



miR-328-3p对氧化型低密度脂蛋白诱导的冠状动脉内皮细胞损伤的保护作用及机制研究*

侯永兰, 李霞, 王建美, 刘振, 韩明磊, 刘杰昊, 金卫东[△]

新乡市中心医院 心血管内科(新乡 453000)

【摘要】目的 探讨miR-328-3p对氧化型低密度脂蛋白(oxidized low-density lipoprotein, ox-LDL)诱导的冠状动脉内皮细胞损伤的保护作用及可能相关的作用机制。**方法** 用ox-LDL诱导人冠状动脉内皮细胞(human coronary artery endothelial cells, HCAECs),将细胞分为对照(control)组(正常培养细胞)、ox-LDL组(ox-LDL处理)、ox-LDL+miR-NC组(转染miR-NC,用ox-LDL处理)、ox-LDL+miR-328-3p组(转染miR-328-3p,用ox-LDL处理)、ox-LDL+miR-328-3p+pcDNA组(共转染miR-328-3p和pcDNA,用ox-LDL处理)、ox-LDL+miR-328-3p+胰岛素样生长因子2(insulin-like growth factor 2, IGF2)组(共转染miR-328-3p和IGF2,用ox-LDL处理)。RT-qPCR检测miR-328-3p表达水平;MTT以及流式细胞术检测细胞增殖和凋亡;Western blot法检测cleaved cas-3、IGF2、Bax、Bcl-2蛋白含量;ELISA法检测肿瘤坏死因子- α (tumor necrosis factor α , TNF- α)、白细胞介素(interleukin, IL)-6、IL-1 β 含量;应用双荧光素酶报告实验验证分子间靶向关系。**结果** 与control组相比,ox-LDL组中miR-328-3p表达水平、细胞活性降低($P<0.05$),凋亡率,cleaved cas-3、IGF2蛋白表达,TNF- α 、IL-6、IL-1 β 水平增加($P<0.05$)。与ox-LDL+miR-NC组相比,ox-LDL+miR-328-3p组miR-328-3p表达水平、细胞活性增加($P<0.05$),凋亡率,cleaved cas-3、IGF2蛋白表达,TNF- α 、IL-6、IL-1 β 水平降低($P<0.05$)。IGF2是miR-328-3p的功能靶标。与共转染ox-LDL+miR-328-3p+pcDNA组比较,共转染ox-LDL+miR-328-3p+IGF2组IGF2蛋白水平升高($P<0.05$),细胞活性降低($P<0.05$),而凋亡率、cleaved cas-3蛋白水平以及TNF- α 、IL-6、IL-1 β 含量升高($P<0.05$)。**结论** miR-328-3p通过靶向负调控IGF2抑制ox-LDL诱导的冠状动脉内皮细胞凋亡和炎性损伤。

【关键词】 miR-328-3p 胰岛素样生长因子2 氧化型低密度脂蛋白 冠状动脉内皮细胞

Protective Effect and Mechanism of miR-328-3p on Coronary Artery Endothelial Cell Injury Induced by Oxidized Low-density Lipoprotein HOU Yonglan, LI Xia, WANG Jianmei, LIU Zhen, HAN Minglei, LIU Zhenghao, JIN Weidong[△]. Department of Cardiovascular Medicine, Xinxiang Central Hospital, Xinxiang 453000, China

