·论著·

miR-202-5p通过靶向抑制*ROCK1*表达减轻急性呼吸窘迫综合征新生大鼠肺损伤

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摘要 **目的** 探讨miR-202-5p对急性呼吸窘迫综合征(ARDS)新生大鼠肺损伤的保护作用及其机制。**方法** 60只新生SD大鼠随机分为对照组(腹腔注射生理盐水)、ARDS组[腹腔注射脂多糖(4 mg/kg)建立ARDS模型]、ARDS+miR-NC组[ARDS大鼠尾静脉注射miR-NC(2 mg/kg),1次/4 h,连续干预12 h]、ARDS+miR-202-5p组[ARDS大鼠尾静脉注射miR-202-5p(2 mg/kg),1次/4 h,连续干预12 h]、ARDS+miR-202-5p+ov-NC组[ARDS大鼠尾静脉注射miR-202-5p(2 mg/kg),1次/4 h,连续干预12 h;脂多糖注射前3 d尾静脉注射6×10^8 PFU过表达对照腺病毒]和ARDS+miR-202-5p+ov-ROCK1组[ARDS大鼠尾静脉注射miR-202-5p(2 mg/kg),1次/4 h,连续干预12 h;脂多糖注射前3 d尾静脉注射6×10^8 PFU过表达*ROCK1*腺病毒],每组10只。实时定量PCR检测大鼠肺组织中miR-202-5p和*ROCK1* mRNA表达;HE染色观察大鼠肺组织病理损伤;计算大鼠肺组织湿重/干重比值来评价大鼠肺水肿程度;Western blotting检测大鼠肺组织中ROCK1、TLR4、p-NF-κB p65和p-IκBα蛋白表达。双萤光素酶报告基因实验验证miR-202-5p与*ROCK1*的关系。**结果** miR-202-5p在ARDS大鼠肺组织中表达下调,过表达miR-202-5p可减轻ARDS大鼠肺组织病理损伤和肺水肿。*ROCK1* mRNA在ARDS大鼠肺组织中表达上调;过表达miR-202-5p降低ARDS大鼠肺组织中ROCK1表达,而过表达*ROCK1*逆转了过表达miR-202-5p对ARDS新生大鼠肺损伤的保护作用。过表达miR-202-5p抑制ARDS大鼠肺组织中TLR4、p-NF-κB p65和p-IκBα蛋白表达,过表达*ROCK1*逆转此作用。双萤光素酶报告基因实验结果显示miR-202-5p靶向结合*ROCK1* mRNA的3'UTR。**结论** miR-202-5p通过靶向抑制*ROCK1*表达减轻ARDS大鼠肺损伤,其机制可能与抑制*ROCK1*介导的TLR4/NF-κB信号通路激活有关。

关键词 急性呼吸窘迫综合征; miR-202-5p; ROCK1; TLR4/NF-κB信号通路; 肺损伤
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miR-202-5p alleviates lung injury in neonatal rats with acute respiratory distress syndrome by targeting the inhibition of *ROCK1* expression

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Abstract **Objective** To explore the protective effect and mechanism of miR-202-5p on acute respiratory distress syndrome (ARDS)-induced lung injury in neonatal rats. **Methods** Sixty newborn SD rats were randomly divided into six groups: the control group (intraperitoneal injection of normal saline by tail vein), ARDS group (ARDS model established via intraperitoneal injection of 4 mg/kg lipopolysaccharide by tail vein), ARDS+miR-NC group (ARDS rats receiving 2 mg/kg miR-NC via tail vein injection once every 4 h, with intervention for 12 h), ARDS+miR-202-5p group (ARDS rats receiving 2 mg/kg miR-202-5p via tail vein injection once every 4 h, with intervention for 12 h), ARDS+miR-202-5p+ov-NC group, and ARDS+miR-202-5p+ov-ROCK1 group (ARDS rats receiving 2 mg/kg miR-202-5p once every 4 h, with intervention for 12 h; with 6×10^8 plaque-forming units control or overexpression *ROCK* adenovirus administered via tail vein 3 days before lipopolysaccharide injection). Real-time quantitative PCR was employed to measure miR-202-5p and *ROCK1* mRNA expression in rat lung tissue. Hematoxylin and eosin staining was performed to assess pathological lung injury. The lung tissue wet-to-dry weight ratio was determined to evaluate pulmonary edema. Western blotting was utilized to analyze ROCK1, Toll-like receptor 4 (TLR4),

