

Fig.3 Detection of circDOCK1, miR-128-3p and HMGB3 expression in each treatment group

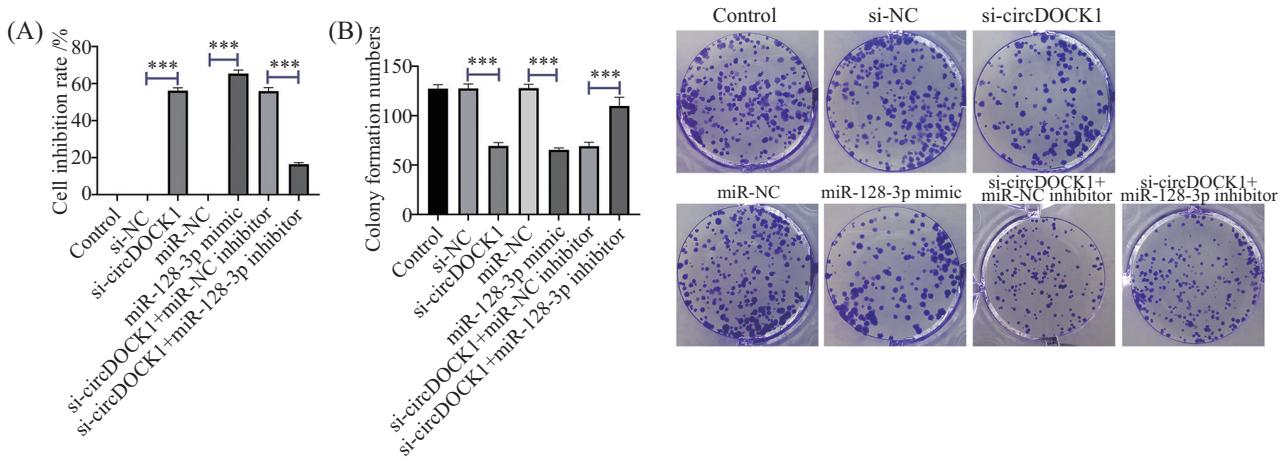


A: Starbase和Targetscan分别预测miR-128-3p与circDOCK1/*HMGB3*的互补结合位点; B: 双荧光素酶报告实验分析miR-128-3p与circDOCK1的互作关系; C: 双荧光素酶报告实验分析miR-128-3p与HMGB3的互作关系。红色代表突变碱基。***P<0.001; ns: P>0.05。

A: Starbase and Targetscan were used to predicted the complementary binding sites of miR-128-3p with circDOCK1/HMGB3, respectively; B: dual-luciferase reporter assay was used to analyze the interaction between miR-128-3p and circDOCK1; C: dual-luciferase reporter assay was used to analyze the interaction between miR-128-3p and HMGB3. The red color represents the mutated bases. ***P<0.001; ns: P>0.05.

图4 miR-128-3p与circDOCK1/*HMGB3*的互补序列及双荧光素酶报告实验

Fig.4 The miR-128-3p and circDOCK1/*HMGB3* complementary sequence and dual-luciferase reporter assay

