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重症哮喘发生机制研究新进展

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摘　要

支气管哮喘(Asthma)是儿童及成人常见的慢性气道炎症性疾病，我国的哮喘整体诊断率、治疗率、控制率仍不理想，给患者、家庭及社会带来了沉重的疾病负担。糖皮质激素(Glucocorticoids)为哮喘治疗的一线核心药物，但部分患者存在糖皮质激素抵抗，甚至进展为重症哮喘(Severe Asthma)，其发病机制尚未完全阐明。本文围绕哮喘表型的异质性、气道上皮屏障功能损伤、气道上皮炎症调控紊乱、感染及遗传因素五大关键环节，系统综述其在重症哮喘发生及糖皮质激素抵抗中的作用机制。上述多因素相互作用、协同调控，共同构成重症哮喘与糖皮质激素抵抗的核心病理生理网络。未来针对上述关键靶点开展精准干预研究，有望进一步提高哮喘治疗效能、降低重症哮喘发生率，为重症哮喘的个体化防治提供新的理论依据与方向。

关键词

重症哮喘，哮喘表型，气道上皮，感染，遗传因素

Research Progress in the Pathogenesis of Severe Asthma

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Abstract

Bronchial asthma is a common chronic inflammatory airway disease in children and adults. In

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China, the overall rates of diagnosis, treatment, and well-controlled of asthma remain unsatisfactory, imposing a heavy disease burden on patients, families, and society. Glucocorticoids are the first-line core drugs for asthma therapy; however, some patients exhibit glucocorticoid resistance and even progress to severe asthma, whose pathogenesis has not yet been fully elucidated. This article systematically reviews the mechanisms of five key components, namely the heterogeneity of asthma phenotypes, impaired airway epithelial barrier function, dysregulated inflammatory regulation function of airway epithelium, infection, and genetic factors, in the development of severe asthma and glucocorticoid resistance. These multiple factors interact and regulate synergistically, jointly constituting the core pathophysiological network of severe asthma and glucocorticoid resistance. Future studies targeting the precise intervention of above key nodes are expected to further improve the efficacy of asthma treatment, reduce the incidence of severe asthma, and provide new theoretical basis and directions for individualized prevention and treatment of severe asthma.

Keywords

Severe Asthma, Asthma Phenotypes, Airway Epithelial, Infection, Genetic Factors

1. 引言

支气管哮喘(Asthma)是儿童最常见的慢性气道疾病，我国的相关调查显示，1990 年、2000 年、2010 年 0~14 岁城市儿童哮喘的累积患病率分别为 1.09%、1.97%和 3.02%，呈显著上升趋势[1]。与此同时，我国儿童哮喘的控制现状仍不容乐观，研究表明约 30%的城市哮喘患儿未能得到及时诊断[2]，超 20%的患儿病情未达到理想控制效果[3]。成人方面，一项 2019 年发表的纳入我国 50,991 名成人的研究提示我国成人哮喘的总体患病率约为 4.2%，而伴有气流受限的哮喘患病率为 1.1% [4]。该调查同时显示，15.5% (95%置信区间 11.4%~20.8%)的成人哮喘患者一年因呼吸系统症状加重急诊就诊至少 1 次，而 7.2% (95%置信区间 4.9%~10.5%)的成人哮喘患者一年因呼吸系统症状加重至少住院 1 次。因此，哮喘给患者、家庭及社会带来了沉重的疾病负担，早期诊断、及时干预并提升治疗效能，对于改善哮喘控制水平、降低疾病负担具有重要意义。

糖皮质激素(Glucocorticoids)是目前哮喘治疗的核心药物，目前认为，其主要通过下调气道炎症、减轻气道上皮屏障损伤、抑制气道上皮重塑等多种机制实现哮喘控制。吸入性糖皮质激素(Inhaled Corticosteroids, ICS)作为糖皮质激素治疗的主要给药形式，是哮喘的一线治疗方案，但临床及研究表明，有 5%~10%的患者对糖皮质激素治疗反应不佳，甚至无应答[5]。其中，排除用药依从性差、吸入操作不规范等因素后的难治性哮喘被定义为重症哮喘(Severe Asthma) [5]。重症哮喘的发病机制尚未完全阐明，但其可能与哮喘表型、气道上皮屏障、感染、糖皮质激素在哮喘中的多效性作用及其对气道上皮屏障的潜在损伤效应密切相关[5]-[8]。

