哮喘中脂质代谢紊乱的病理作用及干预策略

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[摘 要] 哮喘是一种异质性的慢性呼吸系统疾病，其病理生理学特征包括气流阻塞、平滑肌收缩、黏液分泌过多。近年来，随着肥胖型哮喘的流行和脂质组学等技术的进步，脂质代谢紊乱在哮喘病理生理学中的核心作用日益受到关注。脂质代谢通过调控能量转换、炎症信号转导及脂质介质(如白三烯、前列腺素)的生成，在哮喘发病机制(如炎症反应、气道高反应性和气道重塑)中发挥关键作用。靶向脂质代谢已成为药物开发策略且被证明有效。然而，目前尚无单一疗法能对所有哮喘患者有效。对哮喘患者进行代谢状态评估，有助于实现更精准的分型；对脂质营养与生活方式进行管理，有望为哮喘患者提供预防性保护。从脂质代谢角度审视哮喘能为精准治疗提供新的理论依据和实践方向。

[关键词] 哮喘；脂质代谢；脂质介质；炎症；气道重塑

Pathological roles of lipid metabolism disorders in asthma and related intervention strategies

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ABSTRACT Asthma is a heterogeneous chronic respiratory disease characterized by airflow obstruction, smooth muscle contraction, and excessive mucus secretion. In recent years, with the increasing prevalence of obesity-associated asthma and advances in technologies such as lipidomics, the central role of lipid metabolism disorders in the pathophysiology of asthma has attracted growing attention. Through regulating energy conversion, inflammatory signal transduction, and the generation of lipid mediators (such as leukotrienes and prostaglandins), lipid metabolism plays a critical role in the pathogenesis of asthma, including inflammatory responses, airway hyperresponsiveness, and airway remodeling. Targeting lipid metabolism has become an important strategy for drug development and has been proven effective. However, no single therapy is currently effective for all patients with asthma. Evaluation of the metabolic status of asthma patients may contribute to more

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precise phenotyping, while management of lipid nutrition and lifestyle may provide preventive protection for asthma patients. Examining asthma from the perspective of lipid metabolism may provide new theoretical foundations and practical directions for precision therapy.

KEY WORDS　asthma; lipid metabolism; lipid mediators; inflammation; airway remodeling

哮喘是一种以慢性气道炎症和气道高反应性为特征的异质性疾病。传统观点主要关注免疫细胞和细胞因子的作用[1]。近年来，随着脂质组学等技术的进步，脂质代谢紊乱在哮喘病理生理学中的核心作用日益受到关注[1-4]，为开发新治疗策略提供了新视角。

常见的脂质主要分为脂肪、固醇和磷脂3种类型。其中，磷脂(包含甘油磷脂和鞘磷脂)及胆固醇构成了生物膜的主要成分[1]。构成脂质基本成分之一的脂肪酸不仅参与能量代谢，其酯化形成的甘油三酯也是细胞内能量储存和传递的主要形式[1]。脂质也参与第二信使的合成，这些信使源于膜脂的磷脂酶(phospholipase，PL)依赖性水解和必需脂肪酸的转化。PL(包括PLC、PLD和PLA)可以产生许多具有生物活性的第二信使，如二酰甘油、磷脂酸、溶血磷脂酸和花生四烯酸(eicosatetraenoic acid，AA)[2]。这些证据表明，脂质代谢在维持机体正常功能和稳态方面发挥了关键作用。

越来越多的证据[3-4]表明，脂质不仅仅是细胞的结构成分和能量来源，更是重要的信号分子，其代谢网络的失调是驱动哮喘慢性炎症和免疫功能紊乱的核心环节之一。肥胖型哮喘的流行进一步凸显了代谢-免疫交互作用的重要性。

1 脂质代谢紊乱在哮喘中的病理作用

1.1 脂质代谢紊乱与气道炎症

哮喘患者的脂质代谢呈现特征性失衡，主要表现为脂肪酸和ω-6/ω-3多不饱和脂肪酸(polyunsaturated fatty acid，PUFA)的水平变化[5-10]。

饱和脂肪酸(saturated fatty acid，SFA)与肥胖相关，并能加重屋尘螨诱导的小鼠气道炎症[7]。SFA为Toll样受体(Toll-like receptor，TLR)4的配体，可通过脂肪酸介导的细胞毒性诱导小鼠巨噬细胞和脂肪细胞中核因子κB(nuclear factor κB，NF-κB)和c-Jun氨基端激酶(c-Jun N-terminal kinase，JNK)的激活[8]。肥胖型哮喘患者中，SFA和单不饱和脂肪酸水平升高，且与痰液中的中性粒细胞比例呈正相关[9]。

