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综述

支气管哮喘气道重塑机制的研究进展*

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摘要： 气道重塑是哮喘难以根治的主要原因，预防气道重塑具有重要的临床意义。普遍认为气道重塑是由于气道慢性炎症导致气道反复损伤和异常修复引起的。与此同时，也有研究显示单纯治疗气道炎症并不能直接缓解气道重塑，但气道收缩引发的机械力也能导致气道结构的改变。笔者将近年来关于气道重塑发生机制的研究进行综述，从而为哮喘的治疗提供新思路。

关键词： 支气管哮喘；气道炎症；气道重塑；气道收缩；机械力
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Research progress in the mechanism of airway remodeling in bronchial asthma*

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Abstract: Airway remodeling represents the main cause for that asthma is difficult to be cured, and prevention of airway remodeling is of important clinical significance. It is traditionally believed that airway remodeling results from the repetitive airway injury and abnormal repair caused by the chronic airway inflammation. Meanwhile, some studies revealed that treating airway inflammation alone cannot directly alleviate the airway remodeling and that the mechanical force via airway contraction can also lead to changes in the airway structure. This paper reviews the advances in the mechanism of airway remodeling in recent years, so as to provide novel insights for the treatment of asthma.

Keywords: bronchial asthma; airway inflammation; airway remodeling; airway contraction; mechanical force

全球哮喘防治倡议中指出哮喘是以气道慢性炎症为主要特征的异质性疾病，其症状反复发作导致的气道结构改变称为气道重塑[1]。气道重塑能导致持续性气道狭窄、气道高反应性和肺功能下降，是导致哮喘难以根治的主要原因[2-3]。因此抑制气道重塑这一病理过程，对于改善哮喘患者肺功能、提高生活质量具有极为重要的意义。现将近年来关于气道重塑发生机制的研究综述如下。

1 气道慢性炎症

慢性的、持续存在的气道炎症会导致哮喘气道上皮反复损伤、修复[4-5]，气道组织中炎症细胞和结构细胞释放多种细胞因子、趋化因子和生长因子，从而驱动气道重塑[6]。随着近年来对于哮喘不同表型的认知，炎症对于气道重塑的作用机制研究也有了新的进展。

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1.1 气道炎症促进重塑

目前普遍认为哮喘主要分为两种常见的表型，包括以嗜酸性粒细胞气道炎症为特征的高T2型炎症表型哮喘，和以伴有或不伴有中性粒细胞气道炎症为特征的低T2炎症表型哮喘[7]。在高T2型炎症表型哮喘中，Th2细胞通过释放多种细胞因子，如白细胞介素4（Interleukin-4, IL-4）、IL-13等，对促进气道平滑肌增生和黏液分泌产生至关重要的影响，从而调节气道炎症反应[8-9]。但Th2细胞因子的过表达会促进哮喘气道重塑。IL-4、IL-13均能刺激成纤维细胞及气道上皮细胞分泌骨膜蛋白[10-11]，而骨膜蛋白通过诱导肿瘤坏死因子β信号转导，进一步促进细胞外基质（extracellular matrix, ECM）沉积，在哮喘气道重塑中起重要作用[12]。因此，针对TH2炎症反应的靶向治疗，能够在一定程度上抑制气道重塑[13-14]。

在低T2炎症表型哮喘中，炎症主要由非嗜酸性T1和T17通路介导，伴有或不伴有中性粒细胞炎症和氧化应激[15]。Th1/Th17炎症通路调节失衡时，Th17细胞通过分泌IL-17，刺激纤维原性细胞因子如IL-11和肿瘤坏死因子α的产生，促进成纤维细胞、肌成纤维细胞和平滑肌细胞的增生沉积，继而延长气道重塑[16]。有研究报道，针对IL-17的靶向治疗可明显改善哮喘临床症状[17]，也反过来证实了这一点。

