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LncRNA PART1通过靶向miR-301b-3p减轻高糖诱导的肾小管上皮细胞损伤

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摘要 该文旨在探讨lncRNA PART1是否参与调控高糖诱导的人肾小管上皮细胞HK-2损伤。采用高糖诱导的HK-2细胞建立细胞损伤模型, 随机分组: Con组、HG组、HG+pcDNA组、HG+pcDNA-PART1组、HG+anti-miR-NC组、HG+anti-miR-301b-3p组、HG+pcDNA-PART1+miR-NC组、HG+pcDNA-PART1+miR-301b-3p组; qRT-PCR法检测lncRNA PART1、miR-301b-3p的表达量; ELISA法检测IL-6、TNF-α的水平; 经流式细胞术检测细胞凋亡率; 利用双荧光素酶报告实验证实lncRNA PART1与miR-301b-3p的关系; Western blot检测cleaved-caspase3、cleaved-caspase9蛋白表达量。相对于Con组, lncRNA PART1的表达量在HG组中减少(P<0.05), 而miR-301b-3p的表达水平、炎症因子(IL-6、TNF-α)水平、凋亡率以及cleaved-caspase3、cleaved-caspase9水平均增加(P<0.05); 相对于HG+pcDNA组, IL-6、TNF-α的水平, 凋亡率以及cleaved-caspase3、cleaved-caspase9水平在HG+pcDNA-PART1组中均降低(P<0.05); lncRNA PART1可靶向结合miR-301b-3p; 相对于HG+anti-miR-NC组, IL-6、TNF-α水平, 凋亡率以及cleaved-caspase3、cleaved-caspase9水平在HG+anti-miR-301b-3p组中均降低(P<0.05); 相对于HG+pcDNA-PART1+miR-NC组, IL-6、TNF-α水平, 凋亡率以及cleaved-caspase3、cleaved-caspase9水平在HG+pcDNA-PART1+miR-301b-3p组中均提高(P<0.05)。LncRNA PART1靶向下调miR-301b-3p抑制了高糖诱导的炎症反应及细胞凋亡, 进而减轻了肾小管上皮细胞损伤。

关键词 HK-2细胞; lncRNA PART1; miR-301b-3p; 炎症; 细胞凋亡

LncRNA PART1 Alleviates High Glucose-Induced Renal Tubular Epithelial Cell Injury by Targeting miR-301b-3p

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Abstract This study aims to explore the effect of lncRNA PART1 on the injury of human renal tubular epithelial cells HK-2 induced by high glucose and its possible mechanism. High glucose-induced HK-2 cells were used to establish a cell injury model, and randomly grouped into groups: Con group, HG group, HG+pcDNA group, HG+pcDNA-PART1 group, HG+anti-miR-NC group, HG+anti-miR-301b-3p group, HG+pcDNA-PART1+miR-NC group, HG+pcDNA-PART1+miR-301b-3p group. qRT-PCR was used to detect the expression of lncRNA PART1 and miR-301b-3p. ELISA method was used to detect the levels of IL-6 and TNF-α. Flow cytometry was used to detect the rate of apoptosis. The dual luciferase reporter experiment was used to verify the targeting relationship between lncRNA PART1 and miR-301b-3p. Western blot was used to detect the protein expression of cleaved-cas-

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pase3 and cleaved-caspase9. Compared with the Con group, the expression of lncRNA PART1 in the HG group was decreased (P<0.05), while the expression of miR-301b-3p, the levels of IL-6 and TNF-α, cell apoptosis rate, and cleaved-caspase3 and cleaved-caspase9 protein levels were increased (P<0.05). Compared with the HG+pcDNA group, IL-6, TNF-α levels, the apoptosis rate and the protein levels of cleaved-caspase3 and cleaved-caspase9 were decreased in the HG+pcDNA-PART1 group (P<0.05). LncRNA PART1 could target miR-301b-3p. Compared with the HG+anti-miR-NC group, the levels of IL-6, TNF-α, apoptosis rate and cleaved-caspase3 and cleaved-caspase9 protein levels were decreased in the HG+anti-miR-301b-3p group (P<0.05). Compared with the HG+pcDNA-PART1+miR-NC group, the levels of IL-6, TNF-α, the rate of apoptosis and the protein levels of cleaved-caspase3 and cleaved-caspase9 were increased in the HG+pcDNA-PART1+miR-301b-3p group (P<0.05). LncRNA PART1 can inhibit the inflammatory response and apoptosis by down-regulating the expression of miR-301b-3p, thereby reducing the damage of renal tubular epithelial cells induced by high glucose.