哮喘患者的ω-6/ω-3 PUFA的比例显著高于健康人[5-6]。PUFA是细胞膜的重要组成部分和功能性脂质介质，可以分为ω-6 PUFA和ω-3 PUFA[10]。AA是主要的ω-6 PUFA，也是许多促炎性脂质介质的前体，如前列腺素(prostaglandin，PG)和白三烯(leukotriene，LT)[11-12]。半胱氨酰LT(cysteinyl LT，CysLT)包括LTC4、LTD4和LTE4，是过敏性炎症的强效介质，可通过结合相应受体介导支气管收缩、黏液分泌、嗜酸性粒细胞募集和炎症反应[13]。严重哮喘患者的支气管肺泡灌洗液(bronchoalveolar lavage fluid，BALF)或血液中的LTB4和血栓素B2水平高于中度哮喘患者和正常人，LTB4和血栓素B2可直接招募中性粒细胞、诱发支气管痉挛和血管渗漏[14]。ω-3 PUFA如二十碳五烯酸(eicosapentaenoic acid，EPA)和二十二碳六烯酸(docosahexaenoic acid，DHA)，可以竞争性地抑制环氧合酶(cyclooxygenase，COX)或脂加氧酶(lipoxygenase，LOX)对ω-6 PUFA的氧化，并抑制ω-6 PUFA生成促炎性类花生酸[11]，通常被认为具有抗炎作用。ω-3和ω-6 PUFA也是特异性促炎症消退介质(specialized pro-resolving mediator，SPM)的前体，包括脂氧素(lipoxin，LX)、消退素(resolvin，Rv)、保护素(protectin，PD)等，这些介质能够主动终止炎症，并启动组织修复。例如，LXA4通过与其受体结合，可抑制嗜酸性粒细胞和T细胞的募集、积累和活化，减少PGE2和细胞因子白细胞介素(interleukin，IL)-25、IL-33的释放，并促进自然杀伤(natural killer，NK)细胞介导的嗜酸性粒细胞凋亡，从而减轻过敏性气道炎症[15]。

磷脂和视黄醇的代谢也与哮喘炎症表型密切相关。轻度、中度和重度哮喘患者的血清代谢谱存在差异，其中油酸乙醇胺水平随哮喘严重程度加重而上升[16]。非结合胆红素与儿童哮喘及婴幼儿期反复喘息密切相关[17]。同时患有食物过敏和哮喘的儿童患者，其脂质代谢物(尤其是鞘脂与神经酰胺)的代谢特征谱亦发生显著改变[18]。嗜酸性与非嗜酸性粒细胞性哮喘患者的血清甘油磷脂代谢谱存在显著差异[19]。嗜酸性哮喘患者代谢谱中溶血磷脂酰甘油

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(lysophosphatidylglycerol，LPG)水平显著升高，LPG可能成为哮喘分型的关键生物标志物[20]。

以上变化可通过多条途径加剧气道炎症：脂肪酸过氧化、磷脂双层损伤和甘油磷脂代谢异常导致膜结构完整性被破坏，其中磷脂双层损伤还可导致气道上皮屏障功能障碍[21]；胆固醇富集的脂筏微域结构改变，增强TLR4聚集并激活NF-κB，促进胸腺基质淋巴细胞生成素(thymic stromal lymphopoietin，TSLP)释放，驱动辅助性T细胞(helper T cell，Th)介导的炎症；而脂筏内聚集的鞘磷脂通过磷脂酰肌醇3激酶(phosphoinositide 3-kinase，PI3K)/蛋白激酶B(protein kinase B，Akt)通路抑制糖皮质激素受体核转位，导致激素抵抗[22-23]；游离脂肪酸激活巨噬细胞，诱导其释放肿瘤坏死因子(tumor necrosis factor，TNF)-α、IL-6、IL-1β等促炎因子[24]；从头脂肪酸合成控制着调节性T细胞(regulatory T cell，Treg)和Th17之间的命运决定[25]。羟基固醇作为维甲酸相关孤核受体(retinoic acid-related orphan receptor，ROR)γt的配体驱动Th17分化[26]，SFA促进Th2/Th17反应，增加IL-4、IL-5、IL-13分泌[27]。脂质介质通过促炎和促消退的双重作用动态调控气道炎症。在哮喘中，ω-6/ω-3 PUFA比例失衡、SPM合成缺陷及巨噬细胞脂质重编程均导致炎症失控。