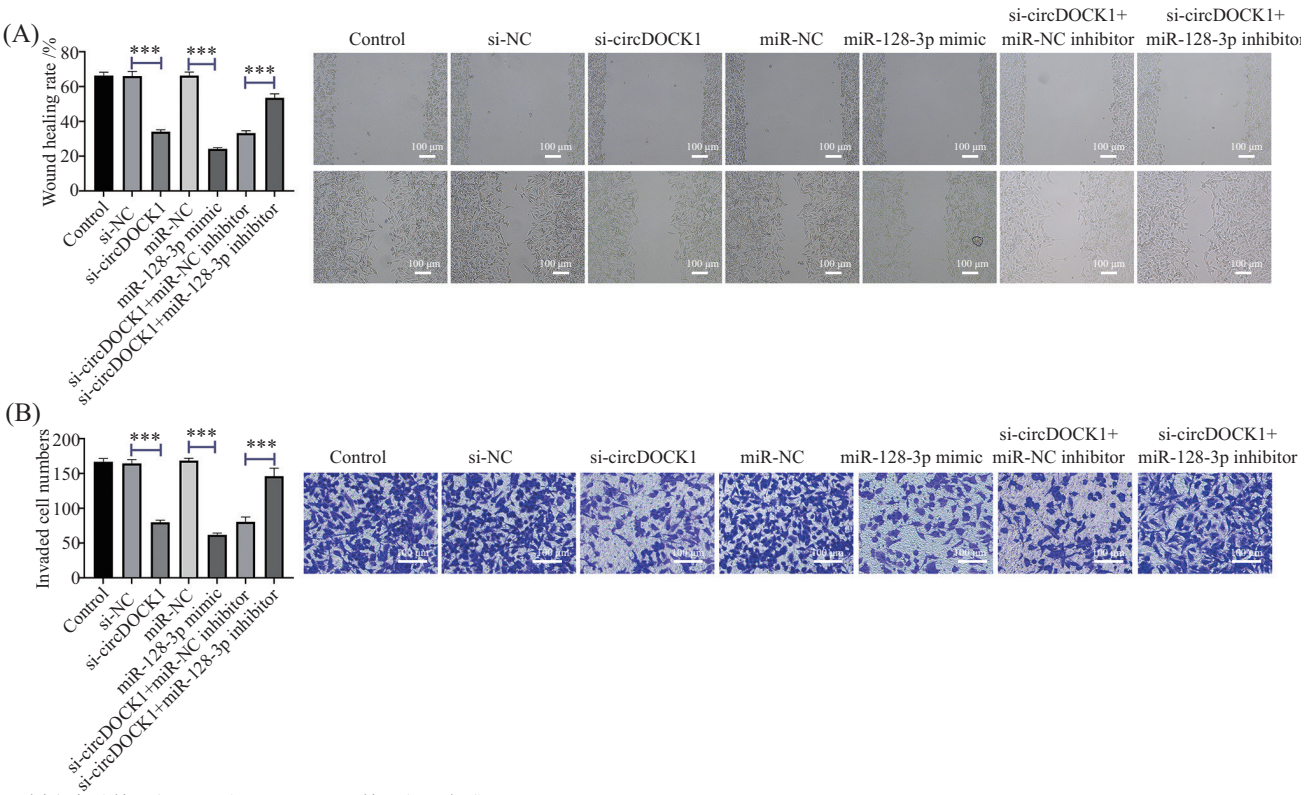


A: CCK-8实验检测细胞抑制率; B: 克隆形成实现评估细胞增殖。***P<0.001。

A: CCK-8 assay was used to measure cell inhibition rate; B: colony formation assay was performed to assess cell proliferation. ***P<0.001.

图5 CircDOCK1/miR-128-3p/HMGB3影响细胞抑制率和克隆形成数

Fig.5 CircDOCK1/miR-128-3p/HMGB3 affects cell inhibition rate and colony formation



A: 划痕实验检测细胞迁移; B: Transwell检测细胞侵袭。***P<0.001。

A: cell migration was measured by wound healing assay; B: cell invasion was detected by Transwell assay. ***P<0.001.