[△] Corresponding author, E-mail: jwdtreasure@163.com

【Abstract】 Objective To investigate the protective effect of miR-328-3p on oxidized low-density lipoprotein (ox-LDL)-induced coronary artery endothelial cell injury and the potentially relevant mechanisms. **Methods** Human coronary artery endothelial cells (HCAECs) were induced with ox-LDL, and the cells were divided into a control group consisting of normal cells, an ox-LDL group receiving ox-LDL treatment, an ox-LDL+miR-NC group transfected with miR-NC and treated with ox-LDL, an ox-LDL+miR-328-3p group transfected with miR-328-3p and treated with ox-LDL, and ox-LDL+miR-328-3p+pcDNA group co-transfected miR-328-3p and pcDNA and treated with ox-LDL, and an ox-LDL+miR-328-3p+insulin-like growth factor 2 (IGF2) group co-transfected miR-328-3p and IGF2 and treated with ox-LDL. The expression level of miR-328-3p was determined with RT-qPCR. Cell proliferation was determined by MTT. Cell apoptosis was measured by flow cytometry. Western blot was conducted to examine the protein expression levels of cleaved cas-3 and IGF2. ELISA was performed to determine the levels of tumor necrosis factor α (TNF- α), interleukin (IL)-6, and IL-1 β . Dual luciferase reporter experiment was performed to verify the targeting relationship between miR-328-3p and IGF2. **Results** Compared with those of the control group, miR-328-3p expression level and cell activity were significantly reduced in the ox-LDL group ($P<0.05$), while the apoptotic rate, the protein expression levels of cleaved cas-3, IGF2, Bax, and Bcl-2, and the levels of TNF- α , IL-6, and IL-1 β were significantly increased ($P<0.05$). Compared with those of the ox-LDL+miR-NC group, miR-328-3p expression level and cell activity significantly increased in the ox-LDL+miR-328-3p group ($P<0.05$), while the apoptosis rate, the protein expression levels of cleaved cas-3 and IGF2, and the levels of TNF- α , IL-6, and IL-1 β were significantly reduced. IGF2 was a functional target of miR-328-3p. Compared with those of the ox-LDL+miR-328-3p+pcDNA co-transfection group, the IGF2 protein level was significantly increased ($P<0.05$) and cell activity was significantly decreased ($P<0.05$) in the ox-LDL+miR-328-3p+IGF2 co-transfection group, while the apoptosis rate, cleaved cas-3 protein level, and the levels of TNF- α , IL-6, and IL-1 β were significantly elevated ($P<0.05$). **Conclusion** miR-328-3p inhibits ox-LDL-induced apoptosis and inflammatory in coronary artery endothelial cell injury through targeted negative regulation of IGF2.

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[△] 通信作者, E-mail: jwdtreasure@163.com

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Coronary artery endothelial cells

动脉粥样硬化是心血管疾病常见的疾病之一,也是冠心病、脑梗死、缺血性心脏病等心血管疾病主要的原因^[1]。研究报道显示,氧化型低密度脂蛋白(oxidized low-density lipoprotein, ox-LDL)与动脉粥样硬化的形成密切相关,常用于诱导建立动脉粥样硬化细胞模型^[2]。miRNA是单链非编码RNA的转录本,不具有编码蛋白质的能力,与细胞增殖、凋亡、炎症反应等有关,进而影响动脉粥样硬化等疾病的发展^[3-4]。有研究结果显示,miR-328-3p与ox-LDL、颈动脉内中膜厚度(carotid intima-media thickness, cIMT)有关^[5],在ox-LDL诱导的人脐静脉内皮细胞(human umbilical vein endothelial cells, HUVEC)中表达下调,过表达miR-328-3p可抑制ox-LDL诱导的HUVEC增殖、迁移和侵袭,并促进细胞凋亡、自噬和炎症损伤^[6],但是对ox-LDL诱导的人冠状动脉内皮细胞(human coronary artery endothelial cells, HCAECs)的研究机制尚不清楚。胰岛素样生长因子2(insulin-like growth factor 2, IGF2)与动脉粥样硬化的发病有关^[7],在动脉粥样硬化患者和ox-LDL诱导的HUVEC中表达上调,SNHG12通过调控miR-218-5p/IGF2轴促进ox-LDL诱导的HUVEC凋亡和炎症反应^[8],但是对ox-LDL诱导的HCAECs的研究尚不清楚。使用生物信息学软件预测显示miR-328-3p与IGF2存在相互结合位点,鉴于此,本研究采用ox-LDL诱导的HCAECs,探究miR-328-3p可能通过调控IGF2对ox-LDL诱导的HCAECs细胞损伤的保护作用及机制。