Keywords HK-2 cell; lncRNA PART1; miR-301b-3p; inflammation; cell apoptosis

糖尿病肾病是一种常见的慢性疾病, 据报道高糖诱导肾小管上皮细胞凋亡及氧化应激的发生从而促进细胞损伤, 进而影响糖尿病肾病的发展[1-2]。先前的研究已经表明了非编码RNA可以作为竞争性内源RNA(competitive endogenous RNA, ceRNA), 调控一些微小RNA(microRNA, miRNA)的表达, 进而参与调控糖尿病肾病的进程[3-4]。早期的研究已经表明, lncRNA PART1在缺氧/复氧诱导的心肌细胞损伤中低表达, 其上调可缓解因缺氧/复氧引发的心肌细胞的损伤[5]。但尚未知lncRNA PART1是否与糖尿病肾病相关。在本研究中, LncBase Predicted v.2软件分析显示lncRNA PART1与miR-301b-3p之间存在互补序列。此外, 目前的文献已经表明miR-301b-3p的下调可减轻炎症反应, 进而减轻大鼠心肌缺血再灌注损伤[6]。然而, 尚未知miR-301b-3p是否参与了高糖介导的肾小管上皮细胞损伤。在本研究中, 我们的目的是分析lncRNA PART1是否通过靶向miR-301b-3p来调控高糖引发的肾小管上皮细胞损伤。

1 材料与方法

1.1 材料与试剂

人肾小管上皮细胞HK-2购于上海通派生物科技有限公司; DMEM培养基、胎牛血清购于上海碧云天生物技术有限公司; Lipofectamine2000试剂购于美国Invitrogen公司; Trizol试剂购于美国ThermoFisher Scientific公司; 反转录与荧光定量PCR试剂购于北京天根生化科技有限公司; pcDNA、pcDNA-PART1购于上海吉满生物科技有限公司; miR-NC(5′-UUA UCU CCU GUG CGA TT-3′)、miR-301b-3p mimics(5′-CAG UGC AAU GAU AUU GUC AAA GC-3′)、si-NC(上游引物5′-UUC UCC GAA CGU GUC ACG UTT-3′, 下游引物5′-ACG UGA CAC GUU CGG AGA ATT-3′)、si-PART1(上游引物5′-UCU UAA AGC UUC UAA GAA CUG-3′, 下游引物5′-GUU CUU AGA AGC UUU AAG AUU-3′)、anti-miR-NC(5′-CAG UAC AUU GGU UCU GCA A-3′)、anti-miR-301b-3p(5′-GCU UUG ACA AUA UCA UUG CAC UG-3′)购于广州锐博生物科技有限公司; IL-6、TNF-α检测试剂盒购于上海酶联生物科技有限公司; 细胞凋亡检测试剂盒购于北京索莱宝科技有限公司; 双荧光素酶报告基因载体及其活性检测试剂盒购于美国Promega公司; 兔抗人cleaved-caspase3抗体(1:1 000, #9661)、cleaved-caspase9抗体(1:1 000, #20750)、内参GAPDH抗体(1:2 000, #2118)与HRP标记的山羊抗兔IgG二抗(1:3 000, #7074)购于美国CST公司。

1.2 方法

1.2.1 实验处理及分组 用5.5 mmol/L葡萄糖处理HK-2细胞24 h, 标记为正常对照组(Con)。用25 mmol/L葡萄糖处理HK-2细胞24 h模拟糖尿病肾病病理环境[7], 记为高糖组(HG)。依据脂质体转染法, 将pcDNA、pcDNA-PART1、anti-miR-NC、anti-miR-301b-3p分别转染至HK-2细胞, 37 °C转染24 h后再经25 mmol/L葡萄糖处理24 h, 记为HG+pcDNA、HG+pcDNA-PART1、HG+anti-miR-NC、HG+anti-miR-301b-3p组。此外, 将pcDNA-PART1分别与miR-NC、miR-301b-3p mimics共转染至HK-2细胞, 37 °C转染24 h后再经25 mmol/L葡

萄糖处理24 h, 记为HG+pcDNA-PART1+miR-NC、HG+pcDNA-PART1+miR-301b-3p组。

1.2.2 qRT-PCR 用Trizol试剂提取HK-2细胞总RNA后, 通过反转录合成cDNA。其中, *GAPDH*和*U6*分别作为lncRNA PART1和miR-301b-3p的内参, 依据$2^{-\Delta\Delta Ct}$法计算它们的相对表达量。循环条件为95 °C预变性5 min; 95 °C变性30 s, 60 °C退火30 s, 72 °C延伸30 s, 共40个循环。引物序列如下: lncRNA PART1上游引物5′-GCT GGA ATA ACC CTG CCA GT-3′, 下游引物5′-CTG TGT TGT TCC AGT GCA GC-3′; *GAPDH*上游引物5′-TCG GAG TCA ACG GAT TTG GT-3′, 下游引物5′-TTC CCG TTC TCA GCC TTG AC-3′; miR-301b-3p上游引物5′-CGC GCA GTG CAA TGA TAT TGT-3′, 下游引物5′-AGT GCA GGG TCC GAG GTA TT-3′; *U6*上游引物5′-CTC GCT TCG GCA GCA CA-3′, 下游引物5′-AAC GCT TCA CGA ATT TGC GT-3′。

