Asian Case Reports in Emergency Medicine 亚洲急诊医学病例研究, 2025, 13(1), 33-43
Published Online February 2025 in Hans. https://www.hanspub.org/journal/acrem
https://doi.org/10.12677/acrem.2025.131006

Hans汉斯

哮喘相关生物标志物的研究进展

廖明月，李建保

成都中医药大学临床医学院，四川 成都

收稿日期：2024年12月23日；录用日期：2025年2月3日；发布日期：2025年2月12日

摘　要

哮喘异质性强，随着对哮喘机制与治疗手段的认识要求提高，现有的哮喘诊断体系亟需随之更新。生物标志物是可以反映生理、病理机制与治疗效果的指标，理想的生物标志物应具有敏感性、特异性，能够提供阳性和阴性预测值，同时测量简单且具有成本效益。目前已有许多着眼于哮喘生物标志物的研究，但尚未获得更多经过验证可供于投入临床的生物标志物。本文就典型与新兴哮喘诊断相关生物标志物的研究进展进行综述。

关键词

哮喘，诊断，生物标志物

Advances in Asthma-Related Biomarkers

Mingyue Liao, Jianbao Li

Clinical Medical College, Chengdu University of Traditional Chinese Medicine, Chengdu Sichuan

Received: Dec. 23rd, 2024; accepted: Feb. 3rd, 2025; published: Feb. 12th, 2025

Abstract

Asthma is highly heterogeneous, and as the understanding of asthma mechanisms and therapeutic means increases, there is an urgent need to update the existing asthma diagnostic system accordingly. Biomarkers are indicators of physiologic and pathologic mechanisms and therapeutic efficacy. Ideally, biomarkers should be sensitive, specific, providing positive and negative predictive values, and be simple and cost-effective to measure. There have been many studies focusing on asthma biomarkers, but more validated biomarkers are not yet available. This article provides a review of the progress of research on typical and emerging biomarkers relevant to asthma diagnosis.

Keywords

Asthma, Diagnosis, Biomarker

文章引用: 廖明月, 李建保. 哮喘相关生物标志物的研究进展[J]. 亚洲急诊医学病例研究, 2025, 13(1): 33-43.
DOI: 10.12677/acrem.2025.131006

1. 引言

哮喘是一组在临床特征、疾病严重程度、潜在疾病机制模式和对特定治疗的反应性等方面具有显著异质性的疾病，可导致复发性、可逆性支气管阻塞[1] [2]。目前哮喘的诊断基于特征性的呼吸道症状以及可变的呼气气流受限证据[3]。然而部分患者由于年老或年幼、肺大疱、心脏功能不全、支气管扩张剂过敏、活动性出血等原因而不能完成肺功能测试[4]，且现有诊断体系难以对哮喘细分表型及内型，从而满足对哮喘个体化精准治疗的要求，反映哮喘不同病理机制的哮喘生物标志物的介入有潜力改善这一现状[5]。

生物标志物是正常生理过程、病理过程及对治疗干预的药理学反应的可客观测量和评价的指标[6]。理想的生物标志物应具有敏感性、特异性，能够提供阳性和阴性预测值，同时测量简单且具有成本效益[1]。由于哮喘的异质性，缺乏对哮喘内型定义的权威共识，在建立和验证高度特异性生物标志物方面还未达到理想标准，所以生物标志物在哮喘中的应用尚不充分[7]-[9]。

根据哮喘临床表现(发病年龄和特应性合并症的存在)以及是否以 2 型免疫途径参与为主，可将哮喘分为 2 型与非 2 型哮喘，但由于哮喘异质性，2 型与非 2 型哮喘也可合并存在，本文将分述 2 型、非 2 型与其他不同机制的经典及新兴哮喘生物标志物[10] [11]。

2. 2 型哮喘的生物标志物

2.1. 2 型哮喘的病理生理机制

2 型哮喘是最常见的内/表型，大约 50%~70%的哮喘患者以 2 型炎症反应为主要类型[12]。其典型特征是 2 型辅助(Th2)细胞、2 型先天淋巴细胞(ILC2s)活化，以及 2 型细胞因子的产生[13] [14]。然而由于有 ILC2s 的参与，以及细胞因子 IL-4、-5 和-13 和 Th2 通路中的其他细胞因子可由非 Th2 细胞例如嗜碱性粒细胞、肥大细胞和嗜酸性粒细胞产生，将这种炎症状态标记为 2 型，而不是 Th2，更能反映它们更多样化的免疫起源[15] [16]。

2.2. 2 型哮喘生物标志物

2.2.1. 免疫球蛋白 E (IgE)

IgE 是过敏性炎症发生和维持的关键介质，在过敏反应中，只要微量的过敏原与高亲和力 IgE 受体(FcεRI)结合的 IgE 发生交联，就会引发细胞脱颗粒并释放促炎介质[17]。

血清特异性免疫球蛋白 E (sIgE)的水平可以确定变应性状态，辅助判断哮喘过敏表型[18]。有研究表明呼吸道过敏原特异性 IgE 的累积水平可能是检测严重哮喘过敏表型的有用筛查方法，并可能作为提高 IgE 靶向治疗成功率的生物标志物[19]。