1 材料与方法

1.1 细胞和主要试剂

ox-LDL购于上海经科化学公司;HCAECs购于武汉普诺赛公司;miR-NC、miR-328-3p、pcDNA、IGF2、引物由上海吉玛公司设计合成;胎牛血清、DMEM培养基、Lipofectamine 2000试剂盒购于美国Thermo公司;北京百奥莱博科技有限公司提供Trizol试剂盒、逆转录试剂盒以及PCR试剂盒;由碧云天生物提供MTT试剂盒、BCA试剂盒以及凋亡试剂盒;一抗(cleaved cas-3、IGF2、Bax、Bcl-2以及GAPDH抗体)购于美国Abcam公司;二抗购于北京中杉金桥公司;于上海江莱生物购买肿瘤坏死因子- α (tumor necrosis factor α , TNF- α)、白细胞介素(interleukin, IL)-6以及IL-1 β 试剂盒;北京索莱宝公司提供双荧光素酶检测试剂盒以及电化学发光试剂。

1.2 细胞培养和分组

于含有10%胎牛血清的DMEM培养基内培养HCAECs,

培养条件:37℃以及5%CO₂(体积分数)。取对数期的HCAECs,以 1×10^5 个/孔接种于24孔内,细胞融合至60%时,按照Lipofectamine 2000试剂盒说明书将miR-NC、miR-328-3p、miR-328-3p和pcDNA、miR-328-3p和IGF2转染至细胞内,转染6 h换细胞液用50 mg/L ox-LDL处理细胞,记为ox-LDL+miR-NC组、ox-LDL+miR-328-3p组、ox-LDL+miR-328-3p+pcDNA组、ox-LDL+miR-328-3p+IGF2组;另设control组(正常培养细胞)和ox-LDL组(用50 mg/L ox-LDL处理细胞)。细胞培养48 h用于后续实验。

1.3 RT-qPCR检测miR-328-3p表达水平

将细胞与1 mL Trizol混合均匀提取总RNA,随后逆转录生成cDNA。以cDNA为模板在PCR仪上进行扩增反应。用2^{- $\Delta\Delta C_t$} 法计算miR-328-3p相对内参U6的表达量。

1.4 MTT检测细胞增殖活性

将处理后的各组细胞(2×10^3 个)与20 μ L MTT试剂共置于96孔板每孔中,室温孵育4 h后,每孔加入150 μ L二甲基亚砷溶解MTT结晶,随后检测490 nm处的吸光度(A)值。

1.5 流式细胞术

收集处理后的各组细胞,磷酸缓冲液洗涤后,重悬于含有5 μ L Annexin V-FITC和5 μ L PI染液的结合缓冲液,避光反应15 min,于1 h内检测凋亡细胞。

1.6 Western blot

将各组细胞与蛋白裂解液共孵育提取总蛋白,用10% SDS-PAGE分离蛋白,然后电转移到PVDF膜上,随后5%脱脂奶粉封闭1 h。清洗后,将cleaved cas-3(稀释1:500)、IGF2(稀释1:500)、Bax(稀释1:500)、Bcl-2(稀释1:500)、以及GAPDH(稀释1:1000)一抗与膜4℃下孵育过夜,随后37℃下将膜二抗(稀释1:2500)孵育1 h。最后加入电化学发光试剂,显色、曝光,Image Lab软件分析灰度值。

1.7 ELISA法

通过离心收集各组细胞的上清液,然后按照试剂盒说明书,检测细胞内TNF- α 、IL-6以及IL-1 β 表达量。

1.8 双荧光素酶报告实验检测miR-328-3p、IGF2靶向关系

miR-328-3p与IGF2 3'UTR区域存在结合位点,构建IGF2 3'UTR区域野生型荧光素酶载体和突变型荧光素酶载体(IGF2 WT和IGF2 MUT)。收集HCAECs接种24孔板中,按照脂质体法将IGF2 WT和IGF2 MUT分别与miR-NC或miR-328-3p共转染至细胞内,48 h后检测胞内荧光素酶活性。