1.2.3 ELISA 收集HK-2细胞, 于4 °C、1 000 ×*g*离心10 min后获得上清液, 依据IL-6 ELISA试剂盒、TNF-α ELISA试剂盒的说明书进行实验操作。使用酶标仪在450 nm波长处检测细胞的吸光度(*D*)值, 根据标准曲线分析IL-6、TNF-α的水平。

1.2.4 流式细胞术检测 经0.25%胰蛋白酶于37 °C消化1 min后, 将HK-2细胞于4 °C、1 000 ×*g*离心5 min, PBS洗涤。随后, 利用500 μL结合缓冲液对其进行重悬, 并添加5 μL Annexin V-FITC和5 μL PI室温避光孵育10 min, 1 h内依据FACS Calibur流式细胞仪评估细胞凋亡率。

1.2.5 双荧光素酶报告实验 首先, 构建野生型载体WT-PART1与突变型载体MUT-PART1, 随后将其分别与miR-NC或miR-301b-3p mimics共转染HK-2细胞24 h。收集细胞, 通过双荧光素酶活性检测试剂盒评估细胞的荧光素酶活性。此外, 将pcDNA、pcDNA-PART1、si-NC、si-PART1分别转染至HK-2细胞, 于37 °C温育48 h后, 经qRT-PCR检测miR-301b-3p的表达水平。

1.2.6 Western blot 使用RIPA裂解液提取HK-2细胞的总蛋白。于4 °C、10 000 ×*g*离心5 min后, 经BCA法测定蛋白浓度。SDS-PAGE电泳后, 取40 μg蛋白样本进行转模。室温封闭1 h后, 加入cleaved-caspase3(1:1 000)、cleaved-caspase9(1:1 000)和GAPAH(1:2 000)一抗于4 °C孵育24 h。随后, 在二抗(1:3 000)的稀释液中浸泡2 h, 滴加ECL曝光显影。最后, 蛋白条带经Quantity One软件进行定量。

1.3 统计学分析

每个独立实验均重复3次, 样本量均为3。本研究所有数据均录入SPSS 21.0统计学软件进行数据分析, 并以($\bar{x}\pm s$)表示。分别采用独立样本*t*检验和单因素方差分析进行两组间和多组间的比较。$P<0.05$表示差异具有统计学意义。

2 结果

2.1 LncRNA PART1和miR-301b-3p在高糖诱导的肾小管上皮细胞中差异表达

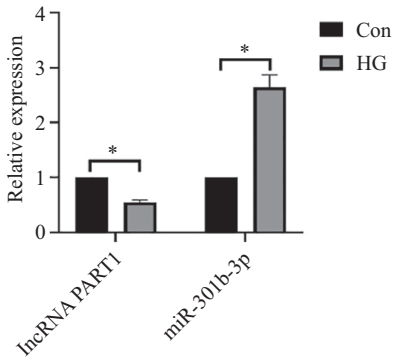
首先, 我们通过qRT-PCR检测了lncRNA PART1和miR-301b-3p在高糖诱导的肾小管上皮细胞中的表达情况。如图1所示, 相对于Con组, lncRNA PART1在HG组中表达量减少($P<0.05$), 而miR-301b-3p的表达量升高($P<0.05$)。这些结果表明, lncRNA PART1和miR-301b-3p在高糖诱导的肾小管上皮细胞中的表达趋势相反。

2.2 上调lncRNA PART1抑制高糖诱导的HK-2细胞炎症和凋亡

为了确定lncRNA PART1在高糖诱导的肾小管上皮细胞损伤中的作用, 我们在HG诱导的HK-2细胞中转染pcDNA-PART1以对PART1进行过表达, 并通过检测炎症因子表达水平、凋亡相关蛋白水平以及细胞凋亡情况评估lncRNA PART1对细胞损伤的影响。如图2所示, 相对于Con组, HG组中lncRNA PART1表达水平降低, 而IL-6、TNF-α、cleaved-caspase3、cleaved-caspase9水平和凋亡率升高($P<0.05$); 相对于HG+pcDNA组, HG+pcDNA-PART1组中lncRNA PART1表达水平升高, 而IL-6、TNF-α、cleaved-caspase3、cleaved-caspase9水平和凋亡率降低($P<0.05$)。以上结果表明, lncRNA PART1可能抑制高糖诱导的HK-2细胞炎症和凋亡。