1.2 脂质代谢异常驱动气道重塑

气道重塑是重症哮喘的核心病理改变，其特征包括基底膜增厚、平滑肌增生和杯状细胞化生。脂质代谢紊乱通过以下机制参与此过程：1)脂质信号分子介导平滑肌增殖与迁移。氧化三酰甘油等脂质过氧化物激活Ras同源家族成员(Ras homolog gene family member，Rho)A鸟苷三磷酸酶及下游Rho激酶(Rho-kinase，ROCK)通过磷酸化肌球蛋白轻链[28]，增强气道平滑肌(airway smooth muscle，ASM)收缩力。ASM的增殖、肥大导致气道狭窄，同时促进气道高反应性，并释放生长因子参与气道重塑[29]。临床证据[30]显示，哮喘患者ASM中RhoA表达升高2.3倍，ROCK活性增加与第1秒用力呼气量(forced expiratory volume in one second，FEV_1)下降呈负相关。胆固醇合成中间体甲羟戊酸通过香叶基香叶基化修饰RhoA，促进其膜转位与激活。辛伐他汀[羟基甲基戊二酸酰辅酶A(hydroxymethylglutaryl-coenzyme A，HMG-CoA)还原酶抑制剂]阻断此过程，可抑制70%血清诱导的ASM增殖[31]。2)脂质代谢产物促进细胞外基质沉积。哮喘患者支气管肺泡灌洗液中神经酰胺水平升高3.5倍，其通过激活转化生长因子(transforming growth factor，TGF)-β/Sma和Mad相关蛋白(Sma- and Mad-related protein，Smad)通路，刺激成纤维细胞向肌成纤维细胞转化，增加胶原I/III合成[21]。磷脂酰胆碱/磷脂酰乙醇胺比例倒置导致上皮细胞膜流动性改变，紧密连接蛋白[如闭锁小带蛋白-1(zonula occludens-1，ZO-1)]表达减少，加剧上皮屏障损伤；受损的上皮组织释放TGF-β1，诱导成纤维细胞增殖及基底膜增厚[32]。胆固醇合成中间体甲羟戊酸通过组蛋白修饰影响促炎基因表达[33]。

1.3 肥胖与哮喘共病的代谢病理机制

肥胖是哮喘的风险因素，且二者共病率在全球范围内显著增加，具有复杂的共同代谢基础[34]，主要涉及氧化应激与线粒体功能障碍、胰岛素抵抗与糖代谢异常以及脂肪因子网络失衡。

氧化应激与线粒体功能障碍。支气管哮喘患者表现出较高的氧化应激水平[21]，其体内活性氧(reactive oxygen species，ROS)主要来源于线粒体呼吸链功能障碍及免疫细胞的激活。此外，脂质介质、趋化因子、黏附分子等其他因素也可促进ROS的产生[35]。ROS通过直接氧化损伤上皮细胞并导致细胞脱落，引发肺损伤[36]。ROS也可导致哮喘的多种病理生理变化，包括AA释放增强、ASM收缩、气道反应性和分泌物增加、血管通透性升高。氧化应激可能损害支气管上皮细胞中的TLR3，进一步加剧气道炎症[37]。哮喘患者的脂肪酸摄入与脂肪酸氧化(fatty acid oxidation，FAO)过程增强[38]，因此，抑制FAO可减轻气道高反应性和炎症细胞的活化[39]。研究[40]显示，氧化应激和炎症水平增加可能促进气道重塑，最终导致不可逆的气道阻塞。在肥胖哮喘患者中，脂质过氧化代谢物也可能对呼吸道上皮损伤起到促进作用[21]。肥胖导致脂肪组织和气道细胞线粒体DNA损伤、复合体I/III活性下降，促进ROS堆积[41]。ROS通过激活炎症小体核苷酸结合结构域富含亮氨酸重复序列和含热蛋白结构域受体(nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor，NLRP3)，剪切IL-1β/IL-18的前体并促进其成熟和释放，加剧气道炎症。哮喘患者气道上皮细胞肉碱棕榈酰转移酶1A表达降低，导致乙酰辅酶A积累。后者通过组蛋白乙酰化开放促纤维化基因[如1型胶原蛋白α1(collagen α1 type 1，COL1A1)]，促进气道重塑[42]。肥胖哮喘患者中线粒体生物合成标志物过氧化物酶体增殖物激活受体γ共激活因子1α(peroxisome proliferator-activated receptor-gamma coactivator 1-alpha，PGC-1α)表达降低，与FEV_1下降相关[43]。

胰岛素抵抗与糖代谢异常。高胰岛素血症下调

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胰岛素受体底物(insulin receptor substrate，IRS-1)磷酸化水平，减弱糖皮质激素受体转录活性，导致激素抵抗。高血糖还可通过激活细胞胞外信号调节激酶(extracellular signal-regulated kinase，ERK)1/2途径促进ASM增殖，诱导晚期糖基化终末产物(advanced glycation end product，AGE)的形成和积累，破坏上皮屏障[44]。研究[45]表明，合并胰岛素抵抗的哮喘患者急性发作风险增加80%，FEV_1改善率降低50%。