1.9 统计学方法

采用SPSS 19.0软件对实验数据进行分析,计量结果以 $\bar{x} \pm s$ 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,两两比较采用Dunnett-*t*法。 $\alpha=0.05$ 。

2 结果

2.1 miR-328-3p在ox-LDL诱导冠状动脉内皮细胞内表达与control组比较,ox-LDL组miR-328-3p表达水平降低($P<0.05$);与ox-LDL+miR-NC组相比,ox-LDL+miR-328-3p组miR-328-3p表达水平升高($P<0.05$)。见图1。

2.2 上调miR-328-3p对ox-LDL诱导冠状动脉内皮细胞凋亡的影响

ox-LDL组相较于control组细胞活性降低,而凋亡率以及cleaved cas-3、Bax蛋白表达升高,Bcl-2蛋白表达降低($P<0.05$);ox-LDL+miR-328-3p组对比ox-LDL+miR-NC组细胞活性升高,而凋亡率及cleaved cas-3、Bax蛋白表达下降,Bcl-2蛋白表达升高($P<0.05$)。见图2。

2.3 上调miR-328-3p对ox-LDL诱导冠状动脉内皮细胞炎症因子的影响

ox-LDL处理后,对比control组,细胞中TNF- α 、IL-6、IL-1 β 表达上调($P<0.05$);ox-LDL+miR-328-3p组对比ox-