现有的研究表明，包括哮喘表型、气道上皮屏障功能、气道上皮炎症调控作用、感染、遗传因素在内的多种因素都能够影响重症哮喘的发生(图 1)。本文就目前对于哮喘糖皮质激素抵抗和重症哮喘发生机制的认识展开综述。

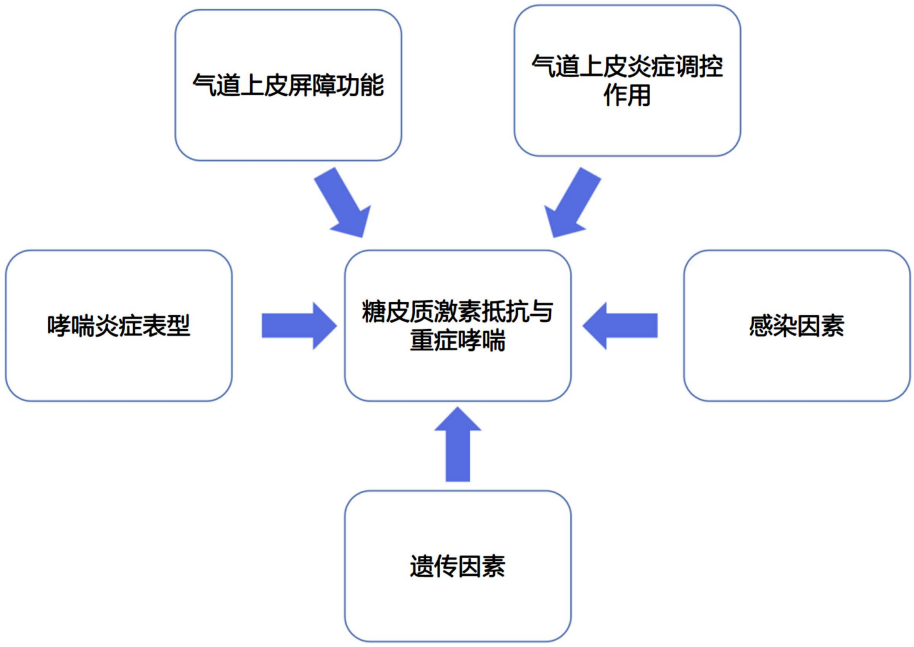

Figure 1. Variables associated with the development of severe asthma from the review
图 1. 本综述涉及的重症哮喘发生的参与因素

2. 哮喘表型与重症哮喘的发生密切相关

近年来的研究表明，哮喘患者可根据其气道炎症类型分为不同的哮喘表型。哮喘患者根据诱导痰、支气管肺泡灌洗液等反映的气道内不同种类炎症细胞的浸润情况分为中性粒细胞型、嗜酸性粒细胞型、混合型和寡粒细胞型等哮喘表型，不同的炎症表型反映了患者气道的主导炎症类型不同。

不同哮喘表型之间的临床表现、治疗疗效，尤其是对糖皮质激素治疗的反应性有所不同，且哮喘表型与糖皮质激素抵抗与重症哮喘的发生密切相关[7]。研究表明，重症哮喘儿童以寡粒细胞型哮喘表型为主，而嗜酸性粒细胞型哮喘最少[7] [9]。嗜酸性粒细胞型重症哮喘患儿的临床特征与混合粒细胞型患儿相近，且尽管他们中接受全身性泼尼松治疗的比例较高，仍具有更高的 BALF 嗜酸性粒细胞水平[7]。

在接受吸入性糖皮质激素或口服糖皮质激素(Oral Corticosteroids, OCS)治疗的患者中，气道内嗜酸性粒细胞水平升高可能是重症哮喘的特征之一。在接受包括激素在内的常规哮喘治疗的哮喘患者中，无论是 BALF、诱导痰还是气道活检中的嗜酸性粒细胞升高都与更重的病情有关[7] [10] [11]。这可能是因为，尽管接受了糖皮质激素治疗，嗜酸性粒细胞仍升高，这反映了患者存在激素抵抗，并预示糖皮质激素治疗可能效果欠佳。