脂肪因子网络失衡。肥胖者瘦素水平较正常人群升高3~5倍，其可通过激活Janus激酶(Janus kinase，JAK2)/信号转导及转录活化因子(signal transducer and activator of transcription，STAT)3通路，促进Th1/Th17分化，增加TNF-α、IL-6分泌，同时增强ASM收缩[46]；同时，脂联素水平降低60%，削弱过氧化物酶体增殖物激活受体(peroxisome-proliferator-activated receptor，PPAR)-γ的抗炎作用，导致NF-κB持续活化[45]。

2 针对脂质代谢的哮喘干预策略

基于上述病理机制，靶向脂质代谢通路为哮喘治疗提供了极具前景的新策略，包括药物治疗和非药物干预。

2.1 药物治疗

基于脂质代谢异常与哮喘的交互作用机制，探索降脂药物对改善气道炎症及组织重塑的潜在治疗价值，已成为哮喘靶向治疗的重要研究方向。

抗LT药物是一类抗炎药物，通过抑制LT通路发挥治疗作用，主要包括：5-LOX抑制剂(阻断LT合成)和LT受体拮抗剂(阻断LT受体)[47]。5-LOX是AA代谢通路的限速酶，其在LT生物合成中具有关键地位，特异性抑制5-LOX活性可阻断下游炎症介质的产生[48]，为哮喘治疗提供可能。目前，Zileuton是唯一可用的抑制剂，其可有效改善气道功能并减轻哮喘症状，成为哮喘管理的重要手段[49]。新型抑制剂Setileuton(MK-0633)的临床试验数据[50]显示，其在100毫克剂量下表现出一定的抗哮喘疗效。此外，在哮喘治疗中，LT受体拮抗剂联合吸入性糖皮质激素能显著改善肺功能[如FEV_1、最大呼气流量(maximal expiratory flow，MEF)][51]，降低需全身性糖皮质激素治疗的急性加重风险[52]，有效改善哮喘控制问卷(Asthma Control Questionnaire，ACQ)评分[53]。其中，LT受体拮抗剂代表药物孟鲁司特已通过多项研究[54-55]验证，其在减少哮喘急性发作和维持长期病情控制方面具有明确疗效。

瑞舒伐他汀已被证明可通过抑制Th2和Th17介导的细胞因子产生来改善肺组织病理损伤[56]。瑞舒伐他汀可以减轻气道炎症和氧化损伤，通过影响一氧化氮合酶活性，降低体外促炎细胞因子水平，并减轻炎症细胞浸润[57]。辛伐他汀可以降低支气管肺泡灌洗液中IL-4和IL-5的水平，并在哮喘早期阻止气道重塑的进展。在临床队列研究[58]中发现，哮喘患者使用他汀类药物与哮喘发作住院次数减少之间存在关联，且他汀类药物可以提高哮喘患者吸入糖皮质激素的抗炎效果。但是目前使用他汀类药物治疗哮喘的临床试验仍存在一定局限性，其治疗效果仍不稳定。临床试验中他汀对儿童哮喘疗效存疑，提示需个体化用药。

非诺贝特、苯扎贝特等贝特类药物可激活PPAR-α[59]，从而降低血脂水平，同样也是应用于临床上的经典降脂药物。已有研究[60]表明，非诺贝特和地塞米松联合使用可抑制哮喘模型大鼠中IL-23和IL-17的产生，这提示了降脂药联合治疗方案在哮喘治疗中的有效性。此外，非诺贝特可通过抑制TGF-β/Smad2/3信号通路减少哮喘相关成纤维细胞向肌成纤维细胞的转变，从而治疗和预防哮喘支气管重塑[61]。近年来，针对哮喘治疗的脂质代谢药物同样引起了广泛关注。其中，5-脂氧合酶激活蛋白(5-lipoxygenase-activating protein，FLAP)抑制剂和PG靶向药物已进入临床试验阶段[62]。这些药物通过抑制5-LOX和FLAP，能够有效减轻哮喘炎症，改善患者的症状。临床试验结果[62]表明，FLAP抑制剂和PG靶向药物不仅在疗效上表现良好，而且在安全性方面也得到认可，为哮喘患者提供了新的治疗选择。

2.2 非药物干预

营养干预可能是最具成本效益的策略。地中海饮食通过多重途径发挥作用：每日摄入>46 g鱼类(富含EPA/DHA)可使得呼出气一氧化氮(fractional exhaled nitric oxide，FeNO)降低14.15 ppb[63]；高多酚橄榄油调节肠道菌群，增加短链脂肪酸生成，间接抑制肺部炎症[64]。研究[6]发现，优化ω-6/ω-3 PUFA比例、补充EPA/DHA(1.5 g/d)8周后，痰液嗜酸性粒细胞下降35%，急救药物使用减少40%。

代谢负荷管理同样关键。运动训练可通过减少脂肪量和增加去脂体重以及提高有氧适能来改善哮喘[65]。研究[66]表明，减肥至少在一定程度上通过改善肺功能和改变炎症生物标志物来改善哮喘；此外，身体能力的提高会影响炎症和抗炎病理生理途径，从而影响哮喘。这些发现表明，在营养治疗中加入运动是临床控制肥胖患者哮喘的有效策略。