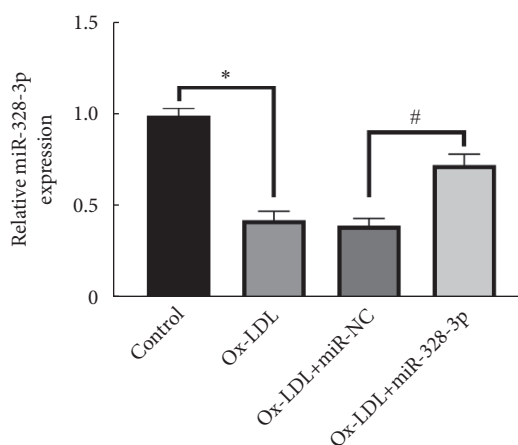


图 1 miR-328-3p在ox-LDL诱导冠状动脉内皮细胞内的表达

Fig 1 miR-328-3p expression in ox-LDL-induced coronary artery endothelial cells

* $P<0.05$, # $P<0.05$. $n=9$

LDL+miR-NC组细胞低表达TNF- α 、IL-6、IL-1 β ($P<0.05$)。见图3。

2.4 miR-328-3p和IGF2关系

生物信息学软件预测显示,miR-328-3p和IGF2存在

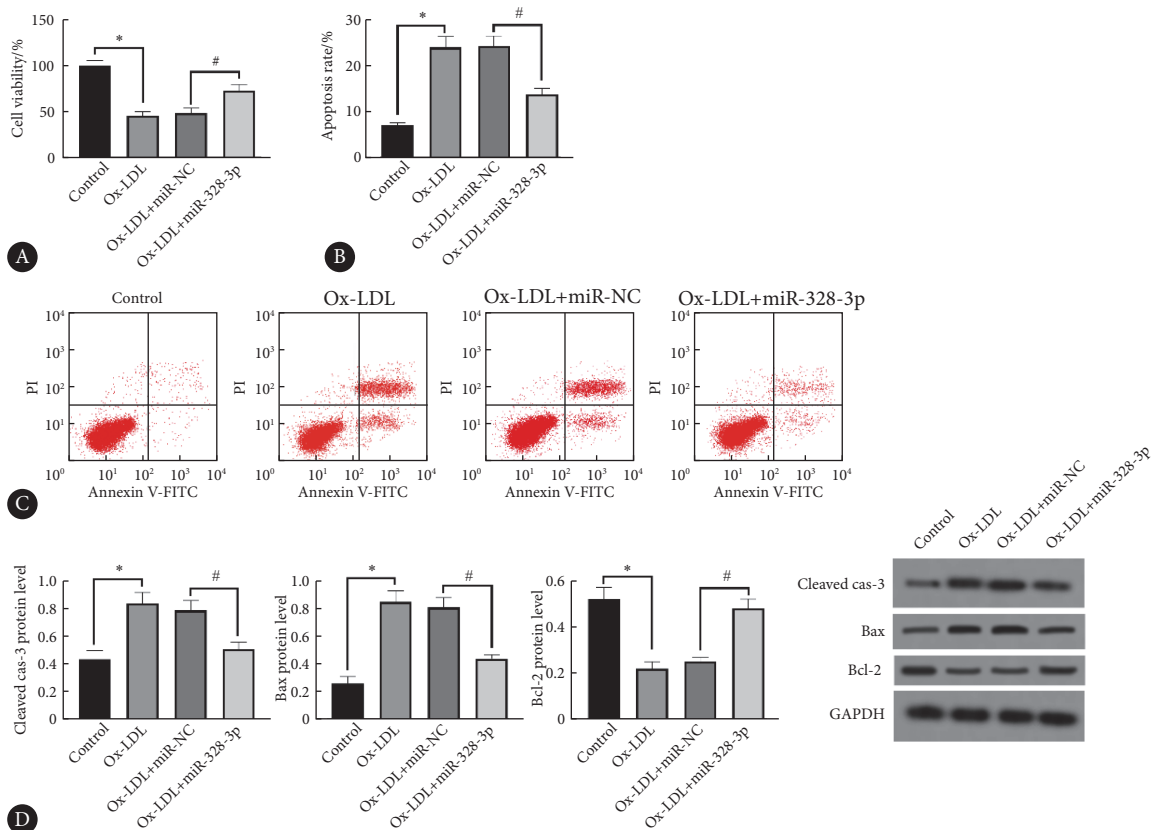


图 2 上调miR-328-3p对ox-LDL诱导冠状动脉内皮细胞凋亡的影响

Fig 2 Effect of upregulation of miR-328-3p on ox-LDL-induced apoptosis in coronary artery endothelial cells

A, MTT assay performed to evaluate cell viability ($n=9$); B, apoptosis rate was determined by flow cytometry ($n=9$); C, flow cytometry; D, relative expression of cleaved cas-3, Bax, and Bcl-2 proteins was assessed by Western blot ($n=3$). * $P<0.05$, # $P<0.05$.

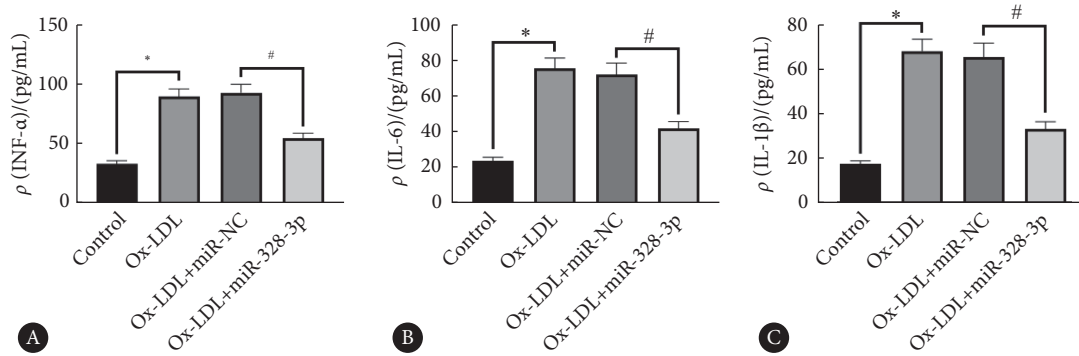


图 3 上调miR-328-3p对ox-LDL诱导冠状动脉内皮细胞炎症因子的影响

Fig 3 Effect of upregulation of miR-328-3p on ox-LDL-induced inflammatory factors in coronary artery endothelial cells

A, TNF-α level was evaluate by ELISA (n=9); B, IL-6 level was determined by ELISA (n=9); C, IL-1β level was measured by ELISA (n=9). * P<0.05, # P<0.05.