此外，部分难治性哮喘与重症哮喘的肺泡灌洗液中的中性粒细胞数目升高明显[12] [13]，反映出哮喘患者 BALF 中性粒细胞增多也与糖皮质激素治疗反应不佳、重症哮喘发生相关。与其他哮喘患儿相比，中性粒细胞型重症哮喘患儿气道内的中性粒细胞尽管处于富含 TGF-β1 的高度免疫抑制环境中，其并未出现更多的凋亡，而反而具有更强的炎症活性[14]。

3. 气道上皮屏障作用受损在重症哮喘的发生中可能起重要作用

气道上皮屏障由气道上皮和气道表面液体层组成，与儿童喘息、哮喘等喘息性疾病的发生密切相关[15]。气道上皮由纤毛柱状上皮细胞(Ciliated columnar epithelial cells)、杯状细胞(Goblet cells)、俱乐部细胞(Club cells)和基底细胞(Basal cells) [16]等多种细胞类型构成，其中基底细胞被认为具有分化为其他上皮

细胞的潜能[17]。各类细胞通过紧密连接、黏着连接和桥粒相互连接，形成连续的细胞屏障，防止变应原和病原体入侵机体，从而避免气道炎症的发生并介导细胞间的信息交流[17] [18]。除细胞屏障外，气道上皮屏障的另一重要组成部分——气道表面液体层，则含有黏蛋白(Mucins)、防御素(Defensins)、抗菌肽(Antimicrobial peptides)等多种防御性蛋白，具有抗菌、抗蛋白酶、抗氧化等特性，进一步增强了气道上皮屏障的防御功能[17] [18]。

气道上皮屏障通过上述物理和化学屏障作用，减少变应原、病原体与免疫细胞的相互作用，从而防止气道发生过度炎症反应[16] [17]。而哮喘患者的气道上皮屏障存在特征性病理改变，包括纤毛柱状上皮细胞的损伤与脱落、杯状细胞的增生和化生等[19] [20]，部分改变在哮喘发病初期即可出现[21]。杯状细胞数量增多并呈高分泌状态，是导致哮喘患者气道表面液体层功能障碍的重要原因[22]-[24]。哮喘中气道上皮屏障的结构破坏、理化屏障功能异常及炎症反应调控紊乱，会增加气道病原体、变应原入侵和致敏的风险；此外，受损的上皮细胞会释放自身抗原，进一步加重气道炎症，最终形成气道炎症与气道上皮屏障损伤的恶性循环。

气道上皮屏障在糖皮质激素治疗哮喘中也发挥着重要的作用。一般认为，糖皮质激素能够保护气道上皮屏障的完整性，从而减少变应原和病原体的入侵与致敏[25]；还能抑制哮喘气道中杯状细胞的增生和黏液高分泌，帮助维持气道表面液层的正常功能，减少黏液栓形成和气道内病原体蓄积[26]，同时维持气道正常结构，抑制气道重塑[26]。然而，最新的研究显示，糖皮质激素对气道上皮屏障的作用具有两面性。糖皮质激素可能诱导气道上皮细胞凋亡，破坏气道上皮屏障的完整性，增加机体接触变应原和病原体的概率[27]。体外研究证实，糖皮质激素可触发气道上皮细胞凋亡并抑制其增殖，这可能会损害受损气道上皮屏障的修复能力[28] [29]。动物实验也为上述发现提供了佐证：在哮喘小鼠和兔模型中，糖皮质激素治疗可能加重上皮细胞的损伤、凋亡与脱落，导致屏障功能受损，引起支气管肺泡灌洗液中的上皮细胞数量升高[30]-[32]。此外，Yilmaz 等人的研究发现，在哮喘小鼠模型中，使用糖皮质激素会降低气道上皮的厚度[26]，这可能会削弱其抵御病原体和变应原的屏障功能。这种看似矛盾的损伤潜能在糖皮质激素抵抗发生中的作用成为亟待解答的重要问题，其可能是糖皮质激素抵抗与重症哮喘发生的关键。