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3 结 语

哮喘中的脂质代谢紊乱不仅是疾病伴随现象，更是驱动气道炎症和重塑的核心病理机制。从脂肪酸谱失衡到胆固醇代谢异常，从膜磷脂改变到脂质介质失调，这些变化共同构成了复杂的代谢炎症网络。深入理解这些脂质代谢异常，可从新维度揭示哮喘的发病机制，也为开发更有效和更特异的干预策略提供了广阔前景。脂质代谢领域的研究正推动哮喘治疗从症状管理转向更深层次的病理生理调控。未来研究需进一步整合多组学技术，解析不同哮喘表型的代谢特征，推动脂质靶向治疗向个体化、精准化迈进。

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参考文献

[1] Kume H, Kazama K, Sato R, et al. Possible involvement of lysophospholipids in severe asthma as novel lipid mediators[J]. Biomolecules, 2025, 15(2): 182. https://doi.org/10.3390/biom15020182.

[2] Barreno-Rocha SG, Guzmán-Silahua S, Rodríguez-Dávila SDC, et al. Antiphospholipid antibodies and lipids in hematological malignancies[J]. Int J Mol Sci, 2022, 23(8): 4151. https://doi.org/10.3390/ijms23084151.

[3] Li WJ, Zhao Y, Gao Y, et al. Lipid metabolism in asthma: Immune regulation and potential therapeutic target[J]. Cell Immunol, 2021, 364: 104341. https://doi.org/10.1016/j.cellimm.2021.104341.

[4] Sharma V, Cowan DC. Obesity, inflammation, and severe asthma: an update[J]. Curr Allergy Asthma Rep, 2021, 21(12): 46. https://doi.org/10.1007/s11882-021-01024-9.

[5] Yoshida K, Morishima Y, Ishii Y, et al. Abnormal saturated fatty acids and sphingolipids metabolism in asthma[J]. Respir Investig, 2024, 62(4): 526-530. https://doi.org/10.1016/j.resinv.2024.04.006.

[6] Zhou J, Chen L, Liu Z, et al. Changes in erythrocyte polyunsaturated fatty acids and plasma eicosanoids level in patients with asthma[J]. Lipids Health Dis, 2018, 17(1): 206. https://doi.org/10.1186/s12944-018-0853-y.

[7] Tashiro H, Kuwahara Y, Takahashi K. Gut-lung axis in asthma and obesity: role of the gut microbiome[J]. Front Allergy, 2025, 6: 1618466. https://doi.org/10.3389/falgy.2025.1618466.

[8] Uribe-Querol E, Rosales C. Neutrophils actively contribute to obesity-associated inflammation and pathological complications [J]. Cells, 2022, 11(12): 1883. https://doi.org/10.3390/cells11121883.

[9] Wood LG, Garg ML, Gibson PG. A high-fat challenge increases airway inflammation and impairs bronchodilator recovery in asthma[J]. J Allergy Clin Immunol, 2011, 127(5): 1133-1140. https://doi.org/10.1016/j.jaci.2011.01.036.

[10] Sandoval C, Nahuelqueo K, Mella L, et al. Role of long-chain polyunsaturated fatty acids, eicosapentaenoic and docosahexaenoic, in the regulation of gene expression during the development of obesity: a systematic review[J]. Front Nutr, 2023, 10: 1288804. https://doi.org/10.3389/fnut.2023.1288804.

[11] Wendell SG, Baffi C, Holguin F. Fatty acids, inflammation, and asthma[J]. J Allergy Clin Immunol, 2014, 133(5): 1255-1264. https://doi.org/10.1016/j.jaci.2013.12.1087.

[12] Oliver PJ, Arutla S, Yenigalla A, et al. Lipid nutrition in asthma [J]. Cell Biochem Biophys, 2021, 79(3): 669-694. https://doi.org/10.1007/s12013-021-01020-w.

[13] Lee M, Boyce JA, Barrett NA. Cysteinyl leukotrienes in allergic inflammation[J]. Annu Rev Pathol, 2025, 20(1): 115-141. https://doi.org/10.1146/annurev-pathmechdis-111523-023509.

[14] Wenzel SE, Szefler SJ, Leung DY, et al. Bronchoscopic evaluation of severe asthma. Persistent inflammation associated with high dose glucocorticoids[J/OL]. Am J Respir Crit Care Med, 1997, 156(3 Pt 1): 737-743[2025-11-01]. https://doi.org/10.1164/ajrccm.156.3.9610046.

[15] Kytikova O, Novgorodtseva T, Denisenko Y, et al. Pro-resolving lipid mediators in the pathophysiology of asthma[J]. Medicina, 2019, 55(6): 284. https://doi.org/10.3390/medicina55060284.