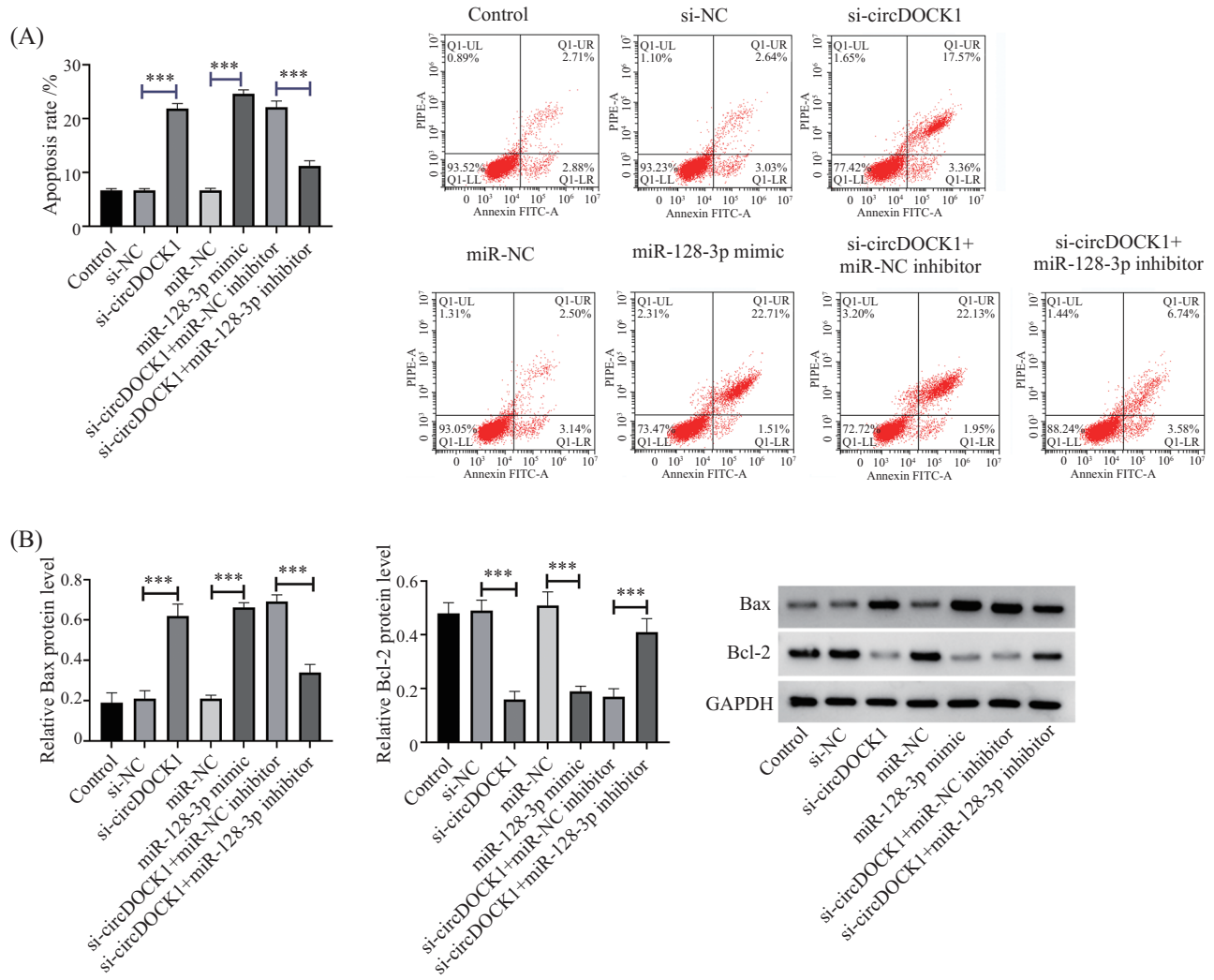
图6 CircDOCK1/miR-128-3p/HMGB3影响划痕愈合率和侵袭细胞数

Fig.6 CircDOCK1/miR-128-3p/HMGB3 affects wound healing rate and invaded cell numbers

和miR-128-3p mimic组中的细胞凋亡率和Bax水平上升, 而Bcl-2水平下降(P<0.05); 与si-circDOCK1+miR-NC inhibitor组相比, si-circDOCK1+miR-128-3p inhibitor组中的细胞凋亡率和Bax水平下降, 而Bcl-2水平上升(P<0.05); 见图7。

3 讨论

CircDOCK1的异常表达参与调控了多种肿瘤生成过程。CircDOCK1在骨肉瘤组织和细胞中高表达, 过表达circDOCK1可以促进体内致癌性和体外恶性转化, 并调控顺铂敏感性[15]。CircDOCK1在结



A: 流式细胞术分析细胞凋亡率; B: Western blot分析Bcl-2和Bax蛋白表达水平。***P<0.001。

A: flow cytometry was used to detect cell apoptosis rate; B: Western blot was used to analyze Bcl-2 and Bax protein levels. ***P<0.001.