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phosphorylated-nuclear factor κB (p-NF-κB) p65, and phosphorylated-inhibitor of nuclear factor-κBα (p-IκBα) protein expression in lung tissue. The interaction between miR-202-5p and *ROCK1* was validated using dual-luciferase reporter gene experiments. **Results** miR-202-5p expression was significantly down-regulated in ARDS rat lung tissue, while overexpression of miR-202-5p ameliorated pathological injury and pulmonary edema in ARDS rats. *ROCK1* mRNA was upregulated in ARDS rat lung tissue; however, overexpression of miR-202-5p decreased the expression of ROCK1 in lung tissue of ARDS rats, while overexpression of *ROCK1* reversed the protective effect of overexpression of miR-202-5p on lung injury in ARDS rats. Furthermore, miR-202-5p overexpression suppressed TLR4, p-NF-κB p65, and p-IκBα protein expression in ARDS rat lung tissue, an effect that was reversed by *ROCK1* overexpression. Dual-luciferase reporter gene experiments confirmed that miR-202-5p directly targets *ROCK1* mRNA 3' UTR. **Conclusion** miR-202-5p ameliorates ARDS-induced lung injury in neonatal rats through targeted suppression of *ROCK1* expression, with the underlying mechanism potentially involving inhibition of *ROCK1*-mediated TLR4/NF-κB signaling pathway activation.

Keywords acute respiratory distress syndrome; miR-202-5p; *ROCK1*; TLR4/NF-κB signaling pathway; lung injury

急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS)是由原发性或继发性肺泡表面活性物质减少引起的呼吸系统疾病,进展迅速且死亡率高,严重威胁新生儿的生命。ARDS临床表现为气促、呼吸窘迫、低氧血症、双肺透光率下降甚至白肺[1]。在临床实践中,呼吸支持、肺表面活性物质替代治疗、体外膜肺氧合、营养支持和液体管理是新生儿ARDS的主要治疗方法[2]。然而,新生儿ARDS仍缺乏有效治疗方法。微RNA(microRNA, miRNA)作为一类基因调控分子,可通过影响靶基因的表达来调节炎症途径和免疫反应,在ARDS的发病机制中发挥重要作用[3]。LIANG等[4]研究发现miR-124-3p通过靶向抑制p65表达改善ARDS模型小鼠的炎症和肺损伤。HE等[5]研究发现miR-574-5p通过靶向抑制高迁移率族蛋白B1(high mobility group box 1, HMGB1)表达抑制核因子κB(nuclear factor-κB, NF-κB)信号通路和NLRP3炎症小体激活,从而抑制ARDS小鼠肺泡白细胞浸润、间质水肿、蛋白渗出和炎症。1项生物信息学研究[6]发现miR-202-5p在ARDS大鼠肺组织中表达下调。目前,miR-202-5p对ARDS诱导的肺损伤的影响及其机制研究尚未见报道。本研究通过腹腔注射脂多糖(lipopolysaccharide, LPS)建立新生大鼠ARDS模型,探讨过表达miR-202-5p对ARDS新生大鼠肺损伤的影响及其机制,旨在为ARDS治疗方法的开发提供新思路。

1　材料与方法

1.1　实验动物和细胞

SD孕鼠购自中国医科大学实验动物部,饲养于23~25 ℃,每日光照/黑暗各12 h的环境中。将新生SD大鼠饲养7 d,选取体重10~13 g的7日龄新生大鼠进行实验。本研究获得中国医科大学实验动物伦理委员会批准(审批号CMUKT2024175)。293T细胞购自武汉普诺赛生命科技有限公司,用DMEM培养基(含10%胎牛血清和1%青链霉素)在37 ℃、5 %CO_2条件下培养。

