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MicroRNA-21对内皮-间充质转化的影响及其在慢性阻塞性肺疾病发病机制中的作用

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[摘 要] 目的：慢性阻塞性肺疾病(chronic obstructive pulmonary disease，COPD)是一种以持续气流受限为特征的疾病。本研究旨在探讨COPD小鼠模型是否存在内皮-间充质转化(endothelial-to-mesenchymal transition，EndMT)，并初步探讨微RNA(microRNA，miR)-21与EndMT的关系。**方法：**建立小鼠COPD模型及*miR-21*基因敲除COPD动物模型(均为香烟烟雾诱导)，将小鼠分为3组(n=4)：对照组、COPD组和*miR-21*基因敲除COPD组(miR-21$^{-/-}$-COPD组)。采用Masson三色染色法观察血管周围胶原纤维沉积的情况，免疫组织化学染色观察肺组织切片中内皮细胞标志物血管内皮钙黏蛋白(vascular endothelial-cadherin，VE-cadherin)、内皮一氧化氮合酶(endothelial nitric oxide synthase，eNOS)、血小板内皮细胞黏附分子-1(platelet endothelial cell adhesion molecule-1，CD31)和间皮细胞标志物α-平滑肌肌动蛋白(α-smooth muscle actin，α-SMA)、神经钙黏蛋白(neural cadherin，N-cadherin)的表达情况。**结果：**与对照组相比，COPD组的胶原纤维沉积面积增加(P<0.05)，VE-cadherin、eNOS、CD31的表达水平降低(均P<0.05)，α-SMA、N-cadherin表达水平均升高(均P<0.05)。与COPD组相比，miR-21$^{-/-}$-COPD组胶原纤维沉积面积减小(P<0.05)，VE-cadherin、eNOS、CD31的表达水平均升高(均P<0.05)，α-SMA、N-cadherin表达水平均降低(均P<0.05)。**结论：**香烟烟雾诱导的COPD动物模型存在EndMT过程，*miR-21*基因敲除可减少COPD小鼠血管周围胶原纤维沉积面积和延缓EndMT过程。

[关键词] 慢性阻塞性肺疾病；miR-21；内皮-间充质转化；血管重塑

Effects of microRNA-21 on endothelial-to-mesenchymal transition and its role in the pathogenesis of chronic obstructive pulmonary disease

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ABSTRACT

Objective: Chronic obstructive pulmonary disease (COPD) is a disease characterized by persistent airflow restriction. This study aims to explore whether there is endothelial-to-mesenchymal transition (EndMT) in COPD mice and to explore the relationship between microRNA-21 (miR-21) and EndMT.

Methods: We established the COPD and the *miR-21* gene knockout COPD animal model (both cigarette smoke-induced). Mice were divided into 3 groups (n=4): a control group, a COPD group, and a *miR-21* knockout COPD (miR-21$^{-/-}$-COPD) group. Masson trichrome staining was used to observe the deposition of collagen around the perivascular. The relative protein levels and positions of endothelial cell markers including vascular endothelial-cadherin (VE-cadherin), endothelial nitric oxide synthase (eNOS), and platelet endothelial cell adhesion molecule-1 (CD31) as well as mesenchymal cell markers including α-smooth muscle actin (α-SMA) and neural cadherin (N-cadherin) in lung tissues were observed by immunohistochemical staining.

Results: Compared with the control group, the area of collagen fibril deposition was increased in the COPD group (P<0.05), the expression levels of VE-cadherin, eNOS, and CD31 were all decreased (all P<0.05), and the expression levels of α-SMA and N-cadherin were increased (both P<0.05). Compared with the COPD group, the miR-21$^{-/-}$-COPD group had a reduced area of collagen fiber deposition (P<0.05), the expression levels of VE-cadherin, eNOS, and CD31 were all increased (all P<0.05), and the expression levels of α-SMA and N-cadherin were decreased (both P<0.05).