2.3 LncRNA PART1靶向调控miR-301b-3p的表达

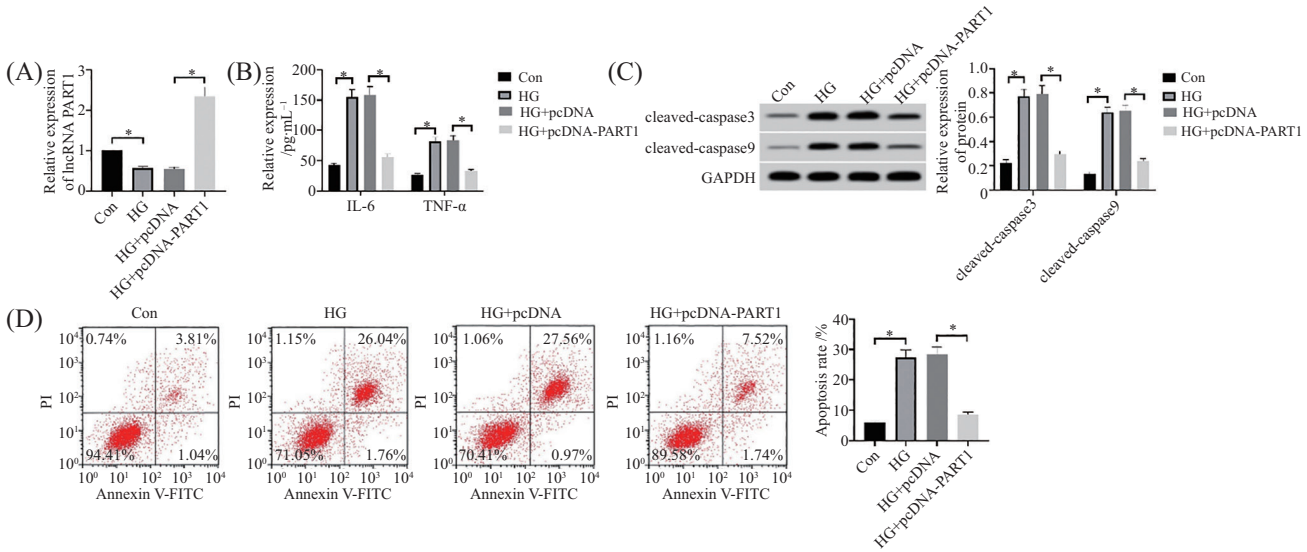
LncBase Predicted v.2软件分析显示lncRNA PART1和miR-301b-3p存在互补片段。为了证实二者的互作, 我们进行了双荧光素酶分析, 结果显示上调miR-301b-3p降低了野生型载体WT-PART1的荧光素酶活性($P<0.05$)。此外, 相对于pcDNA组, miR-301b-3p的表达水平在pcDNA-PART1组中降低



*P<0.05.

图1 高糖诱导的HK-2细胞中lncRNA PART1和miR-301b-3p的表达情况

Fig.1 Expression of lncRNA PART1 and miR-301b-3p in HK-2 cells induced by high glucose



A: qRT-PCR检测lncRNA PART1表达水平; B: ELISA检测炎症因子(IL-6和TNF-α)的水平; C: Western blot检测凋亡相关蛋白(cleaved-caspase3、cleaved-caspase9)的水平; D: 流式细胞术分析细胞凋亡率。*P<0.05。

A: the expression level of lncRNA PART1 was detected by qRT-PCR; B: ELISA was used to detect the levels of inflammatory factors (IL-6 and TNF-α); C: Western blot was used to detect the levels of apoptosis-related proteins (cleaved-caspase3, cleaved-caspase9); D: flow cytometry was used to analyze the apoptosis rate of cells. *P<0.05.

图2 LncRNA PART1抑制了高糖诱导的HK-2细胞炎症和凋亡

Fig.2 LncRNA PART1 alleviates high glucose-induced inflammation and apoptosis in HK-2 cells

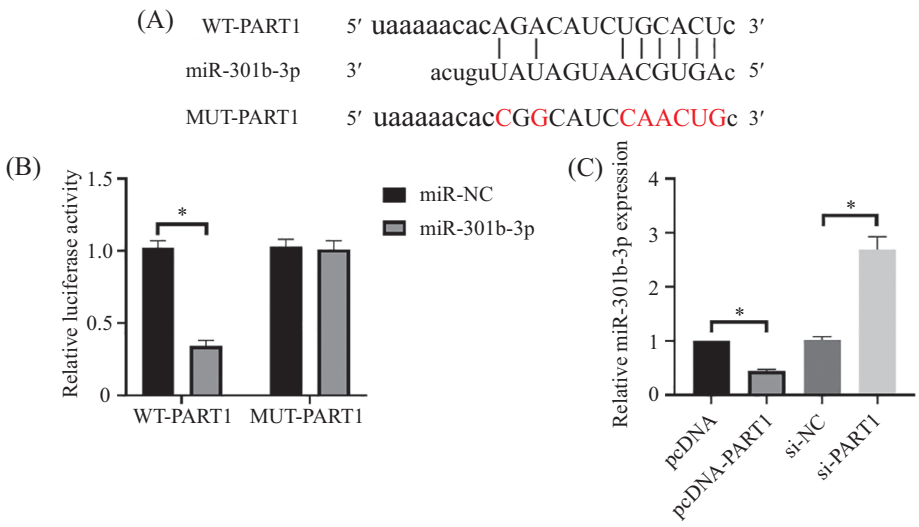
(P<0.05); 相对于si-NC组, miR-301b-3p的表达水平在si-PART1组中升高(P<0.05)(图3)。这些结果提示, PART1靶向miR-301b-3p, 进而负向调控其表达。