1.2　主要试剂和仪器

miR-NC、miR-202-5p、过表达对照腺病毒(ov-NC)和过表达*ROCK1*腺病毒(ov-ROCK1)由苏州吉玛基因股份有限公司合成。HE染色试剂盒购自北京索莱宝科技有限公司;Western blotting相关试剂购自上海碧云天生物技术有限公司;Western blotting一抗以及二抗购自英国abcam公司;实时定量PCR相关试剂购自日本TaKaRa公司。酶标仪购自美国BioTek公司;凝胶扫描成像系统购自美国Bio-Rad公司;普通PCR仪和实时定量PCR仪购自美国ABI公司;光学显微镜购自日本OLYMPUS公司。

1.3　方法

1.3.1　动物分组及处理:新生SD大鼠随机分为对照组、ARDS组、ARDS+miR-NC组、ARDS+miR-202-5p组、ARDS+miR-202-5p+ov-NC组和ARDS+miR-202-5p+ov-ROCK1组,每组10只。除对照组外,各组大鼠腹腔注射LPS (4 mg/kg)建立大鼠ARDS模型[7]。对照组大鼠腹腔注射等量生理盐水。ARDS+miR-NC组大鼠造模后尾静脉注射miR-NC (2 mg/kg), ARDS+miR-202-5p组、ARDS+miR-202-5p+ov-NC组和ARDS+miR-202-5p+ov-ROCK1组造模后尾静脉注射miR-202-5p (2 mg/kg),1次/4 h,连续干预12 h。ARDS+miR-202-5p+ov-NC组和ARDS+miR-202-5p+ov-ROCK1组分别于造模前3 d经尾静脉注射OV-NC、OV-ROCK1 (6×10^8 PFU)。实验结束后大鼠腹腔注射过量2%戊巴比妥钠麻醉处死,打开胸腔并暴露心肺,分离左肺和

右肺用于后续检测。

1.3.2　HE染色：将分离的左肺组织经4%多聚甲醛固定后，常规方法制备石蜡切片。切片经脱蜡水化后依次用苏木素和伊红染色，脱水透明封片后光学显微镜观察并拍照。

1.3.3　肺组织病理损伤：根据文献[8]方法对肺组织损伤程度进行评分。

1.3.4　肺组织水肿程度：将取出的肺组织剪去残存支气管和结缔组织，分离右肺膈叶和副叶，蒸馏水清洗并用吸水纸吸干水分，称量湿重。将称量后的肺组织放入60 ℃恒温烘箱内，烘干24 h至恒质量，称量干重。计算湿重/干重比值来评估肺组织水肿程度。

1.3.5　实时定量PCR：将收集的肺组织置于研钵中，液氮研磨处理。TRIzol法提取组织中总RNA，将RNA反转录为cDNA，检测miRNA的样本反转录时需加入逆转录引物。以cDNA为模板进行实时定量PCR，以*U6*或*β-actin*为内参，采用$2^{-\Delta\Delta Ct}$法计算目的基因的相对表达量。

1.3.6　Western blotting：将收集的肺组织液氮磨碎后用RIPA裂解液裂解，离心收集蛋白。BCA法定量后配置蛋白样品。煮样变性后电泳分离蛋白，湿转法将其转移至PVDF膜上。5%脱脂牛奶封闭后用ROCK1、Toll样受体4（Toll-like receptor 4，TLR4）、NF-κB p65、p-NF-κB p65、核因子κB抑制蛋白α（inhibitor of nuclear factor-κBα，IκBα）、p-IκBα和β-actin抗体4 ℃孵育过夜。PBST洗膜3次。二抗室温孵育1 h，PBST洗膜3次。ECL法发光，分析电泳条带灰度值并计算相对表达量。