[16] Reinke SN, Gallart-Ayala H, Gómez C, et al. Metabolomics analysis identifies different metabotypes of asthma severity [J]. Eur Respir J, 2017, 49(3): 1601740. https://doi.org/10.1183/13993003.01740-2016.

[17] Turi KN, McKennan C, Gebretsadik T, et al. Unconjugated bilirubin is associated with protection from early-life wheeze and childhood asthma[J]. J Allergy Clin Immunol, 2021, 148 (1): 128-138. https://doi.org/10.1016/j.jaci.2020.12.639.

[18] Roshan Lal T, Cechinel LR, Freishtat R, et al. Metabolic contributions to pathobiology of asthma[J]. Metabolites, 2023, 13(2): 212. https://doi.org/10.3390/metabo13020212.

[19] Pité H, Morais-Almeida M, Rocha SM. Metabolomics in asthma: where do we stand?[J]. Curr Opin Pulm Med, 2018, 24 (1): 94-103. https://doi.org/10.1097/MCP.0000000000000437.

[20] Gai XY, Zhang LJ, Chang C, et al. Metabolomic analysis of serum glycerophospholipid levels in eosinophilic and neutrophilic asthma[J]. Biomed Environ Sci, 2019, 32(2): 96-106. https://doi.org/10.3967/bes2019.013.

[21] Wang C, Jiang S, Zhang S, et al. Research progress of metabolomics in asthma[J]. Metabolites, 2021, 11(9): 567. https://doi.org/10.3390/metabo11090567.

[22] Kotlyarov S, Kotlyarova A. Molecular mechanisms of lipid metabolism disorders in infectious exacerbations of chronic obstructive pulmonary disease[J]. Int J Mol Sci, 2021, 22(14): 7634. https://doi.org/10.3390/ijms22147634.

[23] Zhao B, Shi C, Wang X, et al. Kechuan Decoction mitigates

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apoptosis of airway epithelial cells by improving lipid metabolism disorders and mitochondria dysfunction in HDM-induced asthma[J]. Phytomedicine, 2025, 136: 156299. https://doi.org/10.1016/j.phymed.2024.156299.

[24] Jia YM, Wang HX, Ma B, et al. Lipid metabolism-related genes are involved in the occurrence of asthma and regulate the immune microenvironment[J]. BMC Genomics, 2024, 25(1): 129. https://doi.org/10.1186/s12864-023-09795-3.

[25] Kanno T, Nakajima T, Miyako K, et al. Lipid metabolism in Th17 cell function[J]. Pharmacol Ther, 2023, 245: 108411. https://doi.org/10.1016/j.pharmthera.2023.108411.

[26] Kanno T, Miyako K, Endo Y. Lipid metabolism: a central modulator of RORγt-mediated Th17 cell differentiation[J]. Int Immunol, 2024, 36(10): 487-496. https://doi.org/10.1093/intimm/dxae031.

[27] Lim JE, Kim HM, Kim JH, et al. Association between dyslipidemia and asthma in children: a systematic review and multicenter cohort study using a common data model[J]. Clin Exp Pediatr, 2023, 66(8): 357-365. https://doi.org/10.3345/cep.2023.00290.

[28] Amer M, Shi LD, Wolfenson H. The ‘Yin and Yang’ of cancer cell growth and mechanosensing[J]. Cancers, 2021, 13(19): 4754. https://doi.org/10.3390/cancers13194754.

[29] Khalfaoui L, Pabelick CM. Airway smooth muscle in contractility and remodeling of asthma: potential drug target mechanisms[J]. Expert Opin Ther Targets, 2023, 27(1): 19-29. https://doi.org/10.1080/14728222.2023.2177533.

[30] Zhang Y, Saradna A, Ratan R, et al. RhoA/Rho-kinases in asthma: from pathogenesis to therapeutic targets[J/OL]. Clin Transl Immunology, 2020, 9(5): e1134[2025-11-01]. https://doi.org/10.1002/cti2.1134.

[31] Takeda N, Kondo M, Ito S, et al. Role of RhoA inactivation in reduced cell proliferation of human airway smooth muscle by simvastatin[J]. Am J Respir Cell Mol Biol, 2006, 35(6): 722-729. https://doi.org/10.1165/rcmb.2006-0034OC.

[32] Qin Z, Chen Y, Wang Y, et al. Immunometabolism in the pathogenesis of asthma[J]. Immunology, 2024, 171(1): 1-17. https://doi.org/10.1111/imm.13688.

[33] Bekkering S, Arts RJW, Novakovic B, et al. Metabolic induction of trained immunity through the mevalonate pathway[J/OL]. Cell, 2018, 172(1/2): 135-146.e9[2025-11-01]. https://doi.org/10.1016/j.cell.2017.11.025.