2.4 下调miR-301b-3p减轻了高糖诱导的HK-2细胞损伤

为了探究miR-301b-3p在高糖诱导的肾小管上皮细胞损伤中的作用, 我们在HG诱导的HK-2细胞中转染anti-miR-301b-3p, 并通过检测炎症因子表达水平、凋亡相关蛋白水平以及细胞凋亡情况评估miR-301b-3p抑制剂对细胞损伤的影响。如图4所示, 相对于HG+anti-miR-NC组, HG+anti-miR-301b-3p组中miR-301b-3p、IL-6、TNF-α、cleaved-caspase3、cleaved-caspase9水平和凋亡率均降低(P<0.05)。以上结果表明, miR-301b-3p表达下调可以抑制高糖诱导的HK-2细胞炎症和凋亡。

2.5 LncRNA PART1通过靶向miR-301b-3p减轻高糖诱导的HK-2细胞损伤

为了进一步揭示PART1是否通过靶向miR-301b-3p调控高糖诱导的肾小管上皮细胞损伤, 我们在HG诱导的HK-2细胞中共转染pcDNA-PART1和miR-301b-3p, 并通过检测炎症因子表达水平、凋亡相关蛋白水平以及细胞凋亡评估PART1和



A: LncBase Predicted v.2软件显示lncRNA PART1和miR-301b-3p的互作位点(红色表示突变的碱基); B: 双荧光素酶报告实验分析PART1与miR-301b-3p的互作; C: qRT-PCR分析lncRNA PART1过表达或敲低对miR-301b-3p表达的影响。*P<0.05。

A: the LncBase Predicted v.2 software showed the interaction sites of lncRNA PART1 and miR-301b-3p (red indicated the mutated bases); B: dual-luciferase reporter assay was used to analyze the interaction between PART1 and miR-301b-3p; C: qRT-PCR was used to analyze the effect of lncRNA PART1 overexpression or knockdown on the expression of miR-301b-3p. *P<0.05.

图3 LncRNA PART1和miR-301b-3p互作

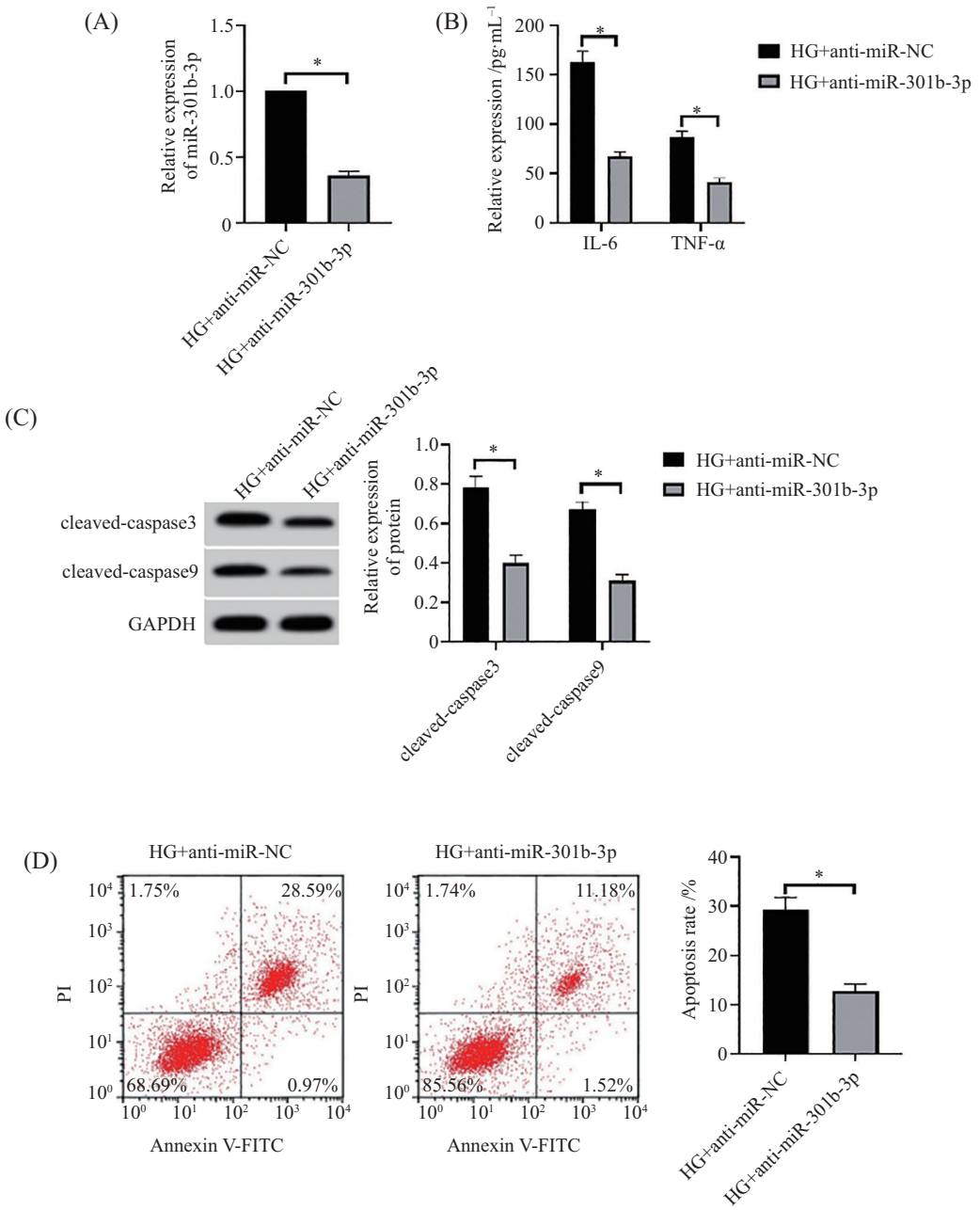
Fig.3 LncRNA PART1 interacts with miR-301b-3p