总 IgE 在哮喘的诊断价值尚未得到肯定[20]。因为总 IgE 升高除可见于过敏性疾病，也可见于如寄生虫感染等其他疾病[21]。目前，抗 IgE 免疫治疗已是严重过敏性哮喘患者的治疗手段之一，但尚无有力证据支持将其作为效果评估的指标[22]。然而一项为期 1 年的前瞻性研究发现血清总 IgE 水平的变异性有助于预测哮喘发作风险[23]。Savran 等人在 60 年的随访研究中也发现持续性哮喘患者比缓解者有更高的总 IgE 水平[24]。

2.2.2. 嗜酸细胞计数(EOS)

血清和痰嗜酸性粒细胞均可用于嗜酸性粒细胞性哮喘的诊断。血清嗜酸性粒细胞相较痰嗜酸粒细胞来说测量简便、可重复，但诊断效能不如后者[25]。且嗜酸性粒细胞记数受鼻息肉、吸烟、季节性、随时间推移的自然变化以及分析差异等影响，若用于哮喘诊断，或需重复测量以及结合患者病史进行解读[26]。

血液嗜酸性粒细胞计数是选择严重哮喘个体的关键生物标志物，这些个体将从靶向 2 型细胞因子的生物制剂治疗中临床受益[27]。全球已有多个指南将血嗜酸性粒细胞计数升高列为抗 IgE、抗 IL-5/IL-5 受体和抗 IL-4 疗法反应的预测指标[28]。Jensen 等发现 18 个月时的血液嗜酸性粒细胞计数不能预测 6 岁时复发性喘息/哮喘或特应性皮炎的持续或发展，提示血液嗜酸性粒细胞水平在早期特应性疾病中临床作用有限[29]。

2.2.3. 呼出气一氧化氮浓度(FeNO)

FeNO 是诱导型一氧化氮合酶的产物，会因关键的 2 型炎症细胞因子 IL-4 和 IL-13 而上调，是现在使用较广的 2 型哮喘标志物[30]。有研究通过分析基线以及随访 8 年后 FeNO 值发现其有一定哮喘样症状预测作用[31]。FENO 水平升高有助于识别有哮喘恶化风险的儿童以及对 dupilumab 有临床反应的疾病患者[32]。使用 FeNO 识别难以控制的哮喘的不依从性可能具有成本效益，而这种成本效益是由没有进展到昂贵的生物疗法的患者的成本节约驱动的[33]。然而也存在局限性，Sunde 等指出 FeNO 仅是并发空气过敏原致敏儿童的有效哮喘生物标志物[34]。作为 2 型哮喘的代表标志物，也无法明确或排除哮喘诊断[3]。

2.2.4. 嗜酸性粒细胞颗粒蛋白

嗜酸性粒细胞颗粒蛋白是哮喘患者嗜酸性粒细胞活化释放的产物，包括嗜酸性粒细胞过氧化物酶(EPO)、嗜酸性粒细胞阳离子蛋白(ECP)和嗜酸性粒细胞衍生神经毒素(EDN)，可以弥补贮存血液、痰液标本无法准确进行细胞计数的不足，也可以反映嗜酸性粒细胞的激活状态[35] [36]。

Tang 等人利用严重哮喘研究计划 3 (SARP-3)收集的生物样本库进行队列研究，发现无论血清或者痰液标本中的 EPO 都比嗜酸性粒细胞计数更能反映全身及气道的炎症水平[36]。且 EPX ELISA 是一种标准的市售检测方法，可供临床实验室很容易地采用和使用[37]。

EDN 具有抗病毒和抗菌活性，与 B-Eos 计数、FEV1%相关而不受药物影响[38] [39]。且易于采样、量化可靠、没有明显的昼夜节律、可长期保存，与嗜酸性粒细胞计数相比，EDN 可能是哮喘控制状态的更好指标[40] [41]。诊断效力方面，有研究证实血清嗜酸性粒细胞来源的神经毒素比血嗜酸性粒细胞计数更能反映哮喘控制状况[42]。

嗜酸性粒细胞阳离子蛋白(ECP)能激活肥大细胞，导致组胺释放，有研究表明其数值与中性粒细胞计数高相关，[43] [44]。Shan 等认为血浆 ECP 浓度可能有助于识别那些复发恶化风险最高且可受益于皮质类固醇治疗的儿童，但检测灵敏度不足[45]。

2.2.5. 2 型哮喘细胞因子

在 2 型炎症中，当过敏原进入呼吸道时，抗原递呈细胞处理过敏原并将其递呈给 Th2 细胞，Th2 细胞分泌 Th2 细胞因子，包括 IL-5、IL-4 和 IL-13，这些细胞因子进一步激活激活 B 细胞产生产生 IgE 与肥大细胞的 FcεRI 结合从而释放炎症介质。此外，源自上皮细胞的细胞因子如 TSLP、IL-33 和 IL-25 可激活 2 型先天性淋巴细胞，后者可产生 Th2 细胞因子如 IL-5 和 IL-13 进一步诱发炎症[46]。

2.2.6. 血清骨膜素

骨膜素是一种细胞外基质蛋白，由嗜酸性粒细胞、上皮细胞和成纤维细胞产生，在 Th2 型过敏性疾病中发挥作用[47]。关于骨膜素作为哮喘标志物的研究较多，但尚未得到一致结论。一项单中心经验发现