1.3.7　双萤光素酶报告基因实验：*ROCK1*与miR-202-5p潜在结合位点采用TargetScan在线数据库（https://www.targetscan.org）预测。将ROCK1-WT或ROCK1-MUT与mimics NC或miR-202-5p mimics（由苏州吉玛基因股份有限公司合成）共转染293T细胞，培养24 h后收集并裂解，依次检测萤火虫和海肾萤光素酶活性。

1.4　统计学分析

采用SPSS 22.0软件进行统计学分析。符合正态分布的计量资料采用$\bar{x} \pm s$表示，组间比较采用单因素方差分析和Tukey法。$P < 0.05$为差异有统计学意义。

2　结果

2.1　ARDS大鼠肺组织miR-202-5p表达情况

实时定量PCR检测结果显示，对照组、ARDS组、ARDS+miR-NC组和ARDS+miR-202-5p组大鼠肺组织中miR-202-5p相对表达水平分别为0.99 ± 0.06、0.44 ± 0.07、0.43 ± 0.10、0.67 ± 0.09。与对照组比较，ARDS组和ARDS+miR-NC组大鼠肺组织中miR-202-5p表达明显降低（$P < 0.05$）；与ARDS组和ARDS+miR-NC组比较，ARDS+miR-202-5p组大鼠肺组织中miR-202-5p表达明显升高（$P < 0.05$）。

2.2　过表达miR-202-5p对ARDS大鼠肺组织病理损伤的影响

HE染色结果显示，对照组大鼠肺泡结构完整且腔内未见渗出物；ARDS组和ARDS+miR-NC组大鼠肺泡萎缩且完整性破坏，可见充血和大量红细胞浸润；ARDS+miR-202-5p组大鼠肺组织上述病理损伤有所改善。ARDS组和ARDS+miR-NC组大鼠肺组织病理损伤评分较对照组明显升高（$P < 0.05$）；与ARDS组和ARDS+miR-NC组比较，ARDS+miR-202-5p组大鼠肺组织病理损伤评分明显降低（$P < 0.05$）。见图1。

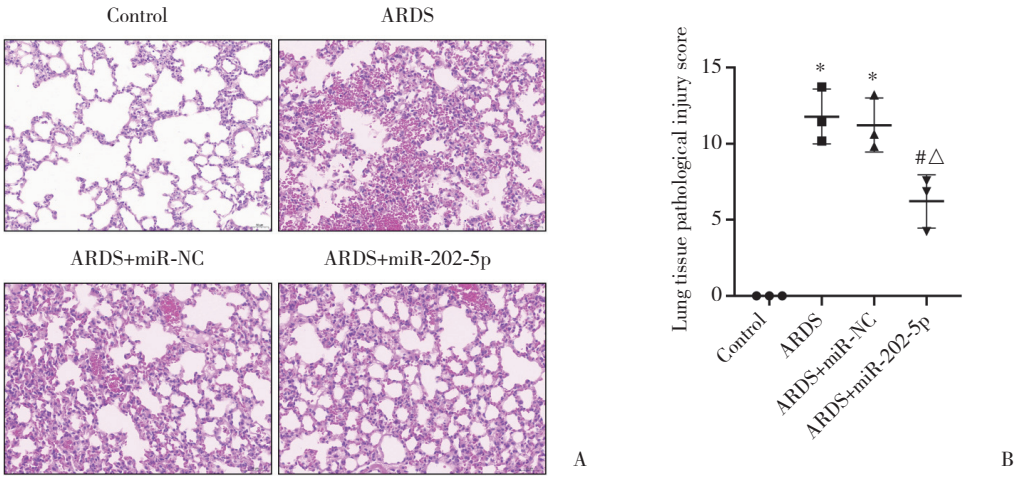
2.3　过表达miR-202-5p对ARDS大鼠肺组织水肿程度的影响

结果显示，对照组、ARDS组、ARDS+miR-NC组和ARDS+miR-202-5p组大鼠肺组织的湿重/干重比值分别为4.89 ± 0.31、10.31 ± 0.42、10.06 ± 0.59、7.69 ± 0.50。ARDS组和ARDS+miR-NC组大鼠肺组织湿重/干重比值较对照组明显升高（$P < 0.05$）；与ARDS组和ARDS+miR-NC组比较，ARDS+miR-202-5p组大鼠肺组织湿重/干重比值明显降低（$P < 0.05$）。可见过表达miR-202-5p可减轻ARDS大鼠肺组织水肿程度。