4. 气道上皮细胞的炎症调控作用受损可能参与了重症哮喘的发生

除气道上皮的屏障功能外，气道上皮细胞也在气道炎症的调控中起到核心作用。气道上皮细胞表达多种模式识别受体，如胞质内的 NOD 样受体(NOD-Like Receptors, NLRs)和跨膜的 Toll 样受体(Toll-like receptors)，这些受体可识别损伤相关分子模式(Damage-Associated Molecular Patterns, DAMPs)和病原体相关分子模式(Pathogen-Associated Molecular Patterns, PAMPs) [33]。当识别到有害刺激时，气道上皮细胞会通过转录和分泌抗菌蛋白、促炎蛋白及黏蛋白等机制，调控早期炎症事件，参与局部急性炎症反应[34] [35]。

此外，气道上皮细胞可通过释放白介素、肿瘤坏死因子、CXCL8、CCL11 和 CCL20 等细胞因子，募集树突状细胞、T 细胞、B 细胞、嗜酸性粒细胞、中性粒细胞等多种炎症细胞[36]-[41]，这一过程对局部免疫的调控至关重要。当接触无害抗原时，气道上皮细胞会通过抑制促炎介质的激活与功能、降低自身的敏感性和反应性以及分泌抗炎因子等方式限制免疫反应，阻止过度炎症的发生[17] [42]。当接触有害病原体或变应原时，未被纤毛黏液系统清除的抗原会被气道上皮细胞识别[36]，进而触发抗原特异性免疫反应。病毒感染时，气道上皮细胞可持续产生 IFN-β，减少病毒复制并促进被感染的上皮细胞凋亡[43]。

气道上皮细胞是驱动并维持哮喘气道炎症的多种促炎细胞因子和趋化因子的主要产生细胞之一[44]。气道上皮细胞分泌的胸腺基质淋巴细胞生成素(Thymic Stromal Lymphopoietin, TSLP)、IL-25、IL-33 等细胞因子，可促进 T 细胞向 2 型辅助性 T 细胞(Th2 细胞)表型分化[45]，可构建利于并维持 Th2 细胞极化炎

症的局部微环境[44]；其分泌的粒细胞－巨噬细胞集落刺激因子(Granulocyte-Macrophage Colony Stimulating Factor, GM-CSF)则为嗜酸性粒细胞的成熟与存活提供支持[46] [47]。在哮喘状态下，气道上皮自身成为气道炎症的攻击靶点，而其损伤、凋亡与脱落能够释放多种趋化因子和大量内源性抗原，激活各类炎症细胞，放大气道炎症[33]，与之相关的 IL-2、IL-4、IL-13 等多种免疫和炎症介质的过表达能够干扰糖皮质激素的信号传导通路，进而导致激素抵抗[48] [49]，与重症哮喘的发生密切相关[50]-[52]。研究证实，这些细胞因子的过表达与糖皮质激素受体亲和力降低相关，其机制可能为 p38 MAPK 的激活，诱导炎症细胞中的糖皮质激素受体磷酸化，降低其核转运能力[53]。此外，Th1 细胞相关细胞因子也可能降低气道上皮对糖皮质激素的敏感性，例如 TNF-α、IFN-γ 可通过多种机制维持气道平滑肌细胞的糖皮质激素抵抗[54]，IL-17A 可降低气道上皮的糖皮质激素敏感性[55]；IFN-γ 还可上调气道和肺巨噬细胞中 miRNA-9 的表达，增加糖皮质激素受体的磷酸化水平，抑制其核转运[56]。

5. 感染是重症哮喘发生的重要原因

感染是重症哮喘发生、病情进展、介导糖皮质激素抵抗及哮喘控制不良的重要因素，在重症哮喘的病理生理进程中发挥核心作用。多项临床与基础研究证实，呼吸道病毒、细菌、真菌等多种病原体，可通过调控特异性炎症信号通路、干扰糖皮质激素受体功能、重塑气道免疫微环境、加重气道结构重塑等机制，系统性降低哮喘患者对糖皮质激素的治疗敏感性并诱发持续性激素抵抗，最终促使疾病进展为重症哮喘[8] [57]-[60]。糖皮质激素虽能抑制气道过度炎症，但同时会抑制气道的固有免疫和适应性抗病毒免疫反应，延缓病毒清除，促进黏液分泌、减少抗菌肽释放、增加细菌载量[60]-[62]。故而，感染在糖皮质激素抵抗形成及重症哮喘发生发展过程中，具有不可替代的关键作用。