1.2 炎症与重塑间的关系

有证据表明，气道炎症并不是气道重塑的唯一原因。首先，支气管壁的结构改变可以发生在儿童早期，以及在发生气道炎症之前[18]。POHUNEK等[19]发现在儿童哮喘患者中，皮下胶原蛋白厚度与患者的年龄或病程长短没有相关性。这些发现证实气道结构改变不仅是由慢性炎症导致的。其次，哮喘治疗中常用的针对气道炎症的药物在抑制支气管壁重构方面效果有限。糖皮质激素能够减轻炎症，却不能使肺功能完全正常化，也不能预防疾病进一步加重。在小鼠模型中，即使炎症得到缓解，气道功能障碍及气道重塑仍然存在[20-21]。

因此，最近有观点提出，哮喘气道重塑与慢性炎症是独立存在的[22]。有研究表明，在过敏性哮喘和非过敏性哮喘患者的气道活检标本中都存在气道重塑的特征性表现[23]。ELLIOT等[24]对哮喘死亡患者进行尸检发现，病理性的气道重塑与当前的气道炎症无关。KARIYAWASAM等[25]研究表明，炎症和气道重塑的变化可以及时分离，在过敏原激发后，气道重塑持续存在，而炎症则是一过性的。现有证据表明，气道重塑与疾病严重程度具有一定的相关性[26]，而消除炎症并不能阻止气道重塑的进展，也无法改善肺功能或延缓疾病进展，这也进一步证实了哮喘并非仅是由炎症引起的[27]。

2 气道收缩产生的机械力

众所周知，机械力会导致组织结构发生改变，如长期高血压导致心脏和血管重构，举重会导致骨骼肌肥大。在动物和人体的体内外试验中，气道收缩引起的机械力不仅会诱发症状，也能导致气道结构的改变，类似于机械力在其他组织中引起的变化[28]。

2.1 机械力对气道重塑的影响

生理情况下，气道平滑肌收缩产生机械力对气道上皮、成纤维细胞和气道平滑肌产生作用，而疾病条件下，异常的机械力可能改变细胞活化[29]，从而出现气道纤维化以及重塑[30]。GRAINGE等[31]纳入48例轻症哮喘患者进行临床试验，吸入4种不同的吸入剂，包括2个实验组分别吸入尘螨和乙酰甲胆碱，以及2个对照组单纯吸入生理盐水以及吸入沙丁胺醇后再吸入乙酰甲胆碱等。结果表明，哮喘患者频繁的气道收缩使上皮细胞活化，进而促进气道重塑，而其程度同引起气道收缩的吸入激发药物种类无关。而使用长效β受体激动剂通过缓解支气管收缩，抑制肌成纤维细胞数量，能够抑制气道重塑[32]。

就其机制而言，MANUYAKORN等[33]对比研究了6例健康者和11例非吸烟哮喘患者的支气管成纤维细胞，结果表明机械力可在mRNA和蛋白水平上显著诱导Ⅰ和Ⅲ型胶原蛋白增生，并能诱导基质金属蛋白酶和IL-8的分泌，促使气道结构改变。也有证据表明，气道上皮细胞在支气管收缩产生的机械力的作用下，诱导具有生物活性的肿瘤坏死因子β的释放，导致收缩蛋白表达，促使ECM沉积，导致气道重塑。机械力在气道平滑肌增殖和迁移中也起到了关键作用，还能诱导血管内皮生长因子表达，此外还增加气道黏液的分泌，改变气道上皮的屏障功能，这些病理变化都会诱使哮喘发作，促进气道重塑[34-35]。

2.2　机械力与气道炎症的关系

机械力与气道炎症有密切的联系。有证据表明炎症作用下的气道局部微环境，更容易促使气道收缩，进而促进重塑的发生[36]。通过敲除调节支气管收缩的胆碱能M3受体，可以减少和防止气道重塑，但对气道炎症没有影响[37]。而WIPARAT等[33]研究表明，机械力反过来也会通过促进气道炎症和重塑，加速哮喘疾病进展。

3　总结

目前关于气道重塑的治疗尚没有突破性进展，这严重制约了哮喘患者的长期控制。虽然气道炎症可能提供了促进支气管重塑的局部微环境，但支气管收缩引发的机械力也在一定程度上导致了气道重塑。因此有待于更多地研究来进一步明确气道炎症与机械力的关系。

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