2.4　过表达miR-202-5p对ARDS大鼠肺组织中ROCK1和TLR4/NF-κB信号通路的影响

对照组、ARDS组、ARDS+miR-NC组和ARDS+miR-202-5p组大鼠肺组织中*ROCK1* mRNA相对表达量分别为1.05 ± 0.08、3.61 ± 0.45、3.35 ± 0.30、1.80 ± 0.21。与对照组比较，ARDS组和ARDS+miR-NC组大鼠肺组织中*ROCK1* mRNA和蛋白以及TLR4、p-NF-κB p65和p-IκBα蛋白表达水平明显升高（$P < 0.05$）；与ARDS组和ARDS+miR-NC组比较，ARDS+miR-202-5p

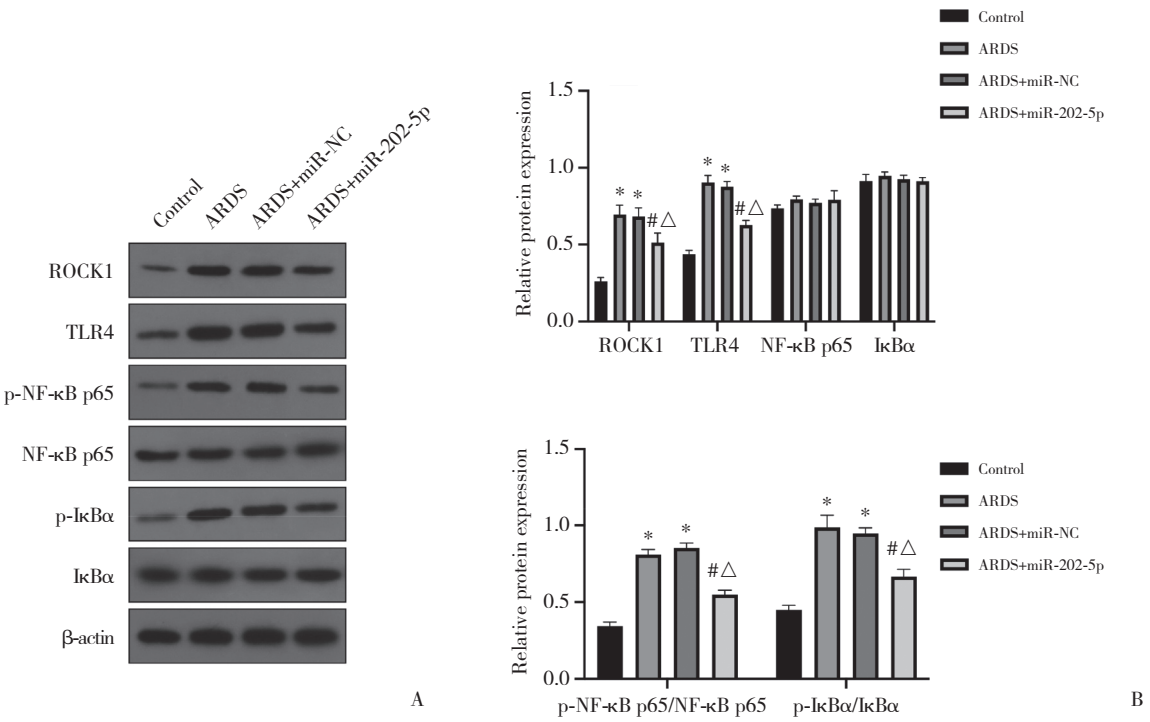
组大鼠肺组织中*ROCK1* mRNA和蛋白以及TLR4、p-NF-κB p65和p-IκBα蛋白表达水平明显降低（$P<0.05$）。各组新生大鼠肺组织中NF-κB p65和IκBα蛋白表达水平比较无统计学差异（$P>0.05$）。见图2。



A, HE staining (×200); B, lung tissue pathological injury score. * $P<0.05$ vs. control group; # $P<0.05$ vs. ARDS group; △ $P<0.05$ vs. ARDS+miR-NC group.