[34] Monga N, Sethi GS, Kondepudi KK, et al. Lipid mediators and asthma: Scope of therapeutics[J]. Biochem Pharmacol, 2020, 179: 113925. https://doi.org/10.1016/j.bcp.2020.113925.

[35] Kirkham P, Rahman I. Oxidative stress in asthma and COPD: antioxidants as a therapeutic strategy[J]. Pharmacol Ther, 2006, 111(2): 476-494. https://doi.org/10.1016/j.pharmthera.2005.10.015.

[36] Wu SJ, Liou CJ, Chen YL, et al. Fucoxanthin ameliorates oxidative stress and airway inflammation in tracheal epithelial cells and asthmatic mice[J]. Cells, 2021, 10(6): 1311. https://doi.org/10.3390/cells10061311.

[37] Menzel M, Ramu S, Calvén J, et al. Oxidative stress attenuates TLR3 responsiveness and impairs anti-viral mechanisms in bronchial epithelial cells from COPD and asthma patients[J]. Front Immunol, 2019, 10: 2765. https://doi.org/10.3389/fimmu.2019.02765.

[38] Esteves P, Blanc L, Celle A, et al. Crucial role of fatty acid oxidation in asthmatic bronchial smooth muscle remodelling [J]. Eur Respir J, 2021, 58(5): 2004252. https://doi.org/10.1183/13993003.04252-2020.

[39] Koh J, Woo YD, Yoo HJ, et al. *De novo* fatty-acid synthesis protects invariant NKT cells from cell death, thereby promoting their homeostasis and pathogenic roles in airway hyperresponsiveness[J]. eLife, 2023, 12: RP87536. https://doi.org/10.7554/eLife.87536.

[40] Mak JCW, Ho SP, Ho ASS, et al. Sustained elevation of systemic oxidative stress and inflammation in exacerbation and remission of asthma[J]. ISRN Allergy, 2013, 2013: 561831. https://doi.org/10.1155/2013/561831.

[41] Włodarczyk M, Nowicka G. Obesity, DNA damage, and development of obesity-related diseases[J]. Int J Mol Sci, 2019, 20(5): 1146. https://doi.org/10.3390/ijms20051146.

[42] Bhatraju NK, Agrawal A. Mitochondrial dysfunction linking obesity and asthma[J/OL]. Ann Am Thorac Soc, 2017, 14(Supplement_5): S368-S373[2025-11-01]. https://doi.org/10.1513/AnnalsATS.201701-042AW.

[43] Hartsoe P, Holguin F, Chu HW. Mitochondrial dysfunction and metabolic reprogramming in obesity and asthma[J]. Int J Mol Sci, 2024, 25(5): 2944. https://doi.org/10.3390/ijms25052944.

[44] Yuan X, Zhang Q, Li J, et al. Nup93-mediated RNA alternative splicing associated with diabetic atherosclerosis[J]. Mol Cell Proteomics, 2025, 24(9): 101029. https://doi.org/10.1016/j.mcpro.2025.101029.

[45] Škrgat S, Harlander M, Janić M. Obesity and insulin resistance in asthma pathogenesis and clinical outcomes[J]. Biomedicines, 2024, 12(1): 173. https://doi.org/10.3390/biomedicines12010173.

[46] Artemniak-Wojtowicz D, Kucharska AM, Pyrżak B. Obesity and chronic inflammation crosslinking[J]. Cent Eur J Immunol, 2020, 45(4): 461-468. https://doi.org/10.5114/ceji.2020.103418.

[47] Zhao Y, Zhang X, Han C, et al. Pharmacogenomics of leukotriene modifiers: a systematic review and meta-analysis[J]. J Pers Med, 2022, 12(7): 1068. https://doi.org/10.3390/jpm12071068.

[48] Bruno F, Spaziano G, Liparulo A, et al. Recent advances in the search for novel 5-lipoxygenase inhibitors for the treatment of asthma[J]. Eur J Med Chem, 2018, 153: 65-72. https://doi.org/10.1016/j.ejmech.2017.10.020.

[49] Israel E, Rubin P, Kemp JP, et al. The effect of inhibition of 5-lipoxygenase by zileuton in mild-to-moderate asthma[J]. Ann Intern Med, 1993, 119(11): 1059-1066. https://doi.org/10.7326/0003-4819-119-11-199312010-00001.

[50] Wasfi YS, Villarán C, Le Bailly de Tilleghem C, et al. The efficacy and tolerability of MK-0633, a 5-lipoxygenase inhibitor, in chronic asthma[J]. Respir Med, 2012, 106(1): 34-46. https://doi.org/10.1016/j.rmed.2011.08.019.