病毒感染是诱发哮喘急性加重、介导激素抵抗的常见原因，鼻病毒、甲型流感病毒、呼吸道合胞病毒均已被证实可参与重症哮喘的发生进程，其中鼻病毒的致病机制研究最为明确。鼻病毒感染人支气管上皮细胞后，能够激活核因子 κB (Nuclear Factor-κB, NF-κB)和 c-Jun 氨基末端激酶(c-Jun N-terminal Kinase, JNK)信号通路，显著抑制糖皮质激素受体的核转运能力，这一通路是病毒感染诱发哮喘激素不敏感的核心分子机制[57] [60]；同时，鼻病毒感染可诱导气道上皮细胞分泌 IL-25，进一步驱动 2 型免疫应答与过敏性气道炎症加剧，参与重症哮喘发生[63]。

细菌感染与中性粒细胞浸润型重症哮喘、顽固性激素抵抗相关。长期低剂量流感嗜血杆菌暴露，可诱导气道产生激素抵抗性中性粒细胞炎症，同时加速气道纤维化与结构重塑，参与重症哮喘发生[8]。此外，细菌感染能够激活 NLRP3 炎症小体，介导 IL-1β 依赖性炎症反应，同样是重症激素抵抗型哮喘发生的重要通路[58] [64]。与细菌感染类似，肺炎衣原体感染可调控激素抵抗型与敏感型哮喘患者的细胞因子表达，进一步加剧激素耐药状态，影响治疗效果[65]。

真菌致敏与气道定植同样与糖皮质激素抵抗、哮喘控制水平欠佳相关，并参与重症哮喘的发生[66]。真菌过敏原能够加剧气道内嗜酸性粒细胞炎症，与包括哮喘在内的多种气道过敏性疾病相关[67]。真菌能够诱导哮喘患者机体产生异常 Th2 细胞免疫应答[66]，与糖皮质激素抵抗密切相关。而 IL-33 介导的激素抵抗通路在儿童重症哮喘患者的真菌致敏中发挥了关键介导作用，是该类重症哮喘的核心致病机制[59]。

6. 遗传因素在重症哮喘发生中扮演关键角色

遗传因素通过调控气道炎症、气道重塑、多种细胞因子通路及抗哮喘药物治疗反应影响哮喘疗效，在重症哮喘的发生中扮演着关键角色。通过全基因组关联分析(Genome-Wide Association Study, GWAS)、表达数量性状位点(Expression Quantitative Trait Locus, eQTL)等方法，既往研究鉴定出了一些与重症哮喘相关的遗传变异及候选基因[68]。例如，解整合素金属蛋白酶 33 (ADAM33)基因的多态性与气道重塑、

支气管高反应性密切相关，在多个人群中均被证实与哮喘易感性及严重程度相关，且可能参与气道平滑肌细胞增殖调控，影响哮喘糖皮质激素治疗的效果、参与重症哮喘的发生[69]。MUC5AC 基因高表达可导致气道黏液分泌异常增多，参与气道高反应及黏液栓塞形成，是重症哮喘的重要病理特征相关基因[70]，而 MUC5AC 区域的 rs11603634 变异与轻度哮喘的关联无统计学意义，应为中重度哮喘特有的基因变异[71]。TSLP、TGF-β、IL-33、IL-1 RL1、IL-4 受体 α 位点、IL-6 受体等区域的突变，均被报道与哮喘严重程度及重症哮喘发生相关[72]-[76]。此外，已发现一些基因变异(如 GLCCI1、CRHR1 等)能够影响哮喘患者对糖皮质激素、白三烯受体拮抗剂、β2 受体激动剂等不同抗哮喘药物的治疗反应性，降低哮喘治疗效果和控制水平，参与重度哮喘的发生[52] [77]-[80]。