哮喘患儿血清骨膜素的较高水平与哮喘控制不良有关[48]。有研究发现血清骨膜素水平与哮喘严重程度之间存在关联，但特异性识别和阳性预测并不理想，诊断准确率中等[49] [50]。在一组 26 名医生诊断为哮喘的印度儿童中，血清骨膜素与嗜酸性粒细胞炎症标志物无显著相关性[51]。另一项针对重症哮喘患者的研究也发现骨膜素高低与病情恶化率没有临床意义的差异[52]。且骨膜素的混杂因素较多，或许与 T2 内型的关系更为密切，而不是哮喘或气道功能障碍的标志物[53] [54]。

2.2.7. 胸腺基质淋巴细胞生成素(TSLP)

1994 年初，TSLP 首次被鉴定为胸腺基质细胞系 Z210R.1 产生的 IL-7 样生长因子，影响 B 系和 T 系细胞[55]。多位于气道中的上皮细胞、肥大细胞、支气管平滑肌细胞、树突状细胞和成纤维细胞中，主要参与 2 型炎症反应[56] [57]。通过阻断 TSLP 可有效治疗过敏性哮喘、嗜酸性粒细胞性哮喘[58]。但在诊断效用方面，Caminati 等认为血清 TSLP 浓度在哮喘表型过程中没有附加价值，它不是哮喘加重的标志物，也不是与肺功能测试结果相关的有价值的生物标志物[59]。

2.2.8. 前列腺素 D2 (PGD2)

前列腺素 D2 (PGD2)是一种脂质信号分子，主要通过 DP2 (CRTH2)受体的信号传导促进气道嗜酸性粒细胞增多和 2 型炎症[60]。在预测呼吸疾病结果的无偏生物标志物(U-BIOPRED)队列的哮喘亚表型中，观察到尿 PGD2 代谢物升高，且与一氧化氮和嗜酸性粒细胞标志物数量增加有关[61]。

3. 非 2 型哮喘的生物标志物

3.1. 非 2 型哮喘的特征

非 2 型哮喘主要是依据 2 型标志物的缺失而进行的排除性诊断，多为中性粒细胞或少粒细胞炎症[62] [63]。常与发病年龄大、肥胖和皮质类固醇反应不佳而常需要使用大剂量激素等有关，可惜目前尚缺乏公认的非 2 型哮喘的生物标志物[64] [65]。

3.2. 非 2 型哮喘生物标志物

3.2.1. 中性粒细胞

气道中性粒细胞增多是部分 2 型哮喘患者的特征[11]。Alam 等发现难治性哮喘与气道中性粒细胞和中性粒细胞生物分子数量的增加有关[66]。Grunwell 等证实以中性粒细胞为主的严重哮喘患儿原代中性粒细胞表现出更强的吞噬能力和更强的中性粒细胞胞外陷阱形成，呼吸爆发受损更严重[67]。基因分析发现中性粒细胞为主的哮喘中绝大多数差异表达基因与皮质类固醇反应有关[68]。

3.2.2. 非 2 型哮喘细胞因子

气道中性粒细胞增多是部分非 2 型哮喘的特征，IL-17 已被证明在严重哮喘患者中增加，并与中性粒细胞气道炎症有关，但也在 Th2 反应中发挥作用，增加了区分难度[69]。Th1 细胞分泌 IL-2、肿瘤坏死因子-α (TNF-α)和干扰素-γ (IFN-γ)，并刺激 Th1 免疫。TNF-α 与 IFN-γ 可在 IL-17 存在前提下促进中性粒细胞募集，也可上调 CD38 的表达进而诱发哮喘。

3.2.3. YKL-40

几丁质酶-3 样蛋白 1 (CHI3L1)也称为 YKL40，由多种细胞分泌表达，如巨噬细胞、上皮细胞等，或与参与气道重塑相关[70]。由于其与痰 IL-1b、IL-6 和 IL-8、B-Neu 数量和 IL-17 介导的炎症的关系，被认为与非 2 型哮喘有关[71]。但也有研究发现在学龄前反复出现喘息的儿童中，YKL-40 的测量结果并未发现可用于预测哮喘[72]。

3.2.4. 8-异前列腺素 F2a (8-iso-PGF2a)

8-异前列腺素 F2a (8-iso-PGF2a)是 F2-异前列腺素中的主要成分，因作为哮喘氧化应激的潜在生物标志物而备受关注[73]。一项研究发现尿液中 8-iso-PGF2a 浓度较高与非嗜酸性支气管炎症和气道重塑病情恶化有关，此外，在患有肥胖和吸烟史的哮喘患者中，尿液中 8-iso-PGF2a 浓度较高，提示有潜力作为非 2 型哮喘生物标志物的潜力[74]。

4. 其他生物标志物

4.1. 微小 RNA

微小 RNA (miRNA)是由大约 18~22 个核苷酸形成的小的非编码 RNA 分子，其在转录后水平负调节基因表达。其可从多种生物标本如血液、痰液、组织、呼气冷凝液等中获得，可无侵入性，目前有许多研究着眼于 miRNA 的哮喘诊断作用，已筛选出多个有潜力的类型，但研究覆盖面广，力度分散，尚未获得最公认的类型[75]-[78]。如有分析认为 miR-185-5p、miR-155、let-7a、miR-21、miR320a、miR-1246、miR-144-5p 和 miR-1165-3p 可作为诊断哮喘的潜在生物标志物[76]。