Conclusion: There is a EndMT process in cigarette smoke-induced COPD animal models. *MiR-21* gene knockdown could reduce collagen deposition area and inhibit the EndMT process in COPD mice.

KEY WORDS chronic obstructive pulmonary disease; miR-21; endothelial-to-mesenchymal transition; vascular remodeling

慢性阻塞性肺疾病(chronic obstructive pulmonary disease，COPD)是一种慢性肺部炎症性疾病，以持续的呼吸道症状和不完全可逆性气流受限为主要特征，在中国发病人数接近1亿，带来沉重的社会和经济负担[1]。目前COPD的发病机制仍不完全明确，吸烟、遗传基因、慢性炎症、蛋白酶和抗蛋白酶的活性失衡及小气道重塑等因素被认为与COPD的发病机制密切相关[2]。

气道重塑是慢性阻塞性肺疾病最突出的病理生理改变，上皮-间充质转化(epithelial-to-mesenchymal transition，EMT)在气道重塑中起了关键作用，可导致小气道的纤维化和闭塞[3]。内皮-间充质转化(endothelial-to-mesenchymal transition，EndMT)的过程与EMT类似，被认为是EMT的一种特殊类型，可影响内皮细胞功能及参与小气道重塑。在EndMT过程中，内皮细胞失去内皮表型，而获得间充质细胞表型。研究[4-5]发现微RNA(microRNA，miRNA)可通过靶向作用于相关mRNA影响EndMT，从而参与多种疾病的发生、发展。本课题组前期研究[6-7]发现COPD患者的血清和单核细胞中miR-21的表达水平显著升高，且miR-21的水平与肺功能下降的严重程度相关，支气管上皮细胞胞外囊泡中miR-21可通过影响M2型巨噬细胞极化改善EMT。也有研究[8]表明在人脐静脉内皮细胞实验中，miR-21可以通过PTEN/Akt信号通路调控EndMT从而参与心肌纤维化过程。

COPD中是否存在EndMT和miR-21对COPD的EndMT的作用机制目前尚不明确。笔者推测miR-21可以促进COPD中EndMT过程，miR-21抑制后可以减轻EndMT从而减轻小气道重塑。本研究拟通过构建野生小鼠COPD模型及*miR-21*基因敲除COPD小鼠模型，比较各组肺组织胶原纤维沉积面积、内皮标志物和间皮标志物的表达水平，来探索*miR-21*基因在COPD和EndMT中的作用。

1 材料与方法

1.1 实验动物和试剂

8只健康C57BL/6J小鼠购自于湖南天勤生物技术公司，4只*miR-21*基因敲除小鼠委托维通利华公司购自美国德克萨斯大学西南医学中心。

改良Masson三色染色液购自北京索莱宝科技有限公司，鼠抗血管内皮钙黏蛋白(vascular endothelial-cadherin，VE-cadherin)多克隆抗体购自美国R&D公司，兔抗内皮一氧化氮合酶(endothelial nitric oxide synthase，eNOS)多克隆抗体购自美国Novus公司，兔抗血小板内皮细胞黏附分子-1(platelet endothelial cell adhesion molecule-1，CD31)单克隆抗体和兔抗α-平滑肌肌动蛋白(α-smooth muscle actin，α-SMA)单克隆抗体购自美国CST公司，兔抗神经钙黏蛋白(neural cadherin，N-cadherin)多克隆抗体购自美国Proteintech公司。

1.2 方法

造模方法参考前期研究[9]，将小鼠分为3组(n=4)：对照组、COPD组和*miR-21*基因敲除COPD(miR-21$^{-/-}$-COPD)组。COPD组和miR-21$^{-/-}$-COPD组模型均利用香烟烟雾暴露联合腹腔注射香烟烟雾提取液(cigarette smoke extract，CSE)的方式建立。造模周期为28 d，COPD组小鼠在造模的第1，12，23天腹腔注射CSE(0.3 mL/20 g)，除第1，12，23天外的其他造模时间内对小鼠进行被动吸烟(每次同时点燃10根香烟进行烟熏15 min，将小鼠放于新鲜空气条件下15 min后再重复烟熏1次)。对照组小鼠在同等条件下腹腔注射磷酸盐缓冲液(phosphate buffer saline，PBS)(0.3 mL/20 g)，呼吸自然空气。4周后处死所有小鼠，取出肺组织进行后续实验。小鼠COPD造模均成功，肺功能及病理评估结果见前期课题组结果[10]。