[51] Chauhan BF, Jeyaraman MM, Singh Mann A, et al. Addition of

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anti-leukotriene agents to inhaled corticosteroids for adults and adolescents with persistent asthma[J/OL]. Cochrane Database Syst Rev, 2017, 3(3): CD010347[2025-11-01]. https://doi.org/10.1002/14651858.CD010347.pub2.

[52] Ducharme F, Schwartz Z, Hicks G, et al. Addition of anti-leukotriene agents to inhaled corticosteroids for chronic asthma [J/OL]. Cochrane Database Syst Rev, 2004, 2004(2): CD003133 [2025-11-01]. https://doi.org/10.1002/14651858.CD003133.pub2.

[53] Price D, Musgrave SD, Shepstone L, et al. Leukotriene antagonists as first-line or add-on asthma-controller therapy[J]. N Engl J Med, 2011, 364(18): 1695-1707. https://doi.org/10.1056/NEJMoa1010846.

[54] Dockhorn RJ, Baumgartner RA, Leff JA, et al. Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients[J]. Thorax, 2000, 55(4): 260-265. https://doi.org/10.1136/thorax.55.4.260.

[55] Al Qahtani SY. Efficacy and safety of intravenous leukotriene receptor antagonists in acute asthma[J]. Am J Med Sci, 2023, 366(1): 22-26. https://doi.org/10.1016/j.amjms.2023.04.012.

[56] Saadat S, Mohamadian Roshan N, Aslani MR, et al. Rosuvastatin suppresses cytokine production and lung inflammation in asthmatic, hyperlipidemic and asthmatic-hyperlipidemic rat models[J]. Cytokine, 2020, 128: 154993. https://doi.org/10.1016/j.cyto.2020.154993.

[57] Sunata K, Miyata J, Kawashima Y, et al. Inflammatory profile of eosinophils in asthma-COPD overlap and eosinophilic COPD: a multi-omics study[J]. Front Immunol, 2024, 15: 1445769. https://doi.org/10.3389/fimmu.2024.1445769.

[58] Park C, Jang JH, Kim C, et al. Real-world effectiveness of statin therapy in adult asthma[J/OL]. J Allergy Clin Immunol Pract, 2024, 12(2): 399-408.e6[2025-11-01]. https://doi.org/10.1016/j.jaip.2023.10.029.

[59] Wang XJ, Zhang J, Wang SQ, et al. Identification of novel multitargeted PPARα/γ/δ pan agonists by core hopping of rosiglitazone[J]. Drug Des Devel Ther, 2014, 8: 2255-2262. https://doi.org/10.2147/DDDT.S70383.

[60] Elaidy SM, Essawy SS, Hussain MA, et al. Modulation of the IL-23/IL-17 axis by fenofibrate ameliorates the ovalbumin/lipopolysaccharide-induced airway inflammation and bronchial asthma in rats[J]. Naunyn Schmiedebergs Arch Pharmacol, 2018, 391(3): 309-321. https://doi.org/10.1007/s00210-017-1459-z.

[61] Paw M, Wnuk D, Kądziołka D, et al. Fenofibrate reduces the asthma-related fibroblast-to-myofibroblast transition by TGF-B/Smad2/3 signaling attenuation and connexin 43-dependent phenotype destabilization[J]. Int J Mol Sci, 2018, 19(9): 2571. https://doi.org/10.3390/ijms19092571.

[62] Gür ZT, Çalışkan B, Banoglu E. Drug discovery approaches targeting 5-lipoxygenase-activating protein (FLAP) for inhibition of cellular leukotriene biosynthesis[J]. Eur J Med Chem, 2018, 153: 34-48. https://doi.org/10.1016/j.ejmech.2017.07.019.

[63] Papamichael MM, Katsardis C, Lambert K, et al. Efficacy of a Mediterranean diet supplemented with fatty fish in ameliorating inflammation in paediatric asthma: a randomised controlled trial[J]. J Hum Nutr Diet, 2019, 32(2): 185-197. https://doi.org/10.1111/jhn.12609.

[64] Perrone P, D'Angelo S. Gut microbiota modulation through Mediterranean diet foods: implications for human health[J]. Nutrients, 2025, 17(6): 948. https://doi.org/10.3390/nu17060948.

[65] Endrigue TC, Lunardi AC, Freitas PD, et al. Characteristics of individuals with moderate to severe asthma who better respond to aerobic training: a cluster analysis[J/OL]. J Bras Pneumol, 2023, 49(1): e20220225[2025-11-01]. https://doi.org/10.36416/1806-3756/e20220225.

[66] Valkenborghs SR, Wood LG, Callister R, et al. Effects of moderate-versus vigorous-intensity exercise training on asthma outcomes in adults[J/OL]. J Allergy Clin Immunol Pract, 2024, 12(10): 2744-2753.e8[2025-11-01]. https://doi.org/10.1016/j.jaip.2024.06.015.

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