4.2. 甘露糖结合凝集素(MBL)

甘露糖结合凝集素(MBL)是一种急性时相反应物[79]。既往研究认为 MBL 可能在哮喘的进展中发挥调节作用，是易患更严重疾病的标志物或独特哮喘表型的标志物[79]。有研究发现支气管哮喘患儿的血浆 MBL 浓度明显高于健康对照组且与外周血样本中的 IgE 水平呈正相关[80]。但也有研究发现 MBL 基因多态性可能与哮喘风险无关[81]。

4.3. 腱生蛋白 C (TNC)

腱生蛋白 C (TNC)是一种细胞外基质糖蛋白，接受 Th2 细胞产生的细胞因子刺激后可促进炎性细胞从间质迁移至气道。一项病例对照研究通过 ELISA 测量血清 TNC 水平，发现在 TNC 水平方面具有显著差异，血清 TNC 测定诊断支气管哮喘的敏感性为 93.75%，特异性为 60.94%，阴性预测值为 90.7%，更惊喜的是血清 TNC 水平与支气管哮喘的严重程度之间存在显著关系($p = 0.004$)，血清 TNC 水平可以作为诊断支气管哮喘的潜在生物标志物和疾病严重程度的潜在预测因子[82]。

4.4. 铁稳态水平

一项研究对比 50 名持续喘息幼儿与 30 名健康对照者的支气管肺泡灌洗液(BAL)中铁稳态水平，发现患有复发性喘息的学龄前儿童气道中的铁水平降低，与铁输出分子溶质载体家族 40 成员 1 (SLC40A1)表达的降低相关，而铁螯合分子转铁蛋白受体(TFR1) mRNA 表达水平、铁储存分子铁蛋白重链(FTH)和铁蛋白轻链(FTL)的表达升高，增加铁相关指标可增强持续性喘息的预后预测。但该研究样本来源单一，需在不同年龄段和更大样本中验证[83]。

4.5. 氧化标志物

一项研究通过评估哮喘患者与健康对照组血清和唾液中氧化和抗氧化标志物，如脂质过氧化丙二醛(MDA)、总谷胱甘肽(tGSH)、过氧化氢酶(CAT)、超氧化物歧化酶(SOD)和总抗氧化能力(TAC)等的水平，发现血清 UA 和 TAC 水平对监测哮喘严重程度非常有效，而唾液 GPx、CAT、UA、MDA 对儿童哮喘的管理有益[84]。

4.6. 脂质

脂质是代谢物的重要成分，除了作为供能物质，在细胞信号转导、参与炎症、免疫反应方面也具有

重要意义[85]。一项研究采用非靶向血浆脂质组学策略筛选甘油磷脂(GPs)代谢物，证明磷脂酸、磷脂酰甘油和磷脂酰乙醇胺可能是嗜酸性粒细胞性哮喘或非嗜酸性粒细胞性哮喘患者的良好预测因子，而磷脂酸和 磷脂酰甘油表现出区分哮喘患者和健康受试者的强大能力，可能是哮喘的潜在诊断生物标志物[86]。另一项进行非靶向代谢组学和脂质组学综合分析的研究则发现哮喘受试者的磷脂酰乙醇胺、磷脂酰甘油和精胺的诱导痰水平显著更高。将其纳入诊断模型的构建，可用于快速准确地区分哮喘和 COPD，但仍有待在更大的前瞻性队列中得到验证[87]。丹麦一项双盲随机对照试验研究妊娠期补充鱼油的代谢组学特征及新生儿鱼油相关生物标志物与哮喘相关结局发展之间的关系，发现新生儿血液中呋喃脂肪酸代谢物 3-羧基-4-甲基-5-丙基-2-呋喃丙酸(CMPF)水平可以反映妊娠期鱼油和富含脂肪的鱼类摄入量，并与两个队列中哮喘风险较低相关，这可能有助于新生儿筛查儿童哮喘[88]。

4.7. 高迁移率族蛋白 B1 (HMGB1)

高迁移率族蛋白 B1 (HMGB1)是一种损伤相关分子模式分子，可与特定受体如高级糖化终产物受体和 Toll 样受体等结合释放炎症介质。一项荟萃分析纳入 13 项研究，发现哮喘患者与健康对照者血清/血浆/痰标本中的 HMGB1 水平存在显著差异，且高水平的 HMGB1 与疾病的严重程度呈正相关，提示 HMGB1 水平升高可能是哮喘严重程度的潜在生物标志物[89]。

4.8. 基质金属蛋白酶-1 (MMP-1)

基质金属蛋白酶-1 (MMP-1)是哮喘细胞外基质重塑的关键介质[90]。一项研究通过 3 个月的随访发现相较健康对照，哮喘患者的血清 MMP-1 水平升高，且可一定程度区分中、重度哮喘，故可作为鉴别中重度哮喘的有用辅助手段[91]。另一项研究同样发现 MMP-1 活性增加与 FEV1 下降相关，也与恶化严重程度有关，但是否可作为生物标志物尚需进一步研究[92]。

4.9. 富脯氨酸蛋白 BstNI 亚家族 1(PRB1)