1.3 Masson三色染色法

肺组织分离后固定、包埋、切片后进行Masson染色。将石蜡切片常规脱蜡至蒸馏水、固定；天青石蓝染色液滴染、水洗，苏木精染色液滴染、水洗，然后弱酸分化，丽春红品红染色液滴染，磷钼酸溶液处理，直接滴入苯胺蓝染色液染5 min，弱酸溶液处理2 min，用乙醇脱水，最后透明中性树胶封固。显微镜下观察切片，电脑采集图像，采用Image J软件分析胶原容积分数。

1.4 免疫组织化学法

免疫组织化学(以下简称“免疫组化”)法检测EndMT相关标志物VE-cadherin、eNOS、CD31、α-SMA和N-cadherin的表达水平。通过脱蜡和水化、抗原修复、阻断内源性过氧化物酶、滴加一抗α-SMA(1∶50)、eNOS(1∶100)、VE-cadherin(1∶100)、N-cadherin(1∶100)、CD31(1∶100)，于4 ℃过夜孵育，随后DAB显色、复染及脱水、透明，取出后再置于二甲苯中，晾干后封片，显微镜观察并拍照，观察每个视野中α-SMA、eNOS、VE-cadherin、N-cadherin、CD31的阳性表达情况。使用Image J图像分析软件分析各组的表达情况。

1.5 统计学处理

采用GraphPad Prism 7.0统计软件分析数据。计量资料以用均数±标准差($\bar{x}\pm s$)表示，各组间比较采用独立样本t检验，P<0.05为差异具有统计学意义。

2 结　果

2.1 各组肺组织血管胶原纤维沉积比较

COPD组血管周围胶原纤维面积沉积(即蓝色染色面积占肺组织总面积的百分比)较对照组增多(图1A)。定量分析后COPD组是对照组的3.24倍(0.110±0.011 vs 0.037±0.012，P<0.001)；与COPD组相比，miR-21$^{-/-}$-COPD组中胶原纤维面积显著减小(0.110±0.011 vs 0.080±0.010，P<0.05；图1B)。

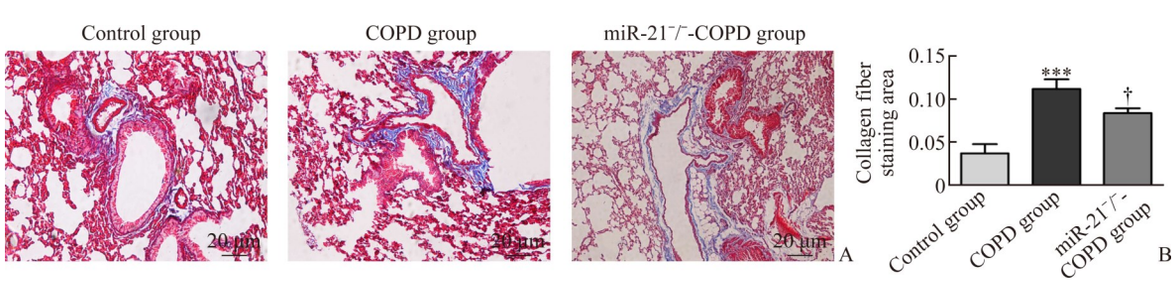

图1　各组肺组织血管胶原纤维沉积分布比较

Figure 1　Comparison of the distribution of vascular collagen fibers in lung tissues of different groups

A: Representative picture of lung tissue (the blue part is collagen fiber); B: Semi-quantitative analysis of collagen fiber percentage. ***P<0.001 vs the control group; †P<0.05 vs the COPD group.