7. 临床启示与未来治疗方向

要将上述研究见解转化为临床治疗效果的提升，亟需制定多维度的研究和临床实践方案。未来的研究应借助气道类器官、单细胞组学和空间组学等先进技术，探究糖皮质激素对气道炎症状态、气道上皮屏障细胞状态及细胞间通讯的影响。

深入阐明哮喘表型背后的炎症机制，重视不同类群辅助 T 细胞炎症在哮喘炎症中的作用，探索相关针对性的靶向治疗手段对改善不同表型的重症哮喘治疗效果至关重要。

通过对气道上皮屏障完整性的生物标志物(如脱落细胞、脱落的细胞连接蛋白片段)的检测，可能实现对糖皮质激素治疗疗效的预测。在临床实践中，可将气道上皮屏障功能评估纳入哮喘管理体系，以此为基础探索更个体化的糖皮质激素治疗方案，并制定辅助干预策略(如靶向补充维生素 A 和维生素 D、研发并使用气道上皮屏障的保护药物、使用靶向抑制上皮源性炎症因子的生物制剂等)，最大限度减少糖皮质激素对气道上皮屏障的潜在损伤。

感染方面，应格外重视感染与重症哮喘之间的关联，对哮喘合并感染的患者应积极予以抗感染治疗，合理应用激素、通过有关辅助治疗减轻激素免疫抑制副作用促进气道感染控制。遗传因素方面，探索并阐明重症哮喘相关基因具有开发高危人群重症哮喘筛查、重症哮喘基因治疗方案的重要潜力。

8. 结论

重症哮喘的发生与进展是哮喘表型异质性、气道上皮屏障功能损伤、气道上皮炎症调控紊乱、感染及遗传因素等多环节、多因素共同参与、相互交织的复杂病理生理过程，各因素相互影响、相互协同，共同调控哮喘糖皮质激素治疗反应性和重症哮喘发生。

哮喘表型的多样性本质上反映了气道内主导炎症类型的差异，这种差异直接影响患者对糖皮质激素的治疗应答，是重症哮喘发生的重要驱动因素之一。气道上皮屏障作为呼吸道防御的核心结构，其理化屏障功能受损会显著增加气道病原体与变应原的侵入风险，进而加剧气道局部炎症反应，形成“气道炎症–上皮屏障损伤”的恶性循环；而糖皮质激素对气道上皮屏障具有的双重调控作用——既可通过抑制黏液高分泌、维持气道结构稳定性发挥保护效应，又可能诱导上皮细胞凋亡、抑制细胞增殖与损伤修复，最终削弱屏障完整性，这一矛盾效应可能是激素抵抗形成的关键机制，进而降低糖皮质激素抗哮喘治疗的反应性、促进重症哮喘发生。

气道上皮细胞不仅是构成气道物理屏障的核心成分，更是气道炎症调控的关键枢纽：其通过多种模式识别受体感知有害刺激并启动早期炎症应答，同时分泌 TSLP、IL-25、IL-33、GM-CSF 等多种细胞因子，精准调控气道炎症细胞募集及活化，其功能紊乱在激素抵抗与重症哮喘发生中具有不可替代的作用。感染是介导重症哮喘发生与激素抵抗的重要诱因，包括病毒、细菌、衣原体、真菌在内的多种病原体可通过激活特定的信号通路驱动激素抵抗，而糖皮质激素对气道固有免疫与适应性免疫的抑制作用会进一

步加重感染负荷，降低哮喘糖皮质激素治疗效果。

遗传因素在哮喘治疗反应性与重症哮喘易感性中发挥关键调控作用：ADAM33、MUC5AC、TSLP、IL-33 等基因多态性可通过调控气道重塑、黏液分泌、炎症通路活化等病理过程，直接参与重症哮喘发生；而 GLCCI1、CRHR1 等基因变异则能够直接调控患者对糖皮质激素及其他抗哮喘药物的治疗反应性，是激素抵抗与重症哮喘发生的重要遗传基础。

综上，哮喘表型、气道上皮屏障、上皮炎症调控、感染及遗传因素通过复杂的相互作用，共同构成重症哮喘发生与激素抵抗的核心病理生理网络。未来针对上述关键环节制定靶向干预策略，有望改善哮喘治疗效果、降低重症哮喘的发生率，为重症哮喘的精准防治提供新的思路与方向。

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