一项研究采用酶联免疫吸附法测定 67 例哮喘患者和 27 例对照组诱导痰中 PRB1 蛋白水平，还进行了诱导痰中 PRB1 与气道炎症指标之间的相关性分析，发现哮喘患者诱导痰上清液中 PRB1 蛋白水平显著上调($p = 0.0098$)，并与临床嗜酸性粒细胞相关指标和 2 型气道炎症相关，潜在机制尚需进一步明确[93]。

5. 结语

哮喘异质性强、机制复杂，现有研究已发现多领域的有助于哮喘分型、评估病情与治疗效果的生物标志物，其中部分已投入临床使用如 FeNO、EOS 等，更多还处于初步发现阶段，亟待进一步研究或更大规模的临床验证。此外，如本文将哮喘从是否为 2 型炎症为主进行分类，实际上哮喘机制多样，现有表型或内型分类间存在一定重叠，或需要多重生物标志物组合来增强诊断的效力。随着研究程度的不断深入，有望在不久的将来找到更多的生物标志物服务于哮喘的诊断与治疗。

参考文献

[1] Rodriguez del Rio, P., Liu, A.H., Borres, M.P., Södergren, E., Iachetti, F. and Casale, T.B. (2022) Asthma and Allergy: Unravelling a Tangled Relationship with a Focus on New Biomarkers and Treatment. *International Journal of Molecular Sciences*, **23**, Article 3881. https://doi.org/10.3390/ijms23073881

[2] Martinez, F.D. and Vercelli, D. (2013) Asthma. *The Lancet*, **382**, 1360-1372. https://doi.org/10.1016/s0140-6736(13)61536-6

[3] 全球哮喘防治创议. 全球哮喘管理和预防策略[Z]. 2023.

[4] Yang, Y., Jia, M., Ou, Y., Adcock, I.M. and Yao, X. (2021) Mechanisms and Biomarkers of Airway Epithelial Cell Damage in Asthma: A Review. *The Clinical Respiratory Journal*, **15**, 1027-1045. https://doi.org/10.1111/crj.13407

[5] Gans, M.D. and Gavrilova, T. (2020) Understanding the Immunology of Asthma: Pathophysiology, Biomarkers, and Treatments for Asthma Endotypes. *Paediatric Respiratory Reviews*, **36**, 118-127. https://doi.org/10.1016/j.prrv.2019.08.002

[6] Biomarkers Definitions Working Group (2001) Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework. *Clinical Pharmacology and Therapeutics*, **69**, 89-95. https://doi.org/10.1067/mcp.2001.113989

[7] Perlikos, F., Hillas, G. and Loukides, S. (2016) Phenotyping and Endotyping Asthma Based on Biomarkers. *Current Topics in Medicinal Chemistry*, **16**, 1582-1586. https://doi.org/10.2174/1568026616666150930120803

[8] Khan, N.S., Rubin, E., McKenna, B., Palowitch, B.L., Sonnenberg, F., Argon, J., *et al*. (2022) Biomarker Underuse Contributes to an Inability to Phenotype Patients with Severe Uncontrolled Asthma. *Allergy and Asthma Proceedings*, **43**, 383-387. https://doi.org/10.2500/aap.2022.43.220038

[9] Goyal, J.P. and Rajvanshi, N. (2023) Periostin: A Novel Biomarker for Asthma. *Indian Journal of Pediatrics*, **90**, 427-428. https://doi.org/10.1007/s12098-023-04511-1

[10] Narendra, D., Blixt, J. and Hanania, N.A. (2019) Immunological Biomarkers in Severe Asthma. *Seminars in Immunology*, **46**, Article 101332. https://doi.org/10.1016/j.smim.2019.101332

[11] Fitzpatrick, A.M., Chipps, B.E., Holguin, F. and Woodruff, P.G. (2020) T2-"Low" Asthma: Overview and Management Strategies. *The Journal of Allergy and Clinical Immunology: In Practice*, **8**, 452-463. https://pubmed.ncbi.nlm.nih.gov/32037109/ https://doi.org/10.1016/j.jaip.2019.11.006

[12] Maspero, J., Adir, Y., Al-Ahmad, M., Celis-Preciado, C.A., Colodenco, F.D., Giavina-Bianchi, P., *et al*. (2022) Type 2 Inflammation in Asthma and Other Airway Diseases. *ERJ Open Research*, **8**. http://publications-ersnet-org-s.webvpn.zju.edu.cn:8001/content/erjor/8/3/00576-2021 https://doi.org/10.1183/23120541.00576-2021

[13] Marone, G., Spadaro, G., Braile, M., Poto, R., Criscuolo, G., Pahima, H., *et al*. (2019) Tezepelumab: A Novel Biological Therapy for the Treatment of Severe Uncontrolled Asthma. *Expert Opinion on Investigational Drugs*, **28**, 931-940. https://doi.org/10.1080/13543784.2019.1672657

[14] Olin, J.T. and Wechsler, M.E. (2014) Asthma: Pathogenesis and Novel Drugs for Treatment. *BMJ*, **349**, g5517-g5517. https://doi.org/10.1136/bmj.g5517

[15] Tindemans, I., Serafini, N., Di Santo, J.P. and Hendriks, R.W. (2014) GATA-3 Function in Innate and Adaptive Immunity. *Immunity*, **41**, 191-206. https://doi.org/10.1016/j.immuni.2014.06.006