2.2 各组EndMT相关蛋白的表达水平比较

2.2.1 内皮特异性标志物eNOS、VE-cadherin和CD31的表达

免疫组化结果显示：eNOS、VE-cadherin和CD31在细胞质、血管内膜呈弥漫性染色(图2A)。与对照组相比，COPD组中eNOS、VE-cadherin和CD31的表达水平降低(均P<0.05)；与COPD组相比，miR-21$^{-/-}$-COPD组eNOS和VE-cadherin的表达水平升高(均P<0.05)，CD31表达水平的差异无统计学意义(P>0.05，图2B~2D)。

2.2.2 间充质标志物α-SMA、N-cadherin的表达

免疫组化结果显示：N-cadherin在细胞质、血管内膜呈弥漫性染色，α-SMA主要集中在气管壁和血管内膜(图3A)。与对照组相比，COPD组α-SMA和N-cadherin的表达水平升高(均P<0.05)；与COPD组相比，miR-21$^{-/-}$-COPD组的α-SMA和N-cadherin表达水平均降低(均P<0.05，图3B、3C)。

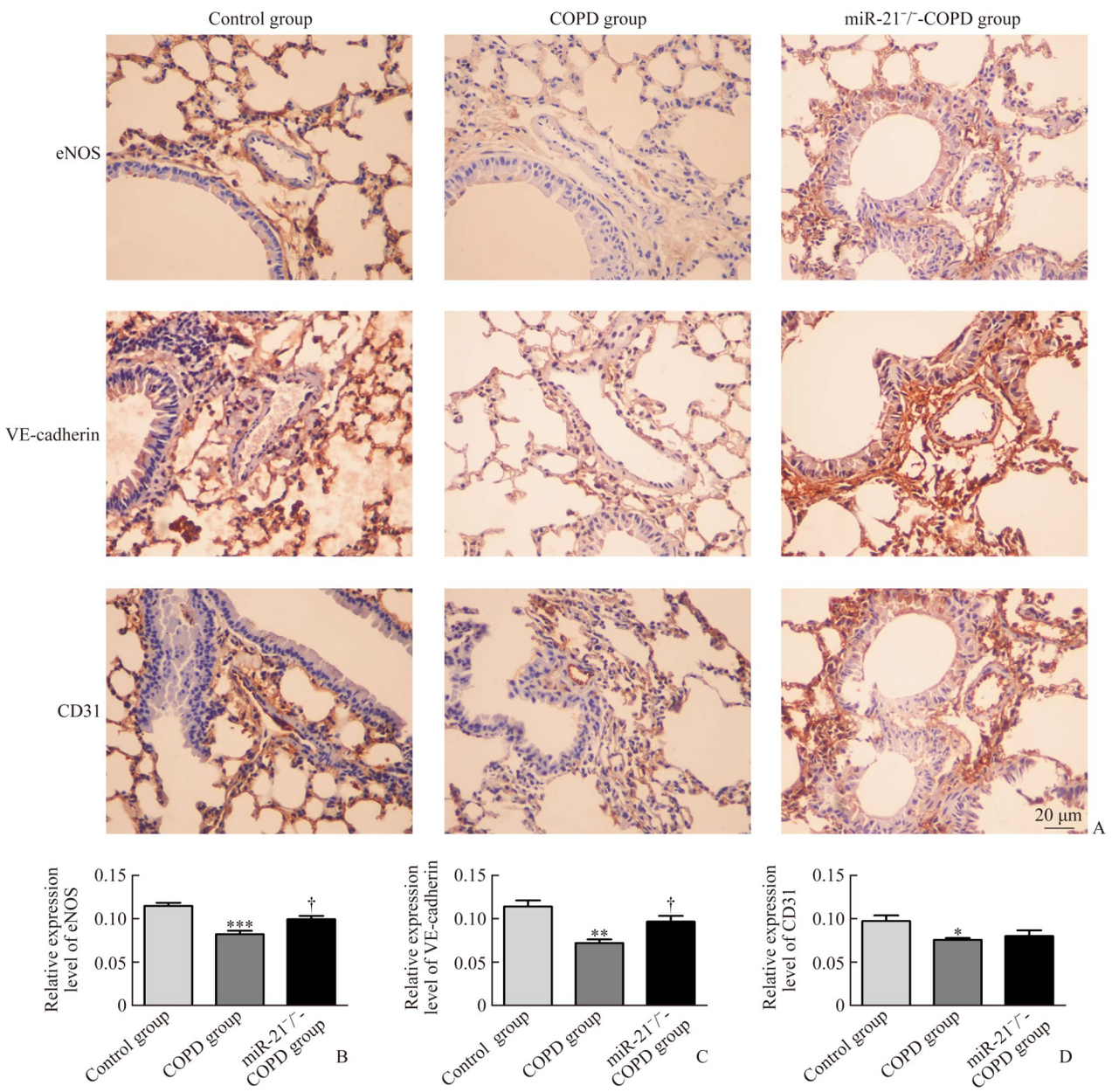

图2 各组肺组织中内皮细胞标志物eNOS、VE-cadherin和CD31的表达

Figure 2 Expression of the endothelial cell marker eNOS, VE-cadherin, and CD31 in lung tissues of different groups

A: Immunohistochemical results of endothelial cell marker eNOS, VE-cadherin, and CD31 of different groups; B－D: Relative expression levels of eNOS (B), VE-cadherin (C), and CD31 (D). *P<0.05, **P<0.01, ***P<0.001 vs the control group; †P<0.05 vs the COPD group. eNOS: Endothelial nitric oxide synthase; VE-cadherin: Vascular endothelial-cadherin; CD31: Platelet endothelial cell adhesion molecule-1.

