circTLK1通过调控miR-374a-5p表达对高糖诱导的肾小球系膜细胞损伤的影响

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摘要 为探讨circTLK1对高糖诱导的肾小球系膜细胞损伤的影响及分子机制, 该研究将人肾小球系膜细胞HMCL分为对照(Con)组、高糖(HG)组、HG+si-NC组、HG+si-circTLK1组、HG+miR-NC组、HG+miR-374a-5p组、HG+si-circTLK1+anti-miR-NC组、HG+si-circTLK1+anti-miR-374a-5p组。采用RT-qPCR检测circTLK1和miR-374a-5p的表达水平; ELISA检测TNF-α、IL-6水平; MTT检测细胞增殖活性; Western blot法检测蛋白表达; 双荧光素酶报告实验验证circTLK1和miR-374a-5p的靶向关系。结果显示, 高糖诱导的肾小球系膜细胞中circTLK1、TNF-α、IL-6、CyclinD1表达水平及细胞活性升高, miR-374a-5p、p21表达水平降低(P<0.05)。下调circTLK1表达或过表达miR-374a-5p, 高糖诱导的肾小球系膜细胞中TNF-α、IL-6、CyclinD1表达水平和细胞活性降低, p21表达水平升高(P<0.05)。circTLK1靶向调控miR-374a-5p; 抑制miR-374a-5p表达逆转了下调circTLK1表达对高糖诱导的肾小球系膜细胞损伤的作用。该研究得出, 下调circTLK1表达可能通过上调miR-374a-5p抑制高糖诱导的肾小球系膜细胞损伤。

关键词 circTLK1; miR-374a-5p; 肾小球系膜细胞; 增殖; 炎症因子

The Effect of circTLK1 on the Glomerular Mesangial Cells Injury Induced by High Glucose by Regulating the Expression of miR-374a-5p

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Abstract To explore the effect of circTLK1 on the glomerular mesangial cells injury induced by high glucose and its molecular mechanism, this study divided the human glomerular mesangial cells HMCL into Con (control) group, HG (high glucose) group, HG+si-NC group, HG+si-circTLK1 group, HG+miR-NC group, HG+miR-374a-5p group, HG+si-circTLK1+anti-miR-NC group, HG+si-circTLK1+anti-miR-374a-5p group. RT-qPCR was used to detect the expressions of circTLK1 and miR-374a-5p; ELISA was used to detect TNF-α and IL-6 levels; MTT was used to detect cell proliferation; Western blot was used to detect protein expression; dual luciferase report experiment was used to verify targeting relationship between circTLK1 and miR-374a-5p. The results showed that in glomerular mesangial cells induced by high glucose, the expression levels of circTLK1, TNF-α, IL-6, CyclinD1 and the cell viability were increased, the expression of miR-374a-5p and p21 was decreased (P<0.05). Down-regulation of circTLK1 expression or over-expression of miR-374a-5p, the expression levels of TNF-α, IL-6, CyclinD1 in glomerular mesangial cells induced by high glucose and the cell viability was decreased, the expression of p21 was increased (P<0.05). circTLK1 targeted and regulated miR-374a-5p; inhibition of miR-374a-5p expres-

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sion reversed the effect of down-regulation of circTLK1 expression on high glucose-induced glomerular mesangial cell damage. The study concluded that down-regulation of circTLK1 expression might inhibit high glucose-induced glomerular mesangial cells injury by up-regulating miR-374a-5p.

Keywords circTLK1; miR-374a-5p; glomerular mesangial cells; proliferation; inflammatory factors

糖尿病肾病是糖尿病的一种常见并发症, 以系膜细胞增生、细胞外基质沉积及肾小球硬化为主要特征[1]。肾小球系膜细胞是肾小球中最活跃的固有细胞成分, 其异常过度增殖可导致肾小球硬化, 且其可分泌炎症因子, 促进细胞外基质的积累, 造成肾小球系膜细胞损伤, 影响糖尿病肾病的发病过程[2-3]。因此, 抑制肾小球系膜细胞损伤对延缓糖尿病肾病进展具有十分重要的意义。研究表明, circRNA与包括糖尿病性肾病在内的肾脏疾病的发病机理有关, 可能参与多种肾脏疾病的病理学过程[4]。研究报道, circTLK1可通过调节miR-136-5p及miR-495-3p/CBL轴促进肾细胞癌的增殖和转移[5-6]。而circTLK1对肾小球系膜细胞损伤的影响及机制尚不清楚。StarBase在线软件预测发现, circTLK1的序列中含有与miR-374a-5p互补的核苷酸序列。研究报道, miR-374a-5p过表达通过抑制NLRP3炎症信号的激活可减轻脑损伤, 并减少促炎因子的释放[7]。miR-374a-5p过表达可改善体内和体外缺血模型中的心肌细胞损伤[8]。但miR-374a-5p在高糖诱导的肾小球系膜细胞损伤中的作用以及circTLK1是否靶向调控miR-374a-5p的表达目前还尚未可知。因此, 本实验旨在研究circTLK1是否通过靶向调控miR-374a-5p影响高糖诱导的肾小球系膜细胞损伤。