miR-301b-3p对细胞损伤的影响。如图5所示，相对于HG+pcDNA-PART1+miR-NC组，HG+pcDNA-PART1+miR-301b-3p组中miR-301b-3p、IL-6、TNF-α、cleaved-caspase3、cleaved-caspase9水平和凋亡率均升高(P<0.05)。结果表明，PART1通过靶向miR-301b-3p抑制其表达，进而抑制高糖诱导的HK-2细胞炎症和凋亡。

3 讨论

先前的研究已经提出了肾小管上皮细胞损伤可促进糖尿病肾病的进展，因而靶向减轻肾小管上皮细胞损伤能够为糖尿病肾病治疗提供新方向[8-9]。目前，大量的证据已经表明lncRNA可作为ceRNA，通过竞争性结合miRNA而影响其靶基因表达，进而调控糖尿病肾病的进展[10-11]。例如，lncRNA MALAT1在糖尿病肾病患者的肾组织和高糖刺激的HK-2细胞中表达显著上调，其敲低可通过促进miR-15b-5p表达逆转高糖对HK-2细胞凋亡和炎症的促进作用[12]。此外，lncRNA TUG1在糖尿病肾病小鼠肾组织和高糖刺激的NRK-52E细胞中表达下调，其可以通过靶向miR-21间接调控TIMP3的表达，进而抑制高糖诱导的NRK-52E细胞纤维化和肾纤维化[13]。LncRNA CASC2在糖尿病肾病小鼠模型和高糖诱导的人肾小球系膜细胞(human renal mesangial cells, HRMCs)中表达下调，其可通过调节miR-144/SOCS2轴减轻糖尿病肾病模型的凋亡、炎症和纤维化程度[14]。LncRNA NEAT2在高糖诱导的HK-2细胞中表达水平升高，下调NEAT2的表达可降低TNF-α、IL-6和MCP-9的表达水平，且NEAT2通过靶向miR-206促进高糖诱导的HK-2细胞炎症和焦亡[15]。以上证据表明，揭示有效的lncRNA和miRNA可能为糖尿病肾病的治疗提供新思路。

PART1是一种与疾病有关的lncRNA，被证实在多种疾病中差异表达。LncRNA PART1在上皮性卵巢癌组织中的表达水平增加，其可以海绵化miR-150靶向上调*MYB*基因的表达，进而促进上皮性卵巢癌细胞的增殖、迁移和侵袭[16]。PART1在喉鳞癌组织和细胞系中均过表达，其敲低可通过调控miR-185-5p/Six1轴显著抑制喉鳞癌细胞的增殖、侵袭和迁移，并促进细胞凋亡[17]。此外，lncRNA PART1在帕金森病模型中表达水平降低，过表达lncRNA PART1可抑制细胞凋亡、降低炎症因子表达水平和减少活性氧的产生[18]。LncRNA PART1在缺血再灌注心脏和缺氧/复氧(hypoxia/reoxygenation, H/R)心肌细胞中表达下调，其敲低可促进H/R心肌细胞凋亡和线粒体损伤，且进一步分析显示lncRNA PART1通过靶