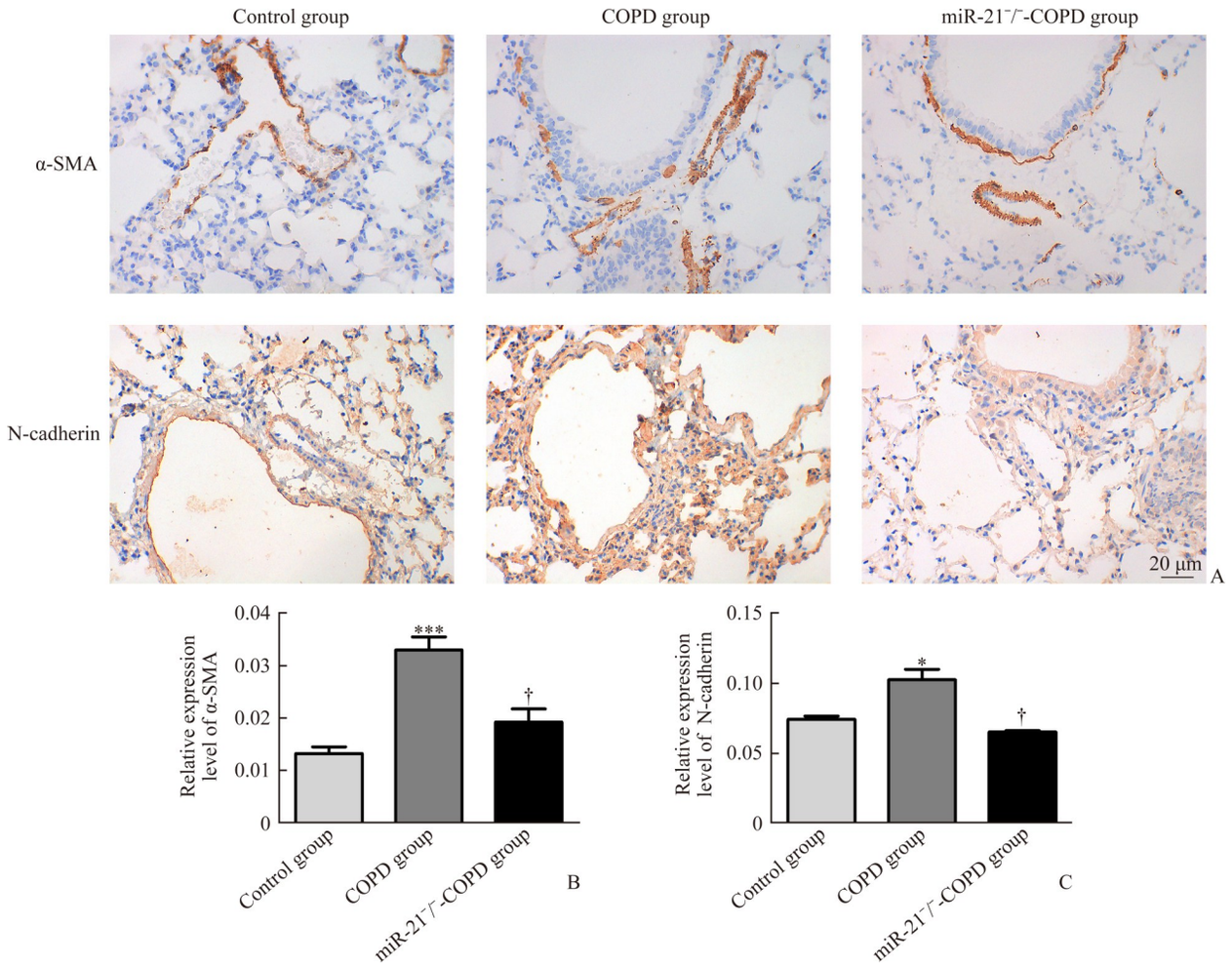

图3　各组肺组织中间皮细胞标志物α-SMA和N-cadherin的表达

Figure 3　Expression of the mesenchymal cell markers α-SMA and N-cadherin in lung tissues of different groups

A: Immunohistochemical results of mesenchymal cell markers α-SMA and N-cadherin of different groups; B and C: Relative expression levels of α-SMA (B) and N-cadherin (C). **P*<0.05, ****P*<0.001 vs the control group; †*P*<0.05 vs the COPD group. α-SMA: α-smooth muscle actin; N-cadherin: Neural cadherin.

3 讨　论