1 材料与方法

1.1 材料

人肾小球系膜细胞株(HMCL)(货号: HTX1990)购自深圳市豪地华拓生物科技有限公司; DMEM培养基(货号: A90113)购自上海吉至生化科技有限公司; 葡萄糖(货号: CS0798)购自北京凯瑞基生物科技有限公司; Trizol试剂(货号: GMS12279)购自厦门慧嘉生物科技有限公司; 荧光定量PCR试剂盒(货号: R6617-01)购自广州威佳科技有限公司; TNF-α、IL-6酶联免疫吸附试剂盒(货号: E-EL-H0109c、E-EL-H0192c)购自武汉巴菲尔生物技术服务有限公司; MTT试剂盒(货号: BYX588C)购自常州贝源鑫生物科技有限公司; RIPA蛋白裂解液(货号: DB0150)购自北京康佳宏原生物科技有限公司; SDS-PAGE试剂盒(货号: PA106-01)购自北京博迈德基因技术有限公司; 双荧光素酶报告基因检测试剂盒(货号: AAT-12535)购自上海宇劲生物技术有限公司。

1.2 方法

1.2.1 细胞处理与分组 人肾小球系膜细胞HMCL用含10%胎牛血清的DMEM培养基培养, 将用含5.5 mmol/L葡萄糖的DMEM培养基培养的细胞作为正常对照组(Con): 将用含30 mmol/L葡萄糖的DMEM培养基培养24 h的细胞作为高糖组(HG); 将si-NC、si-circTLK1、miR-NC、miR-374a-5p转染至HMCL细胞中, 转染6 h后再用含30 mmol/L葡萄糖的DMEM培养基培养细胞24 h, 分别作为HG+si-NC组、HG+si-circTLK1组、HG+miR-NC组、HG+miR-374a-5p组; 将si-circTLK1分别与anti-miR-NC、anti-miR-374a-5p组共转染至HMCL细胞中, 转染6 h后再用含30 mmol/L葡萄糖的DMEM培养基培养细胞24 h, 作为HG+si-circTLK1+anti-miR-NC组、HG+si-circTLK1+anti-miR-374a-5p组。

1.2.2 实时荧光定量PCR(RT-qPCR)检测circTLK1和miR-374a-5p的表达水平 用Trizol试剂提取细胞总RNA, 反转录成cDNA, 然后进行PCR, PCR反应体系: 2 μL反转录产物, 10 μL SYBR Green Mix, 上下游引物各0.5 μL, 7 μL无菌水; 循环条件: 95 °C预变性2 min; 95 °C变性30 s, 60 °C退火30 s, 72 °C延伸30 s, 共40个循环; 熔解曲线: 95 °C 15 s, 60 °C 15 s, 95 °C 15 s。相对表达量用$2^{-\Delta\Delta Ct}$法计算。circTLK1和miR-374a-5p分别以*GAPDH*和*U6*为内参, circTLK1上游引物序列: 5′-CAG TCA ATG GAG CAG AGA A-3′, 下游引物序列: 5′-CCA TTC TTG TTG CCT TTT TG-3′; *GAPDH*上游引物序列: 5′-GAA AGC CTG CCG GTG ACT AA-3′, 下游引物序列: 5′-GCG CCC AAT ACG ACC AAA TC-3′; miR-374a-5p上游引物序列: 5′-TTA TAA TAC AAC CTG ATA AGT G-3′, 下游引物序列: 5′-TAT GGT TGT TCT CTG CTC TGT CTC-3′; *U6*上游引物序列: 5′-CTC GCT TCG GCA GCA CA-3′, 下游引物序列: 5′-AAC GCT TCA CGA ATT