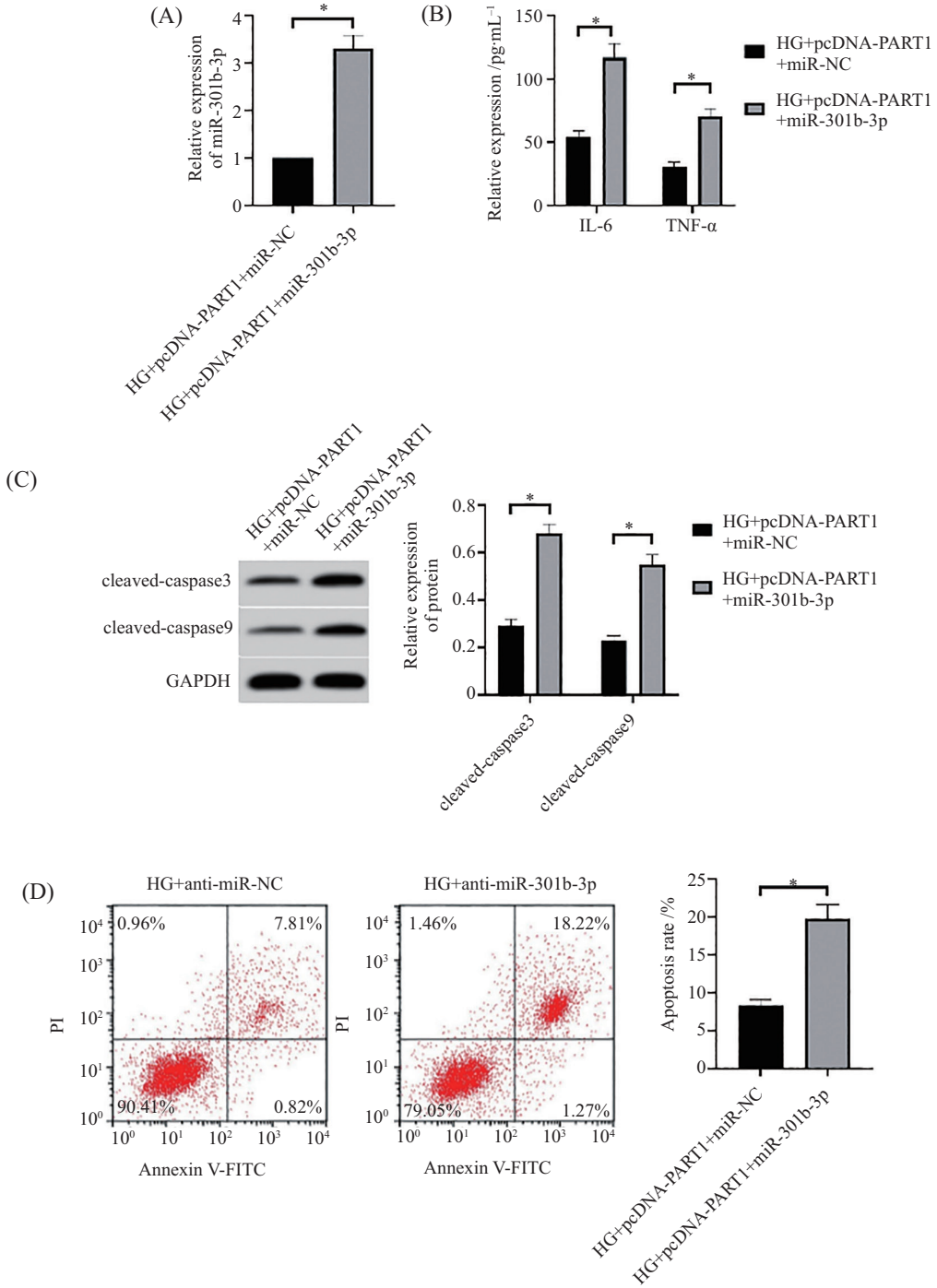
A: qRT-PCR检测miR-301b-3p表达水平; B: ELISA检测炎症因子(IL-6和TNF-α)的水平; C: Western blot检测凋亡相关蛋白(cleaved-caspase3、cleaved-caspase9)的水平; D: 流式细胞术分析细胞凋亡率。*P<0.05。

A: the expression level of miR-301b-3p was detected by qRT-PCR; B: ELISA was used to detect the levels of inflammatory factors (IL-6 and TNF-α); C: Western blot was used to detect the levels of apoptosis-related proteins (cleaved-caspase3, cleaved-caspase9); D: flow cytometry was used to analyze the apoptosis rate of cells. *P<0.05.