图1　各组大鼠肺组织病理损伤比较

Fig.1　Comparison of lung tissue pathological injury of rats in each group



* $P<0.05$ vs. control group; # $P<0.05$ vs. ARDS group; △ $P<0.05$ vs. ARDS+miR-NC group.

图2　各组大鼠肺组织中ROCK1和TLR4/NF-κB信号通路蛋白的表达

Fig.2　Expression of ROCK1 and TLR4/NF-κB signaling pathway related proteins in lung tissue of rats in each group

2.5　miR-202-5p与*ROCK1*的靶向关系

双萤光素酶报告基因实验结果显示，与mimics NC组比较，转染ROCK1-WT的miR-202-5p mimics组293T细胞的相对萤光素酶活性明显降低（$P<0.05$），而转染ROCK1-MUT的mimics NC组与miR-202-5p mimics组293T细胞的相对萤光素酶活性比较无

统计学差异（$P>0.05$），见图3。可见，miR-202-5p可靶向结合*ROCK1*。

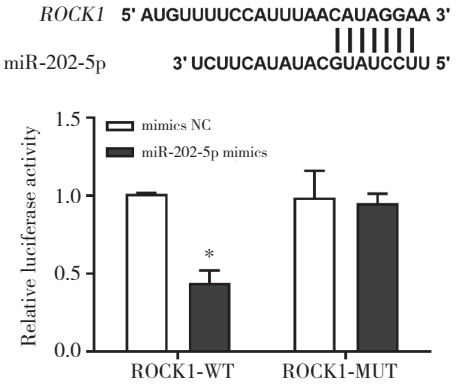


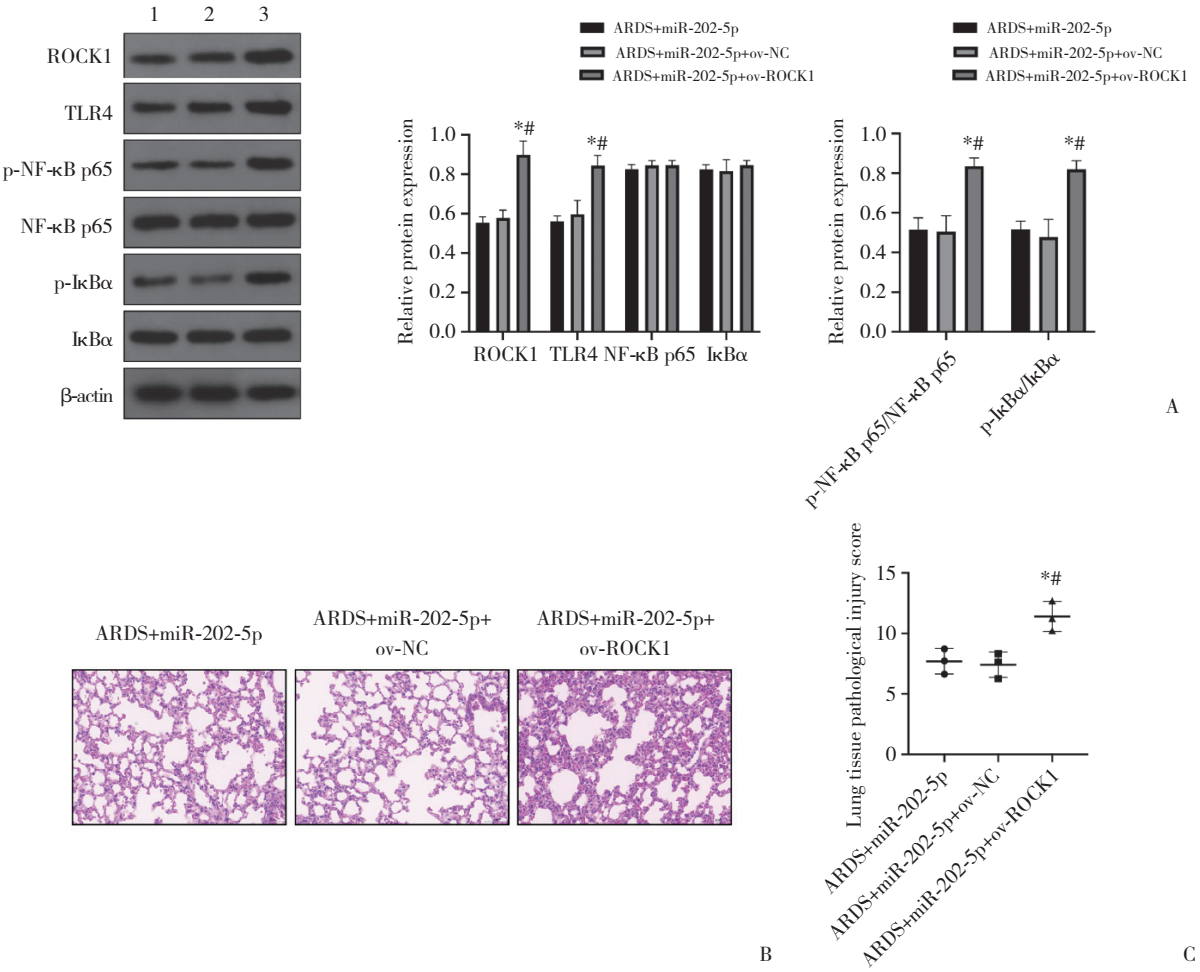
图3　miR-202-5p与*ROCK1*的靶向关系

Fig.3　The targeting relationship between miR-202-5p and *ROCK1*