TGC GT-3′。

1.2.3 酶联免疫吸附试验(ELISA) 各组细胞培养48 h后取上清, 按照ELISA试剂盒说明书操作, 用空白调零, 酶标仪测定D_{450}值。以标准物的浓度为横坐标, D值为纵坐标, 在坐标纸上绘出标准曲线, 根据样品的D值通过标准曲线计算出TNF-α、IL-6相应的浓度。

1.2.4 MTT实验 各组细胞消化后以1×10^4个/孔密度接种细胞于96孔板中, 培养48 h后每孔分别加入20 μL的MTT溶液, 孵育4 h, 每孔加入150 μL DMSO, 振荡反应10 min, 用酶标仪检测波长为450 nm处吸光度(D)值。

1.2.5 Western blot实验 提取细胞总蛋白, 定量后取50 μL蛋白样品于10%的SDS-PAGE上进行电泳, 然后转至PVDF膜上, 用5%的脱脂牛奶在室温下封闭1 h, 分别加入p21、CyclinD1的抗体(1:800), 在4 °C条件下孵育过夜, 洗膜后加入二抗(1:2 000)室温孵育2 h, 暗室中显影、定影; Quantity-One软件分析蛋白条带的灰度值, 然后计算目的蛋白相对表达水平。

1.2.6 双荧光素酶报告实验 构建circTLK1的野生型和突变型荧光素酶表达载体WT-circTLK1和MUT-circTLK1, 用Lipofectamine™ 2000将其分别与miR-NC和miR-374a-5p共转染至肾小球系膜细胞中, 转染48 h后按照试剂盒说明书检测荧光素酶活性。

1.3 统计学分析

用SPSS 20.0软件进行统计学分析, 本研究相关数据均为计量资料, 且符合正态分布, 用均数±标准差($\bar{x}\pm s$)表示, 两组比较行t检验, 多组间比较采用单因素方差分析, 组间两两比较采用LSD-t检验。以P<0.05为差异有统计学意义。

2 结果

2.1 circTLK1和miR-374a-5p在高糖诱导的肾小球系膜细胞中的表达

与正常对照组相比, 高糖组肾小球系膜细胞中circTLK1表达水平升高, miR-374a-5p表达水平降低(P<0.05)(图1)。

2.2 下调circTLK1表达对高糖诱导的肾小球系膜细胞炎症因子表达的影响

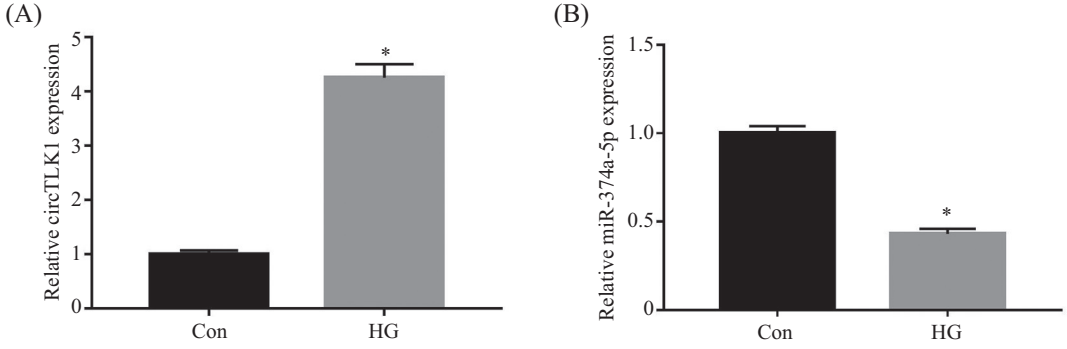
与正常对照组相比, 高糖组肾小球系膜细胞中circTLK1、TNF-α、IL-6表达水平升高(P<0.05); 与HG+si-NC组比较, HG+si-circTLK1组肾小球系膜细胞中circTLK1、TNF-α、IL-6表达水平降低(P<0.05)(图2)。

2.3 下调circTLK1表达对高糖诱导的肾小球系膜细胞增殖的影响

与Con组比较, HG组细胞活性升高, p21表达水平降低, CyclinD1表达水平升高(P<0.05); 与HG+si-NC组比较, HG+si-circTLK1组细胞活性降低, p21表达水平升高, CyclinD1表达水平降低(P<0.05)(图3)。