互补核苷酸序列。miR-328-3p组相较于miR-NC组IGF2 WT荧光素酶活性降低(P<0.05), miR-328-3p以及miR-NC均不影响IGF2 MUT荧光素酶活性, 见图4。

2.5 miR-328-3p调控IGF2的表达

与control组比较, ox-LDL组IGF2蛋白水平升高, 差异有统计学意义(P<0.05); 与ox-LDL+miR-NC组相比, ox-LDL+miR-328-3p组IGF2蛋白水平降低(P<0.05)。见图5。

2.6 过表达IGF2可以逆转miR-328-3p上调对ox-LDL诱导冠状动脉内皮细胞凋亡和炎症因子的影响

与ox-LDL+miR-328-3p+pcDNA组比较, ox-LDL+miR-328-3p+IGF2组IGF2蛋白水平升高, 细胞活性、Bcl-2蛋白水平降低, 而凋亡率、cleaved cas-3和Bax蛋白水平以及TNF-α、IL-6、IL-1β含量升高(P<0.05)。见图6。

3 讨论

动脉粥样硬化发病原因与遗传、肥胖因素、高血压、

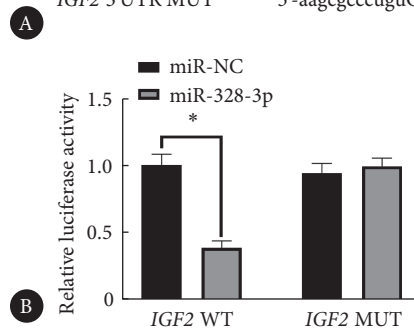
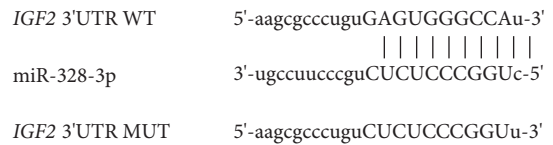


图 4 miR-328-3p和IGF2的关系

Fig 4 Relationship between miR-328-3p and IGF2

A, Complementary nucleotide sequences exist for miR-328-3p and IGF2; B, their relationship was validated using the dual luciferase reporter assay (n=9). * P<0.05.

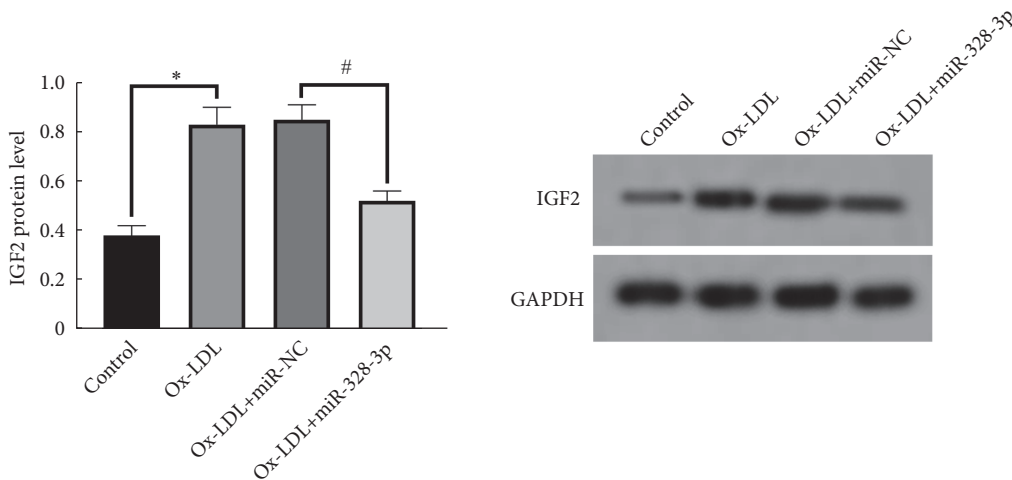


图 5 miR-328-3p调控IGF2的表达

Fig 5 miR-328-3p regulates the expression of IGF2

The relative expression of IGF2 protein was assessed by Western blot (n=3). * P<0.05, # P<0.05.