图7 CircDOCK1/miR-128-3p/HMGB3影响凋亡

Fig.7 CircDOCK1/miR-128-3p/HMGB3 affects cell apoptosis

直肠癌组织和细胞中的表达能力增强, 其可以促进细胞生长、迁移和侵袭, 并抑制细胞凋亡[16]。CircDOCK1在膀胱癌组织和细胞系中表达上调, 抑制其表达可抑制细胞增殖及迁移, 还可抑制体内移植瘤生长[17]。CircDOCK1在口腔鳞状细胞癌中呈高表达, 并可促进细胞生长[18]。以上研究证实了circDOCK1的促癌作用。然而, circDOCK1在胃癌进展中的作用和机制尚未被研究。本结果显示, circDOCK1在胃癌组织与细胞中上调。通过功能缺失实验, 我们发现circDOCK1沉默可抑制胃癌细胞增殖、迁移、侵袭并促进凋亡。*Bcl-2*和*Bax*是凋亡过程中功能相互对立的一对调控基因, 其中*Bcl-2*主要发挥抑制凋亡的作用, 而*Bax*发挥促进凋亡的作用[19-20]。在本研究, circDOCK1敲低显著降低了Bcl-2水平而增加了Bax水平, 表明circDOCK1可能促进Bcl-2水平而降低Bax水平, 进而抑制胃癌细胞凋亡。这些结果表明circDOCK1作为促癌因子加速胃癌细胞的生长和转移, 进而促进胃癌恶性进展。

研究表明, 过表达miR-128-3p显著抑制鼻咽癌细胞的增殖, 诱导DNA损伤和凋亡, 并促进细胞的放射敏感性[21]。miR-128-3p在前列腺癌组织中低表达, 其可抑制前列腺癌细胞的增殖、迁移、侵袭和血管生成[22]。miR-128-3p在宫颈癌组织中下调, miR-128-3p抑制剂可促进宫颈癌细胞体外增殖, 抑制细胞凋亡和细胞周期阻滞[23]。miR-128-3p在乳腺癌患者中低表达, 其可以抑制乳腺癌细胞的增殖和运动能力[24]。这些研究证实了miR-128-3p的抑癌作用。在胃癌中, 较低的miR-128-3p表达水平与

胃癌患者较差的总生存期相关[25]。此外，还有研究显示下调miR-128-3p可以促进胃癌的增殖、迁移和侵袭[26]。以上报道证实了miR-128-3p在胃癌进展中的消极作用。本研究结果显示，miR-128-3p在胃癌组织与细胞中下调，且circDOCK1通过靶向miR-128-3p抑制其表达。本研究结果显示，miR-128-3p过表达可以降低胃癌细胞增殖、迁移和侵袭能力，并促进细胞凋亡，这和既往报道的miR-128-3p具有抑制胃癌进展的结果一致。另外，本研究结果发现，miR-128-3p过表达抑制Bcl-2表达而促进Bax表达，进一步表明miR-128-3p可以加速胃癌细胞凋亡。此外，挽救实验分析显示，抑制miR-128-3p可回复沉默circDOCK1对胃癌细胞增殖、迁移、侵袭、Bcl-2表达的抑制作用以及其对凋亡和Bax表达的促进作用，表明circDOCK1通过靶向抑制miR-128-3p促进胃癌细胞恶性生物学行为。

HMGB3可能是胃癌患者潜在的预后指标，其可以促进胃癌细胞干性，加速胃癌进展[27-28]。HMGB3在胃癌相关成纤维细胞中高表达，其可以加速癌相关成纤维细胞对胃癌细胞顺铂耐药、增殖、侵袭、迁移和上皮–间质转化的促进作用，进而促进胃癌进展[29]。HMGB3在胃癌的进展阶段呈高水平表达，与患者原发肿瘤、淋巴结转移和临床分期显著相关[30]。和既往的报道一致，我们证实HMGB3在胃癌组织与细胞中表达上调。进一步的分析结果显示，HMGB3是miR-128-3p的靶点，且circDOCK1通过靶向miR-128-3p促进HMGB3的表达，这提示circDOCK1通过调控miR-128-3p/HMGB3轴促进胃癌细胞进展。尽管NI等[9]指出circDOCK1通过调控miR-128-3p促进乳腺癌进展，且SUN等[31]指出miR-128-3p靶向HMGB3调控脓毒症相关急性肺损伤，但是circDOCK1是否通过调控miR-128-3p介导胃癌进展，且miR-128-3p是否通过靶向HMGB3调控胃癌进程尚不清楚。我们的研究首次将circDOCK1/miR-128-3p/HMGB3轴结合起来，明确了circDOCK1/miR-128-3p/HMGB3轴对胃癌进展的积极作用，为circDOCK1成为胃癌治疗的潜在分子靶点提供了新的证据。

综上所述，circDOCK1靶向miR-128-3p调控HMGB3，进而促进胃癌细胞生长和转移。本研究结果显示，靶向抑制circDOCK1可能是缓解胃癌进展的有效措施，且circDOCK1/miR-128-3p/HMGB3轴的提出可能为胃癌治疗提供新思路。

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