2.4 circTLK1靶向调控miR-374a-5p的表达

StarBase预测显示, circTLK1的序列中含有与miR-374a-5p互补的核苷酸序列(图4A)。miR-374a-5p与WT-circTLK1共转染后的细胞荧光素酶活性降低(P<0.05), miR-374a-5p与MUT-circTLK1共转染后的细胞荧光素酶活性无显著变化(图4B)。与pcDNA组比较, pcDNA-circTLK1组miR-374a-5p表达水平降低; 与si-NC组比较, si-circTLK1组miR-374a-5p表达水平升高(P<0.05)(图4C)。

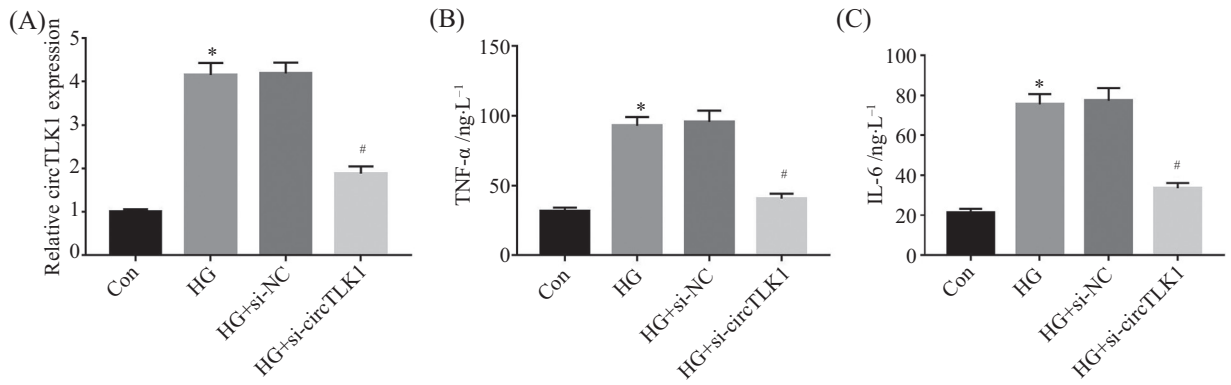


A: circTLK1在高糖诱导的肾小球系膜细胞中的表达; B: miR-374a-5p在高糖诱导的肾小球系膜细胞中的表达。*P<0.05, 与Con组比较。

A: the expression of circTLK1 in the glomerular mesangial cells induced by high glucose; B: the expression of miR-374a-5p in the glomerular mesangial cells induced by high glucose. *P<0.05 compared with Con group.

图1 circTLK1和miR-374a-5p在高糖诱导的肾小球系膜细胞中的表达

Fig.1 The expression of circTLK1 and miR-374a-5p in the glomerular mesangial cells induced by high glucose

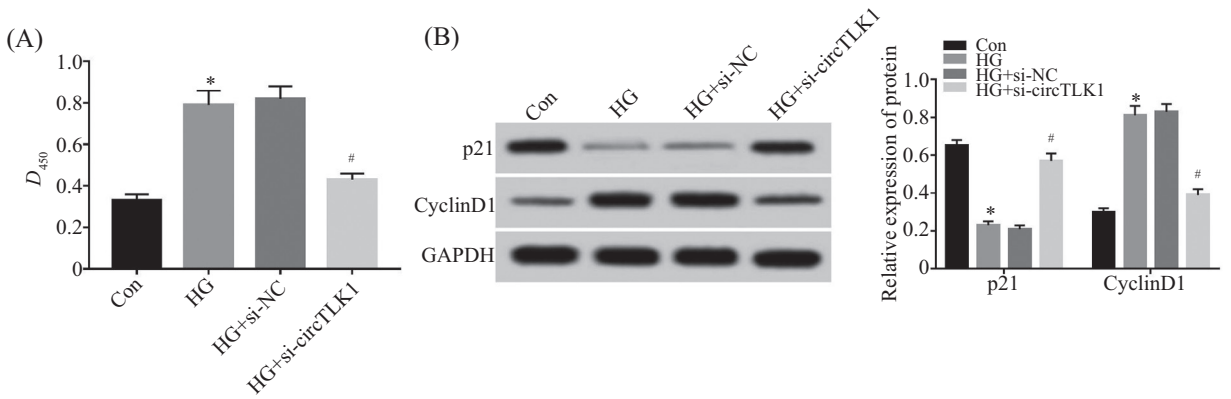


A: circTLK1相对表达量; B: 下调circTLK1表达对高糖诱导的肾小球系膜细胞TNF-α表达的影响; C: 下调circTLK1表达对高糖诱导的肾小球系膜细胞IL-6表达的影响。*P<0.05, 与Con组比较; #P<0.05, 与HG+si-NC组比较。

A: relative expression of circTLK1; B: the effect of down-regulation of circTLK1 expression on the expression of TNF-α in glomerular mesangial cells induced by high glucose; B: the effect of down-regulation of circTLK1 expression on the expression of IL-6 in glomerular mesangial cells induced by high glucose. *P<0.05 compared with Con group; #P<0.05 compared with HG+si-NC group.