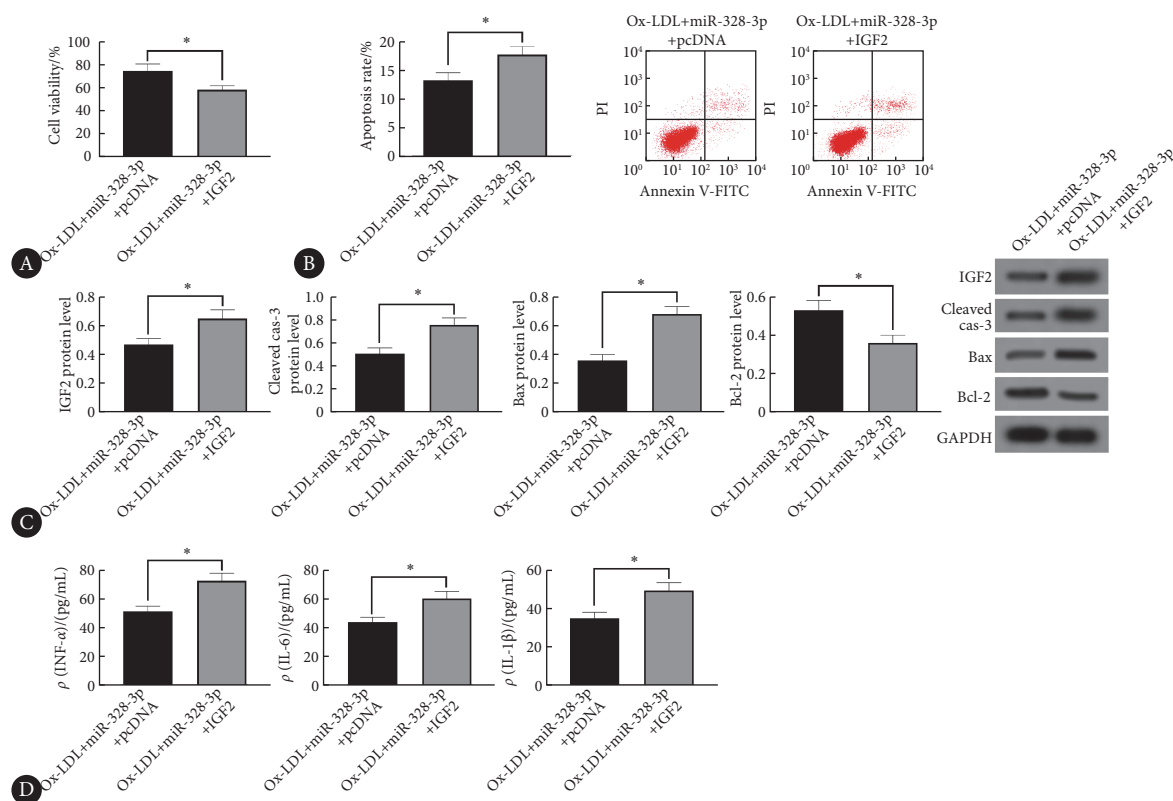


图 6 过表达 IGF2 可以逆转 miR-328-3p 上调对 ox-LDL 诱导冠状动脉内皮细胞凋亡和炎症因子的影响

Fig 6 Overexpression of IGF2 reverses the effects of miR-328-3p upregulation on ox-LDL-induced apoptosis and inflammatory factors in coronary endothelial cells

A, MTT assay was conducted to evaluate cell viability ($n=9$); B, apoptosis rate was determined by flow cytometry ($n=9$); C, the relative expression of IGF2, cleaved cas-3, Bax, and Bcl-2 proteins was assessed by Western blot ($n=3$); D, TNF- α , IL-6, and IL-1 β levels were measured by ELISA ($n=9$). * $P<0.05$.