2.6　过表达*ROCK1*对过表达miR-202-5p的ARDS大鼠肺损伤的影响

Western blotting检测结果显示，与ARDS+miR-202-5p组和ARDS+miR-202-5p+ov-NC组相比，ARDS+miR-202-5p+ov-ROCK1组大鼠肺组织中ROCK1、TLR4、p-NF-κB p65和p-IκBα蛋白表达水平明显升高（$P<0.05$）。见图4A。

HE染色结果显示，ARDS+miR-202-5p+ov-ROCK1组大鼠肺组织病理损伤较ARDS+miR-202-5p组和ARDS+miR-202-5p+ov-NC组加重，见图4B。与ARDS+miR-202-5p组和ARDS+miR-202-5p+ov-NC组相比，ARDS+miR-202-5p+ov-ROCK1组大鼠肺组织病理损伤评分明显升高（$P<0.05$）。见图4C。



A，expression of ROCK1 and TLR4/NF-κB signaling pathway related proteins；B，pathological injury of lung tissue（×200）；C，lung tissue pathological injury score. 1，ARDS+miR-202-5p group；2，ARDS+miR-202-5p+ov-NC group；3，ARDS+miR-202-5p+ov-ROCK1 group. * $P<0.05$ vs. ARDS+miR-202-5p group；# $P<0.05$ vs. ARDS+miR-202-5p+ov-NC group.