图4 干扰miR-301b-3p表达减轻高糖诱导的肾小管上皮细胞损伤

Fig.4 Interfering with miR-301b-3p expression alleviates the injury of renal tubular epithelial cells induced by high glucose

向miR-503-5p/BIRC5抑制心肌缺血再灌注中细胞凋亡并改善线粒体功能[19]。以上研究证实lncRNA PART1具有保护细胞免受损伤的作用。既往的研究显示, 尿PART1可能是糖尿病肾病患者的诊断标志物[20]。然而, 尚未知lncRNA PART1是否通过调控高糖诱导的肾小管上皮细胞损伤介导糖尿病肾病进展。本研究证实了lncRNA PART1的水平在高糖诱导的HK-2细胞中降低, 表明其可能参与了糖尿病肾病进展。与先前文献报道结果[21-22]相似, 我们的数据证实了IL-6、TNF-α的水平在高糖诱导的肾小管上皮细胞中升高, 表明了细胞损伤模型构建成功。此外, 本研究结果显示上调lncRNA PART1可降



A: qRT-PCR检测miR-301b-3p表达水平; B: ELISA检测炎症因子(IL-6和TNF-α)的水平; C: Western blot检测凋亡相关蛋白(cleaved-caspase3、cleaved-caspase9)的水平; D: 流式细胞术分析细胞凋亡率。*P<0.05。

A: the expression level of miR-301b-3p was detected by qRT-PCR; B: ELISA was used to detect the levels of inflammatory factors (IL-6 and TNF-α); C: Western blot was used to detect the levels of apoptosis-related proteins (cleaved-caspase3, cleaved-caspase9); D: flow cytometry was used to analyze the apoptosis rate of cells. *P<0.05.

图5 LncRNA PART1通过靶向miR-301b-3p减轻高糖诱导的HK-2细胞损伤

Fig.5 LncRNA PART1 alleviates high glucose-induced HK-2 cell injury by targeting miR-301b-3p

低高糖诱导的HK-2细胞中IL-6、TNF-α、cleaved-caspase3、cleaved-caspase9水平，并抑制细胞凋亡。与既往的研究[18-19]类似，我们的结果提示lncRNA PART1过表达抑制高糖诱导的肾小管上皮细胞炎症和凋亡，表明lncRNA PART1可以保护细胞免受损伤，进而延缓糖尿病肾病的进展。

miR-301b-3p已经被证实在多种疾病中差异表达，且可以参与调控多种人类疾病进展。既往的研究显示，miR-301b-3p在乳腺癌细胞系中表达水平升高，通过探究其在乳腺癌中的生物学功能，发现miR-301b-3p可以促进乳腺癌细胞增殖、迁移和侵袭，进而加快乳腺癌恶性进展[23]。此外，miR-301b-3p在肺腺癌的恶性进展中发挥重要作用，其在肺腺癌组织和细胞中的表达上调，且过表达后可以促进肿瘤细胞的增殖、迁移和侵袭[24]。另外，miR-301b-3p显著增加LPS诱导的人中耳上皮细胞活力，减轻细胞凋亡和炎症，表明miR-301b-3p可能是急性中耳炎的临床治疗靶点[25]。此外，在帕金森病细胞模型中，miR-301b-3p表达上调，其可通过诱导细胞凋亡而引发神经元细胞损伤[26]。然而，miR-301b-3p在糖尿病肾病进展中的作用尚不清楚。在这次研究中，我们的数据证实了lncRNA PART1可靶向调控miR-301b-3p。同时，本研究证明了miR-301b-3p在高糖诱导的HK-2细胞中高表达，其下调降低高糖诱导的HK-2细胞的中IL-6、TNF-α、cleaved-caspase3、cleaved-caspase9水平，并抑制细胞凋亡。同时，高表达miR-301b-3p可削弱上调lncRNA PART1对高糖诱导的HK-2细胞中IL-6、TNF-α、cleaved-caspase3、cleaved-caspase9水平和凋亡的抑制作用，表明lncRNA PART1可通过靶向miR-301b-3p抑制高糖诱导的肾小管上皮细胞炎症和凋亡，进而减缓糖尿病肾病的进展。

当然，本研究还存在一些局限。目前我们仅在细胞水平进行探究，未来仍然需要收集临床样本以及开展动物实验进一步证实PART1/miR-301b-3p轴的作用。此外，我们仅指出PART1通过靶向miR-301b-3p调控高糖诱导的肾小管上皮细胞损伤，尚未对PART1/miR-301b-3p轴的下游具体靶基因及信号通路进行探究。未来，我们将进一步揭示PART1/miR-301b-3p轴的下游机制，进一步完善PART1调控细胞损伤的全貌。当然，PART1的序列中还存在其他miRNA结合位点，但是目前本研究仅揭示了PART1对miR-301b-3p的调控作用，关于PART1是否也通过调控其他miRNA介导高糖诱导的肾小管上皮细胞损伤还需要在未来进一步揭示。

综上所述，我们的研究显示，lncRNA PART1通过靶向调控miR-301b-3p抑制高糖诱导的肾小管上皮细胞炎症反应及凋亡，进而减轻细胞损伤。PART1/miR-301b-3p轴的发现为糖尿病肾病的治疗提供了潜在分子靶点。但lncRNA PART1是否可通过充当其他miRNA的ceRNA分子而发挥作用尚需进一步探究。

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