[16] Gauthier, M., Ray, A. and Wenzel, S.E. (2015) Evolving Concepts of Asthma. *American Journal of Respiratory and Critical Care Medicine*, **192**, 660-668. https://doi.org/10.1164/rccm.201504-0763pp

[17] McDonnell, J.M., Dhaliwal, B., Sutton, B.J. and Gould, H.J. (2023) IgE, IgE Receptors and Anti-IgE Biologics: Protein Structures and Mechanisms of Action. *Annual Review of Immunology*, **41**, 255-275. https://doi.org/10.1146/annurev-immunol-061020-053712

[18] Arroyave, W.D., Rabito, F.A. and Carlson, J.C. (2013) The Relationship between a Specific IgE Level and Asthma Outcomes: Results from the 2005-2006 National Health and Nutrition Examination Survey. *The Journal of Allergy and Clinical Immunology: In Practice*, **1**, 501-508. https://doi.org/10.1016/j.jaip.2013.06.013

[19] Naumova, V., Beltyukov, E., Niespodziana, K., Errhalt, P., Valenta, R., Karaulov, A., *et al*. (2022) Cumulative IgE-Levels Specific for Respiratory Allergens as Biomarker to Predict Efficacy of Anti-IgE-Based Treatment of Severe Asthma. *Frontiers in Immunology*, **13**, Article 941492. https://doi.org/10.3389/fimmu.2022.941492

[20] Chang, Y., Lee, T., Huang, C., Chang, P., Chen, Y. and Fu, C. (2021) The Role of Phadiatop Tests and Total Immunoglobulin E Levels in Screening Aeroallergens: A Hospital-Based Cohort Study. *Journal of Asthma and Allergy*, **14**, 135-140. https://doi.org/10.2147/jaa.s292710

[21] Roberts, G., Pfaar, O., Akdis, C.A., Ansotegui, I.J., Durham, S.R., Gerth van Wijk, R., *et al*. (2017) EAACI Guidelines on Allergen Immunotherapy: Allergic Rhinoconjunctivitis. *Allergy*, **73**, 765-798. https://doi.org/10.1111/all.13317

[22] Hamilton, R.G. (2016) Monitoring Allergic Patients on Omalizumab with Free and Total Serum IgE Measurements. *The Journal of Allergy and Clinical Immunology: In Practice*, **4**, 366-368. https://doi.org/10.1016/j.jaip.2015.12.002

[23] Yuan, Y.L., Zhang, X., Liu, L., Wang, G., Chen-Yu Hsu, A., Huang, D., *et al*. (2021) Total IgE Variability Is Associated with Future Asthma Exacerbations: A 1-Year Prospective Cohort Study. *The Journal of Allergy and Clinical Immunology: In Practice*, **9**, 2812-2824. https://doi.org/10.1016/j.jaip.2021.04.065

[24] Savran, O., Bønnelykke, K. and Ulrik, C.S. (2024) Characteristics of Adults with Severe Asthma in Childhood: A 60-Year Follow-Up Study. *CHEST*, **166**, 676-684. https://doi.org/10.1016/j.chest.2024.06.005

[25] Shah, S.P., Grunwell, J., Shih, J., Stephenson, S. and Fitzpatrick, A.M. (2019) Exploring the Utility of Noninvasive Type 2 Inflammatory Markers for Prediction of Severe Asthma Exacerbations in Children and Adolescents. *The Journal of*

Allergy and Clinical Immunology: In Practice, **7**, 2624-2633.e2. https://pubmed.ncbi.nlm.nih.gov/31100552/ https://doi.org/10.1016/j.jaip.2019.04.043

[26] Chipps, B.E., Jarjour, N., Calhoun, W.J., Iqbal, A., Haselkorn, T., Yang, M., *et al*. (2021) A Comprehensive Analysis of the Stability of Blood Eosinophil Levels. *Annals of the American Thoracic Society*, **18**, 1978-1987. https://doi.org/10.1513/annalsats.202010-1249oc

[27] Fricker, M., Heaney, L.G. and Upham, J.W. (2017) Can Biomarkers Help Us Hit Targets in Difficult-to-Treat Asthma? *Respirology*, **22**, 430-442. https://doi.org/10.1111/resp.13014

[28] GINA (2024) Global Strategy for Asthma Management and Prevention. https://ginasthma.org/2024-report/

[29] Jensen, S.K., Melgaard, M.E., Pedersen, C.T., Yang, L., Vahman, N., Thyssen, J.P., *et al*. (2023) Limited Clinical Role of Blood Eosinophil Levels in Early Life Atopic Disease: A Mother-Child Cohort Study. *Pediatric Allergy and Immunology*, **34**, e14050. https://doi.org/10.1111/pai.14050

[30] Gaillard, E.A., Kuehni, C.E., Turner, S., Goutaki, M., Holden, K.A., de Jong, C.C.M., *et al*. (2021) European Respiratory Society Clinical Practice Guidelines for the Diagnosis of Asthma in Children Aged 5-16 Years. *European Respiratory Journal*, **58**, Article 2004173. https://doi.org/10.1183/13993003.04173-2020

[31] Barański, K. (2024) Predictive Value of Fractional Exhaled Nitric Oxide (FeNO) in the Diagnosis of Asthma for Epidemiological Purposes—An 8-Year Follow-Up Study. *Advances in Respiratory Medicine*, **92**, 36-44. https://doi.org/10.3390/arm92010006