COPD是全球健康面临的重要公共卫生问题，由于人口老龄化，吸烟和日益严重的空气污染等因素，COPD发病率逐年增加。2022年慢性阻塞性肺病全球倡议组织(Global Initiative for Chronic Obstructive Lung Disease，GOLD)指南[11]推荐COPD的治疗主要集中于改善症状、提高患者生活质量同时减少疾病恶化方面，包括戒烟、吸入支气管舒张剂、吸入抗炎药物等措施，尚无有效的药物能预防或逆转COPD的气道重塑，因此关于COPD气道重塑机制方面的研究对于找寻新的治疗方案具有重要意义。

本课题组前期研究[9]发现短期香烟烟雾暴露的小鼠肺组织存在一定程度的小气道重塑，如气道黏膜增厚、大量炎性细胞浸润、小气道直径变窄等改变，且存在EMT。COPD患者肺血管系统中*S100A4*表达增加，提示除EMT过程外，EndMT可能在COPD发病机制中发挥作用[12-13]。为了进一步探究COPD与EndMT之间的关系，本研究成功构建烟雾诱导COPD小鼠模型，发现COPD动物模型存在血管周围胶原纤维沉积，内皮标志物eNOS、VE-cadherin和CD31的表达水平降低，而间充质标志物α-SMA、N-cadherin表达水平升高，证实存在EndMT。这说明COPD除了存在小气道重塑，还存在血管重塑过程。