图2 下调circTLK1表达对高糖诱导的肾小球系膜细胞炎症因子表达的影响

Fig.2 The effect of down-regulation of circTLK1 expression on the expression of inflammatory factors in glomerular mesangial cells induced by high glucose



A: 下调circTLK1表达对高糖诱导的肾小球系膜细胞D值的影响; B: 下调circTLK1表达对高糖诱导的肾小球系膜细胞增殖相关蛋白表达的影响。*P<0.05, 与Con组比较; #P<0.05, 与HG+si-NC组比较。

A: the effect of down-regulating the expression of circTLK1 on the D value of glomerular mesangial cells induced by high glucose; B: the effect of down-regulating the expression of circTLK1 on proliferation related protein expression of glomerular mesangial cells induced by high glucose. *P<0.05 compared with Con group; #P<0.05 compared with HG+si-NC group.

图3 下调circTLK1表达对高糖诱导的肾小球系膜细胞增殖的影响

Fig.3 The effect of down-regulating the expression of circTLK1 on the proliferation of glomerular mesangial cells induced by high glucose

2.5 miR-374a-5p过表达对高糖诱导的肾小球系膜细胞炎症因子表达及细胞增殖的影响

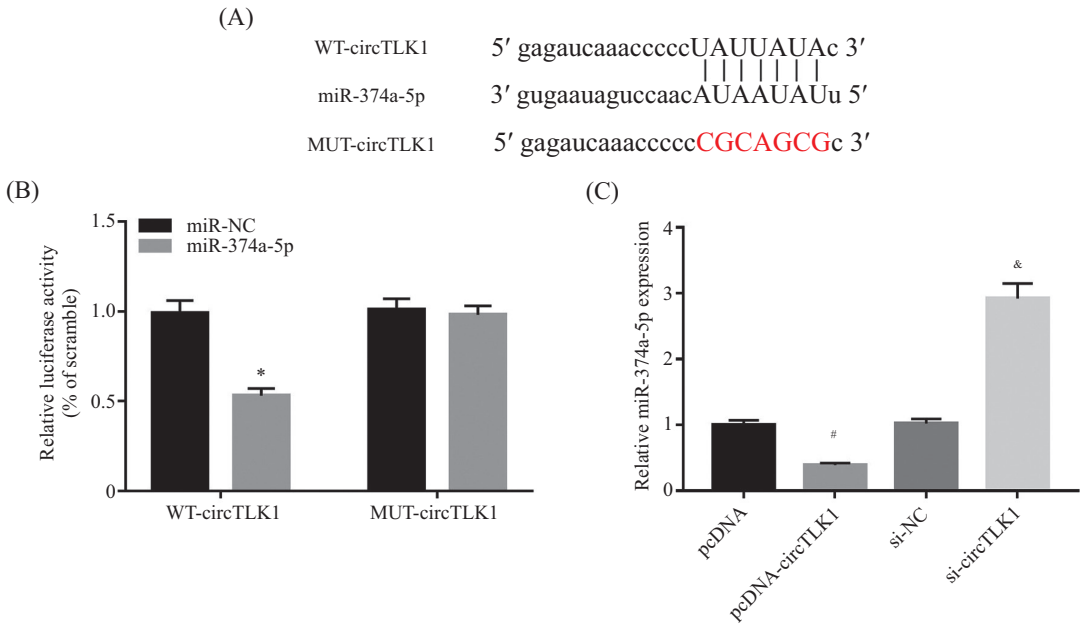
与HG+miR-NC组比较, HG+miR-374a-5p组miR-374a-5p表达水平升高, TNF-α、IL-6水平降低, 细胞活性降低, p21表达水平升高, CyclinD1表达水平降低(P<0.05)(图5)。

2.6 抑制miR-374a-5p表达逆转了下调circTLK1表达对高糖诱导的肾小球系膜细胞损伤的作用

与HG+si-circTLK1+anti-miR-NC组比较, HG+si-circTLK1+anti-miR-374a-5p组miR-374a-5p表达水平降低, TNF-α、IL-6水平升高, 细胞活性升高, p21表达水平降低, CyclinD1表达水平升高(P<0.05)(图6)。