[32] Bacharier, L.B., Pavord, I.D., Maspero, J.F., Jackson, D.J., Fiocchi, A.G., Mao, X., *et al*. (2024) Blood Eosinophils and Fractional Exhaled Nitric Oxide Are Prognostic and Predictive Biomarkers in Childhood Asthma. *Journal of Allergy and Clinical Immunology*, **154**, 101-110. https://doi.org/10.1016/j.jaci.2023.09.044

[33] Barry, L.E., O'Neill, C., Butler, C., Chaudhuri, R. and Heaney, L.G. (2023) Cost-Effectiveness of Fractional Exhaled Nitric Oxide Suppression Testing as an Adherence Screening Tool among Patients with Difficult-to-Control Asthma. *The Journal of Allergy and Clinical Immunology: In Practice*, **11**, 1796-1804.e3. https://doi.org/10.1016/j.jaip.2023.03.008

[34] Sunde, R.B., Thorsen, J., Skov, F., Hesselberg, L., Kyvsgaard, J., Følsgaard, N.V., *et al*. (2023) Exhaled Nitric Oxide Is Only an Asthma-Relevant Biomarker among Children with Allergic Sensitization. *Pediatric Allergy and Immunology*, **34**, e14044. https://doi.org/10.1111/pai.14044

[35] Bystrom, J., Amin, K. and Bishop-Bailey, D. (2011) Analysing the Eosinophil Cationic Protein—A Clue to the Function of the Eosinophil Granulocyte. *Respiratory Research*, **12**, Article No. 10. https://doi.org/10.1186/1465-9921-12-10

[36] Tang, M., Charbit, A.R., Johansson, M.W., Jarjour, N.N., Denlinger, L.C., Raymond, W.W., *et al*. (2024) Utility of Eosinophil Peroxidase as a Biomarker of Eosinophilic Inflammation in Asthma. *Journal of Allergy and Clinical Immunology*, **154**, 580-591.e6. https://doi.org/10.1016/j.jaci.2024.03.023

[37] Ackerman, S.J. (2024) Sputum Eosinophil Peroxidase: Building a Better Biomarker for Eosinophilic Asthma. *Journal of Allergy and Clinical Immunology*, **154**, 546-548. https://doi.org/10.1016/j.jaci.2024.07.004

[38] Kuai, S. and Zhao, P. (2023) Association of EDN Levels in Patients with Asthma and Correlation with Fev_1%: A Meta-Analysis. *Allergy and Asthma Proceedings*, **44**, 244-251. https://doi.org/10.2500/aap.2023.44.230016

[39] Chakraborty, S., Hammar, K.S., Filiou, A.E., Holmdahl, I., Hoyer, A., Ekoff, H., *et al*. (2022) Longitudinal Eosinophil-derived Neurotoxin Measurements and Asthma Development in Preschool Wheezers. *Clinical & Experimental Allergy*, **52**, 1338-1342. https://doi.org/10.1111/cea.14210

[40] Rutten, B., Young, S., Rhedin, M., Olsson, M., Kurian, N., Syed, F., *et al*. (2021) Eosinophil-Derived Neurotoxin: A Biologically and Analytically Attractive Asthma Biomarker. *PLOS ONE*, **16**, e0246627. https://doi.org/10.1371/journal.pone.0246627

[41] Malinovschi, A., Rydell, N., Fujisawa, T., Borres, M.P. and Kim, C. (2023) Clinical Potential of Eosinophil-Derived Neurotoxin in Asthma Management. *The Journal of Allergy and Clinical Immunology: In Practice*, **11**, 750-761. https://doi.org/10.1016/j.jaip.2022.11.046

[42] An, J., Lee, J., Sim, J.H., Song, W., Kwon, H., Cho, Y.S., *et al*. (2020) Serum Eosinophil-Derived Neurotoxin Better Reflect Asthma Control Status than Blood Eosinophil Counts. *The Journal of Allergy and Clinical Immunology: In Practice*, **8**, 2681-2688.e1. https://doi.org/10.1016/j.jaip.2020.03.035

[43] Malik, A. and Batra, J.K. (2012) Antimicrobial Activity of Human Eosinophil Granule Proteins: Involvement in Host Defence against Pathogens. *Critical Reviews in Microbiology*, **38**, 168-181. https://doi.org/10.3109/1040841x.2011.645519

[44] Granger, V., Zerimech, F., Arab, J., Siroux, V., de Nadai, P., Tsicopoulos, A., *et al*. (2021) Blood Eosinophil Cationic Protein and Eosinophil-Derived Neurotoxin Are Associated with Different Asthma Expression and Evolution in Adults. *Thorax*, **77**, 552-562. https://doi.org/10.1136/thoraxjnl-2021-217343

[45] Shah, S.N., Grunwell, J.R., Mohammad, A.F., Stephenson, S.T., Lee, G.B., Vickery, B.P., *et al*. (2021) Performance of Eosinophil Cationic Protein as a Biomarker in Asthmatic Children. *The Journal of Allergy and Clinical Immunology: In Practice*, **9**, 2761-2769.E2. https://doi.org/10.1016/j.jaip.2021.02.053

[46] Carr, T.F., Zeki, A.A. and Kraft, M. (2018) Eosinophilic and Noneosinophilic Asthma. *American Journal of Respiratory and Critical Care Medicine*, **197**, 22-37. https://doi.org/10.1164/rccm.201611-2232pp