高血脂等有关,其可在人体内存在数年不显示病态,早期诊断可有效缓解病情的发展,并减少相关疾病的发生,进而提高人们的生活质量和水平^[9-10]。研究结果显示,ox-LDL 含量过高时,可使胆固醇聚集在动脉壁上,进而引发动脉粥样硬化^[11]。本研究用 ox-LDL 诱导 HCAECs 建立细胞损伤模型,结果显示,细胞活性降低,凋亡率、cleaved cas-3 蛋白表达上调,炎症因子 TNF- α 、IL-6、IL-1 β 含量增加,提示细胞损伤模型构建成功。

研究结果显示,miRNA 在疾病发展中起着重要的作用,包括高血压、动脉粥样硬化等^[12-13],如 miR-328-3p 在氧糖剥夺的 HUVEC 中表达下调,上调 miR-328-3p 可减轻氧糖剥夺诱导的内皮细胞损伤^[6,14]。ZHANG 等^[6]研究结果显示,ox-LDL 诱导的 HUVEC 中 miR-328-3p 表达下调,过表达 miR-328-3p 可通过调控 TRIM14 减轻 ox-LDL 诱导的 HUVEC 凋亡和炎症反应。本研究结果显示,ox-LDL 诱导 HCAECs 后 miR-328-3p 表达下调,上调 miR-328-3p 可增加 ox-LDL 诱导的 HCAECs 细胞活性,降低凋亡率、cleaved cas-3 和 Bax 蛋白表达,提高 Bcl-2 蛋白表达,抑制炎症因子 TNF- α 、IL-6、IL-1 β 含量,提示上调 miR-328-3p 可减轻 ox-

LDL 诱导的 HCAECs 损伤。

IGF2 是胰岛素类激素家族成员,是一种依赖性多肽,与胰岛素原存在 42% 同源,对神经调节、心血管疾病、肿瘤发生等起着重要的作用^[15-16]。有研究结果显示,IGF2 与动脉粥样硬化发病密切相关,IGF2 在冠心病合并高血压患者血清内表达上调,与冠状动脉狭窄评分呈现正相关^[17]。有研究结果显示,IGF2 在 ox-LDL 诱导的 HUVEC 和血管平滑肌细胞 (VSMC) 内表达上调,miR-216b-5p 通过靶向负调控 IGF2 减轻 ox-LDL 诱导的 HUVEC 和人 VSMC 凋亡和促进增殖^[18]。YANG 等^[19]研究结果显示,ox-LDL 可诱导动脉粥样硬化动物模型中 IGF2 表达上调,miR-637 通过下调 IGF2 抑制动脉粥样硬化的发展。这些先前的数据表明了 IGF2 能够加剧 ox-LDL 诱导的 HUVEC 的损伤。本研究结果显示,ox-LDL 诱导 HCAECs 后 IGF2 蛋白表达上调,这与 miR-328-3p 的表达水平相反。通过生物信息学网站预测和双荧光素酶报告实验证明,IGF2 是 miR-328-3p 的靶基因。同时,本研究数据证实了上调 miR-328-3p 的水平可以使 IGF2 的表达水平下降,说明 miR-328-3p 负调控 IGF2 表达。进一步实验发现,过表达 IGF2 可以逆转上调

miR-328-3p对ox-LDL诱导HCAECs凋亡和炎症因子的抑制作用,提示miR-328-3p可以通过负调控IGF2减轻ox-LDL诱导的HCAECs损伤。

综上所述,上调miR-328-3p可以通过靶向IGF2对ox-LDL诱导的HCAECs损伤起到保护作用,为治疗动脉粥样硬化提供一定的理论证据。然而,相关机制需要进一步进行探究。

* * *

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