3 讨论

在高血糖情况下, 肾小球系膜细胞增殖、细胞外基质积累和炎症的异常调节显著促进糖尿病性肾病的发生和发展[9-10]。因此, 抑制肾小球系膜细胞的异常增殖及炎症反应从而减轻肾小球系膜细胞损伤

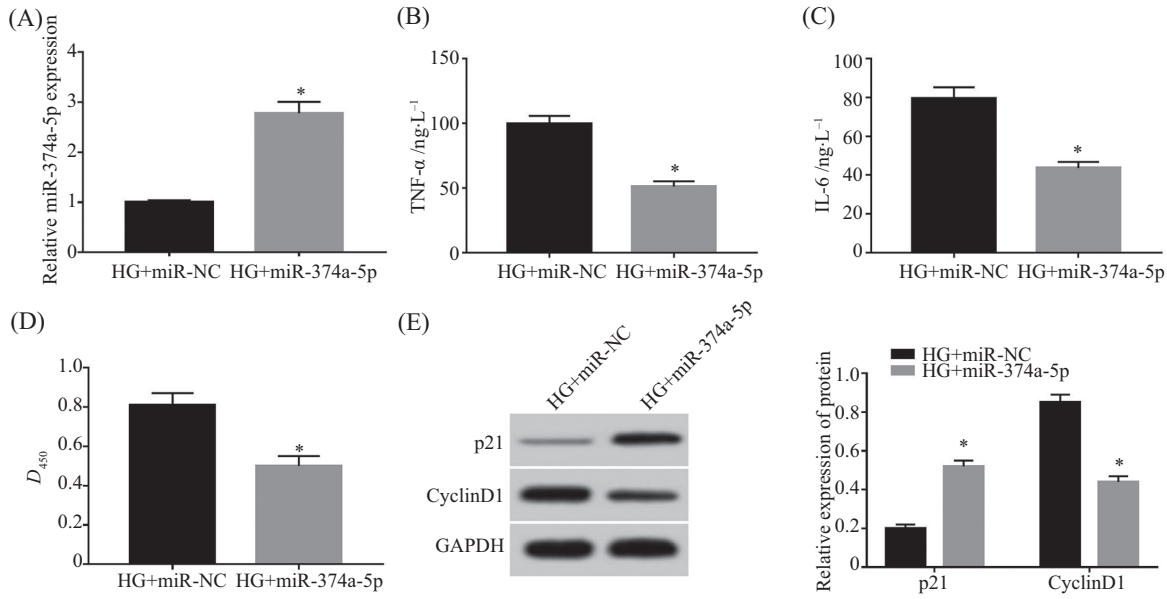


A: circTLK1的序列中含有与miR-374a-5p互补的核苷酸序列(红色字母为突变序列); B: 双荧光素酶报告实验; C: circTLK1调控miR-374a-5p的表达。*P<0.05, 与miR-NC组比较; #P<0.05, 与pcDNA组比较; &P<0.05, 与si-NC组比较。

A: the sequence of circTLK1 contains a nucleotide sequence complementary to miR-374a-5p (the red letters are the mutant sequences); B: double luciferase report experiment; C: circTLK1 regulates the expression of miR-374a-5p. *P<0.05 compared with miR-NC group; #P<0.05 compared with pcDNA group; &P<0.05 compared with si-NC group.