目前关于EndMT和肺血管重塑间的研究主要集中在肺动脉高压、动静脉血管移植和动脉粥样硬化等血管性疾病中[14]。EndMT可能是表达α-SMA的来源，证实EndMT参与肺动脉高压相关的肺血管重塑过程[15]。但是目前关于EndMT和血管重塑的机制研究较少。Chen等[16]证明丹酚酸A可以减弱EndMT，

抑制氧化应激和减轻肺血管重塑，Nrf2/HO-1信号转导途径可能参与上述过程。Zhang等[17]研究发现：在缺氧条件下，肺微血管内皮细胞通过EndMT向平滑肌细胞表型分化，小肺动脉壁中α-SMA的表达增加，且EndMT受HIF-1α/Twist的调节。同样有学者[18]认为缺氧会引起肺血管内皮细胞的EndMT改变，导致血管重塑，继而参与重度肺动脉高压的发展。miRNAs是EndMT的关键调节因子[19]，miR-451通过调节内皮细胞的EndMT参与糖尿病心肌病的病理过程[20]；miR-449a可以通过调节脂质筏中E-cadherin与AdipoR2蛋白的结合，进而参与EndMT和动脉粥样硬化[21]；转化生长因子β(transforming growth factor-β，TGF-β)也可诱导miR-374b，通过TGF-β/miR-374b-MAPK7轴在血管早期病变期间发生EndMT过程中起关键作用，这可能成为抗动脉粥样硬化治疗的一个靶点[22]。然而目前EndMT在COPD中的相关研究较少。

miR-21被认为是具有促纤维化作用的miRNA，参与多种呼吸系统疾病如哮喘、肺纤维化、肺癌等。本课题组前期研究[10]证实miR-21的水平与肺功能呈负相关，*miR-21*基因敲除的COPD小鼠肺组织淋巴细胞、巨噬细胞、中性粒细胞等炎性细胞的浸润数目明显减少。本研究发现*miR-21*基因敲除后，COPD小鼠模型的血管胶原纤维沉积明显改善，而且内皮标志物的表达水平升高，间充质标志物的表达有下降趋势，表明*miR-21*敲除可在一定程度逆转EndMT。Xu等[23]通过香烟烟雾诱导的动物模型、COPD患者肺组织进行实验表明miR-21在吸烟者和吸烟COPD患者的外泌体中过表达，并且miR-21的水平与第1秒用力呼气量/用力肺活量(forced expiratory volume in one second/forced vital capacity，FEV_1/FVC)之间存在负相关，与本研究结果相符。研究[24-25]发现：在博来霉素诱导的肺纤维化小鼠和特发性肺纤维化患者中miR-21表达增强，通过阻断miR-21后肺间质的重塑减弱。这表明miR-21在慢性缺氧诱导的肺血管重塑的发病机制中起重要作用。Guo等[26]指出激肽释放酶可以抑制TGF-β诱导的miR-21及其下游组分的活化，进而抑制EndMT过程，还能减少eNOS的表达抑制氧化应激。这些结果表明抑制miR-21介导的EndMT在预防病理性纤维化疾病起重要作用，因此，笔者推测阻断miR-21的功能可能有助于改善COPD和纤维化疾病的气道重塑与血管重塑。

既往研究[8]表明miR-21的表达水平在EMT和EndMT期间显著升高，TGF-β诱导EndMT形态学变化及标志物变化，阻断miR-21可以抑制Akt活化并逆转EndMT，说明这一过程部分是通过上调miR-21-Akt途径介导[27]。还有研究[28]发现抑制miR-21也可能通过NF-κB/miR-21/SMAD7信号通路减轻EndMT来预防心肌纤维化。本研究发现敲除*miR-21*可以减轻COPD的EndMT，但具体机制尚不明确。

综上所述，COPD小鼠模型存在肺组织血管周围胶原纤维沉积和EndMT相关标志物表达水平变化，而敲除*miR-21*基因后可改善EndMT。本研究也存在一定局限性，如样本量偏少，未涉及机制研究等。未来本课题组将进一步深入研究具体调控机制。

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