图4　过表达*ROCK1*对过表达miR-202-5p的ARDS大鼠肺损伤的影响

Fig.4　Effects of *ROCK1* overexpression on lung injury in ARDS rats with miR-202-5p overexpression

3　讨论

越来越多的证据表明，miR-202-5p在多种疾病发展中发挥作用。LI等[9]研究发现miR-202-5p上调可通过靶向抑制真核细胞翻译起始因子4E表达减轻氧糖剥夺/复氧诱导的神经元损伤。ZHAO等[10]研究发现过表达miR-202-5p通过靶向抑制瞬时受体电位香草样蛋白2表达改善心肌缺血再灌注损伤。此外，最近研究[11]发现miR-202-5p上调还能通过靶向抑制胞苷一磷酸激酶2表达抑制细胞焦亡，从而减轻肺缺血再灌注损伤。基于生物信息学分析的结果显示，miR-202-5p在ARDS大鼠肺组织中表达下调[6]。本研究结果显示，miR-202-5p在ARDS新生大鼠肺组织中表达下调，与上述生物信息学分析结果一致。此外，本研究还发现过表达miR-202-5p改善ARDS新生大鼠肺组织病理损伤，降低肺组织病理损伤评分和肺组织湿重/干重比值。这些结果表明过表达miR-202-5p可改善新生大鼠ARDS诱导的肺损伤。

ROCK1是RhoA的下游效应器，在激活单核细胞促炎反应中发挥分子开关作用，且参与高血压、动脉硬化、阿尔茨海默病和糖尿病等代谢相关疾病的发病[12-13]。多项研究发现miRNA可通过靶向抑制ROCK1表达改善LPS诱导的肺损伤。miR-144通过靶向抑制ROCK1表达改善LPS诱导的肺内皮细胞通透性增高[14]。miR-539-5p通过靶向抑制ROCK1表达改善LPS诱导的小鼠肺微血管内皮细胞的凋亡和炎症[15]。此外，还有研究[16]发现miR-495通过靶向抑制ROCK1表达抑制LPS诱导的WI-38细胞炎症损伤和凋亡。本研究发现miR-202-5p与*ROCK1* mRNA的3'UTR靶向结合；*ROCK1*在ARDS新生大鼠肺组织中表达上调，且过表达miR-202-5p降低ARDS新生大鼠肺组织中ROCK1表达。此外，过表达*ROCK1*逆转了过表达miR-202-5p对ARDS新生大鼠肺损伤的保护作用。这些结果表明miR-202-5p可通过靶向抑制*ROCK1*表达改善新生大鼠ARDS诱导的肺损伤。

已有研究[17]表明，抑制ROCK1可通过抑制TLR4/NF-κB信号通路减轻肝纤维化。ROCK1作为Rho激酶家族成员之一，可能通过调节细胞骨架重排促进TLR4信号复合物的形成[18]。TLR4/NF-κB信号通路是免疫系统中应对感染、炎症和外部刺激的关键信号通路[19]。该信号通路涉及多种分子和细胞因子，包括TLR4受体、途径中的级联激活蛋白以及最终的NF-κB，对调节炎症和免疫反应至关重要[20]。TLR4激活后与位于细胞质中的MyD88形成复合物，激活下游IKK激酶并调节NF-κB激活，NF-κB从细胞质向细胞核转移并参与多种炎性细胞因子产生，从而启动一系列炎症反应[21]。研究[22]表明，黄连素通过抑制TLR4/NF-κB信号通路改善LPS诱导的ARDS肺损伤。本研究结果显示，过表达miR-202-5p抑制ARDS新生大鼠肺组织中TLR4、p-NF-κB p65和p-IκBα蛋白表达，过表达*ROCK1*逆转过表达miR-202-5p对ARDS新生大鼠肺组织中TLR4、p-NF-κB p65和p-IκBα蛋白表达的下调作用。这些结果表明miR-202-5p介导ROCK1对ARDS诱导的新生大鼠肺损伤的改善作用可能与抑制TLR4/NF-κB信号通路激活有关。

综上所述，miR-202-5p通过靶向抑制*ROCK1*表达改善ARDS诱导的新生大鼠肺损伤，其机制可能与抑制ROCK1介导的TLR4/NF-κB信号通路激活有关。本研究为miR-202-5p作为治疗ARDS致新生儿肺损伤的有效药物靶点提供了理论依据。

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