图4 circTLK1靶向调控miR-374a-5p的表达

Fig.4 circTLK1 targets miR-374a-5p expression

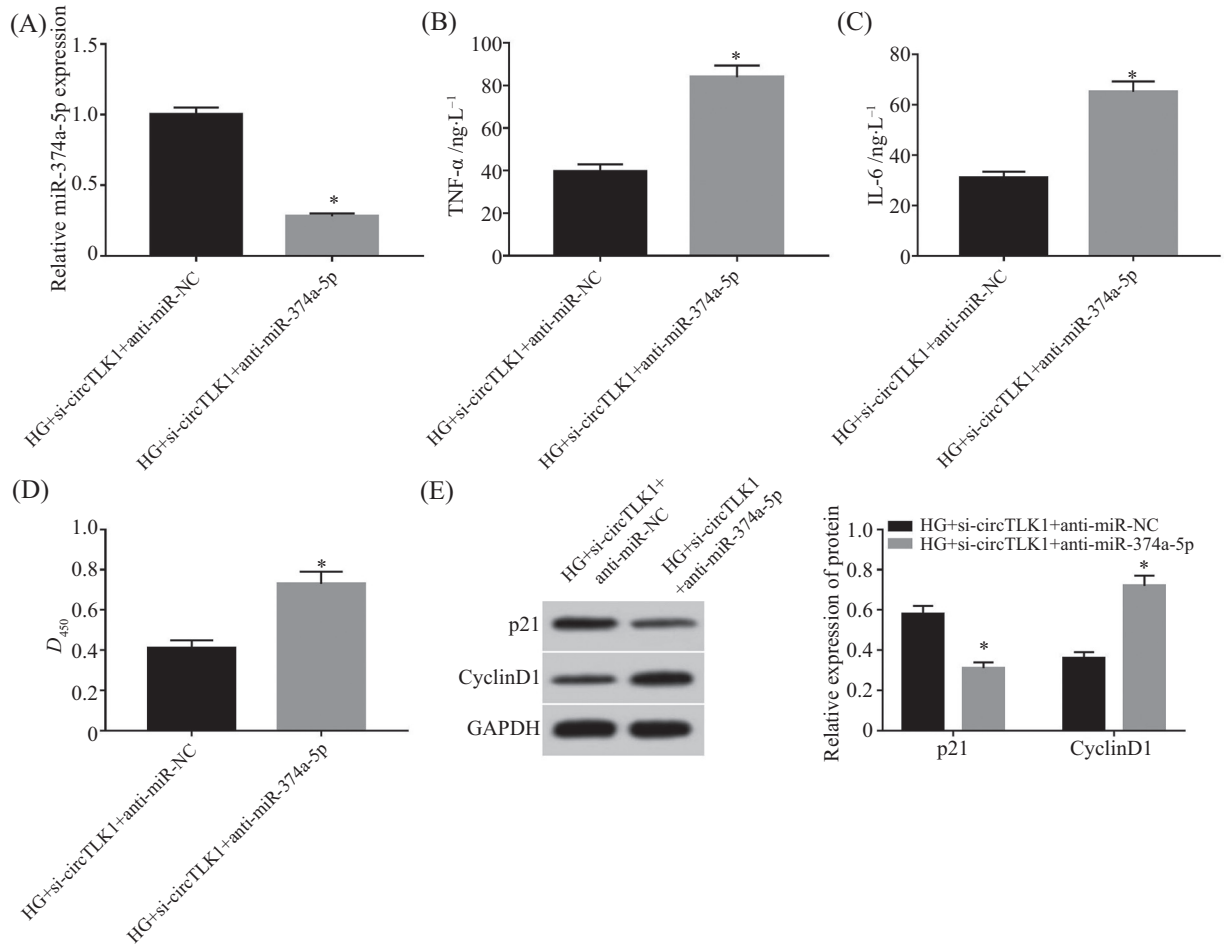


A: miR-374a-5p相对表达量; B: miR-374a-5p过表达对高糖诱导的肾小球系膜细胞TNF-α表达的影响; C: miR-374a-5p过表达对高糖诱导的肾小球系膜细胞IL-6表达的影响; D: miR-374a-5p过表达对高糖诱导的肾小球系膜细胞D值的影响; E: miR-374a-5p过表达对高糖诱导的肾小球系膜细胞增殖相关蛋白表达的影响。*P<0.05, 与HG+miR-NC组比较。

A: relative expression of miR-374a-5p; B: the effect of miR-374a-5p overexpression on the expression of TNF-α induced by high glucose in glomerular mesangial cell; C: the effect of miR-374a-5p overexpression on the expression of IL-6 induced by high glucose in glomerular mesangial cells; D: the effect of miR-374a-5p overexpression on the D value of glomerular mesangial cells induced by high glucose; E: the effect of miR-374a-5p overexpression on proliferation related protein expression of glomerular mesangial cells induced by high glucose. *P<0.05 compared with HG+miR-NC group.

图5 miR-374a-5p过表达对高糖诱导的肾小球系膜细胞炎症因子表达及细胞增殖的影响

Fig.5 The effect of miR-374a-5p overexpression on the expression of inflammatory cytokines and cell proliferation induced by high glucose in glomerular mesangial cells



A: miR-374a-5p相对表达量; B: 抑制miR-374a-5p表达逆转了下调circTLK1表达对高糖诱导的肾小球系膜细胞TNF-α表达的作用; C: 抑制miR-374a-5p表达逆转了下调circTLK1表达对高糖诱导的肾小球系膜细胞IL-6表达的作用; D: 抑制miR-374a-5p表达逆转了下调circTLK1表达对高糖诱导的肾小球系膜细胞*D*值的作用; E: 抑制miR-374a-5p表达逆转了下调circTLK1表达对高糖诱导的肾小球系膜细胞增殖相关蛋白表达的作用; **P*<0.05, 与HG+si-circTLK1+anti-miR-NC组比较。

A: relative expression of miR-374a-5p; B: inhibition of miR-374a-5p expression reversed the effect of down-regulation of circTLK1 expression on TNF-α expression of high glucose-induced glomerular mesangial cells; C: inhibition of miR-374a-5p expression reversed the effect of down-regulation of circTLK1 expression on IL-6 expression of high glucose-induced glomerular mesangial cells; D: inhibition of miR-374a-5p expression reversed the effect of down-regulation of circTLK1 expression on the *D* value of high glucose-induced glomerular mesangial cells; E: inhibition of miR-374a-5p expression reversed the effect of down-regulation of circTLK1 expression on proliferation related protein expression of high glucose-induced glomerular mesangial cells. **P*<0.05 compared with HG+si-circTLK1+anti-miR-NC group.

图6 抑制miR-374a-5p表达逆转了下调circTLK1表达对高糖诱导的肾小球系膜细胞损伤的作用

Fig.6 Inhibition of miR-374a-5p expression reversed the effect of down-regulation of circTLK1 expression on high glucose-induced glomerular mesangial cells injury

是防治糖尿病肾病的重要途径, 研究表明, circRNA参与调控肾小球系膜细胞的增殖外基质积累及炎症反应过程; 如circLRP6可通过海绵化miR-205调节高糖诱导的肾小球系膜细胞增殖、氧化应激、细胞外基质积累和炎症, 造成系膜细胞损伤[11]。circ-AKT3通过调节miR-296-3p/E-cadherin信号抑制糖尿病肾病系膜细胞的外基质积累[12]。Circ_0080425通过使miR-24-3p海绵化抑制糖尿病肾病中系膜细胞增殖和纤维化[13]。研究报道, circTLK1通过靶向miR-214/RIPK1介导的TNF信号通路, 可加重心肌缺血/再灌注损伤[14]。敲除circTLK1通过miR-335-3p/TIPARP可以减轻神经元损伤并改善神经功能缺损[15]。而circTLK1对肾小球系膜细胞损伤的影响尚不清楚。本实验用高糖诱导的肾小球系膜细胞建立损伤模型, 结果显示, 高糖诱导的肾小球系膜细胞中circTLK1表达水平升高; 提示circTLK1可能与高糖诱导的肾小球系膜细胞损伤有关。本实验进一步下调circTLK1表达后, 高糖诱导的肾小球系膜细胞

中TNF-α、IL-6水平降低, 细胞活性降低; 表明下调circTLK1可抑制高糖诱导的肾小球系膜细胞增殖及炎性因子的释放, 即下调circTLK1可减轻高糖诱导的肾小球系膜细胞损伤。

为进一步研究circTLK1影响肾小球系膜细胞损伤的可能机制, 我们通过在线软件预测circTLK1可能靶向结合的miRNA, 结果发现circTLK1与miR-374a-5p有结合位点。研究报道, miR-374a过表达可抑制糖尿病性肾病中的炎症反应[16]。miR-374a还可抑制金柑苷对大鼠结肠炎的作用[17]。本实验中, 高糖诱导的肾小球系膜细胞中miR-374a-5p表达水平降低; 过表达miR-374a-5p可降低高糖诱导的肾小球系膜细胞中TNF-α、IL-6水平及细胞活性; 表明miR-374a-5p可能也影响糖尿病性肾病的炎症反应。然后通过实验验证circTLK1靶向调控miR-374a-5p; 且抑制miR-374a-5p表达逆转了下调circTLK1表达对高糖诱导的肾小球系膜细胞损伤的作用。提示, circTLK1可能通过调控miR-374a-5p影响高糖诱导的肾小球系膜细胞损伤。

综上所述, 下调circTLK1表达可抑制高糖诱导的肾小球系膜细胞损伤, 在糖尿病肾病的发生发展中具有重要作用, 其机制可能与上调miR-374a-5p表达有关。

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