[47] Cristiane Baldo1,2, D., Gustavo Romaldini1, J., Margaret Menezes Pizzichini3, M., Eduardo D. Cançado1, J., Dellavance2, A. and Stirbulov1, R. (2023) Periostin as an Important Biomarker of Inflammatory Phenotype T2 in Brazilian Asthma Patients. *Jornal Brasileiro de Pneumologia*, **49**, e20220040. https://doi.org/10.36416/1806-3756/e20220040

[48] Choudhary, S., Kumar, P., Banerjee, M., Singh, K. and Goyal, J.P. (2023) Relationship of Serum Periostin with Asthma Control in Children: Single Center Experience. *Indian Pediatrics*, **60**, 822-825. https://doi.org/10.1007/s13312-023-3012-0

[49] Yang, L., Zhao, Q. and Wang, S. (2020) The Role of Serum Periostin in the Diagnosis of Asthma: A Meta-Analysis. *Allergy and Asthma Proceedings*, **41**, 240-247. https://doi.org/10.2500/aap.2020.41.200038

[50] Yavuz, S.T., Bagci, S., Bolat, A., Akin, O. and Ganschow, R. (2021) Association of Serum Periostin Levels with Clinical Features in Children with Asthma. *Pediatric Allergy and Immunology*, **32**, 937-944. https://doi.org/10.1111/pai.13444

[51] Kumar, K., Singh, M., Mathew, J.L., Vaidya, P.C. and Verma Attri, S. (2022) Serum Periostin Level in Children with Asthma. *Indian Journal of Pediatrics*, **90**, 438-442. https://doi.org/10.1007/s12098-022-04282-1

[52] Buhl, R., Korn, S., Menzies-Gow, A., Aubier, M., Chapman, K.R., Canonica, G.W., *et al*. (2020) Prospective, Single-Arm, Longitudinal Study of Biomarkers in Real-World Patients with Severe Asthma. *The Journal of Allergy and Clinical Immunology: In Practice*, **8**, 2630-2639.E6. https://doi.org/10.1016/j.jaip.2020.03.038

[53] Al-Shaikhly, T., Murphy, R.C., Lai, Y., Frevert, C.W., Debley, J.S., Ziegler, S.F., *et al*. (2023) Sputum Periostin Is a Biomarker of Type 2 Inflammation but Not Airway Dysfunction in Asthma. *Respirology*, **28**, 491-494. https://doi.org/10.1111/resp.14491

[54] Busby, J., Holweg, C.T.J., Chai, A., Bradding, P., Cai, F., Chaudhuri, R., *et al*. (2019) Change in Type-2 Biomarkers and Related Cytokines with Prednisolone in Uncontrolled Severe Oral Corticosteroid Dependent Asthmatics: An Interventional Open-Label Study. *Thorax*, **74**, 806-809. https://doi.org/10.1136/thoraxjnl-2018-212709

[55] Friend, S.L., Hosier, S., Nelson, A., *et al*. (1994) A Thymic Stromal Cell Line Supports *in vitro* Development of Surface IgM^+ B Cells and Produces a Novel Growth Factor Affecting B and T Lineage Cells. *Experimental Hematology*, **22**, 321-328.

[56] Chen, X., Deng, R., Chi, W., Hua, X., Lu, F., Bian, F., *et al*. (2019) IL-27 Signaling Deficiency Develops Th17-Enhanced Th2-Dominant Inflammation in Murine Allergic Conjunctivitis Model. *Allergy*, **74**, 910-921. https://doi.org/10.1111/all.13691

[57] Hong, H., Liao, S., Chen, F., Yang, Q. and Wang, D. (2020) Role of IL-25, IL-33, and TSLP in Triggering United Airway Diseases toward Type 2 Inflammation. *Allergy*, **75**, 2794-2804. https://doi.org/10.1111/all.14526

[58] Caminati, M., Buhl, R., Corren, J., Hanania, N.A., Kim, H., Korn, S., *et al*. (2023) Tezepelumab in Patients with Allergic and Eosinophilic Asthma. *Allergy*, **79**, 1134-1145. https://doi.org/10.1111/all.15986

[59] Vrsalović, R., Korošec, P., Štefanović, I.M., Bidovec-Stojkovič, U., Čičak, B., Harjaček, M., *et al*. (2022) Value of Thymic Stromal Lymphopoietin as a Biomarker in Children with Asthma. *Respiratory Medicine*, **193**, Article 106757. https://doi.org/10.1016/j.rmed.2022.106757

[60] Fricker, M., McDonald, V.M., Winter, N.A., Baines, K.J., Wark, P.A.B., Simpson, J.L., *et al*. (2021) Molecular Markers of Type 2 Airway Inflammation Are Similar between Eosinophilic Severe Asthma and Eosinophilic Chronic Obstructive Pulmonary Disease. *Allergy*, **76**, 2079-2089. https://doi.org/10.1111/all.14741

[61] Kolmert, J., Gómez, C., Balgoma, D., Sjödin, M., Bood, J., Konradsen, J.R., *et al*. (2021) Urinary Leukotriene E_4 and Prostaglandin D_2 Metabolites Increase in Adult and Childhood Severe Asthma Characterized by Type 2 Inflammation. A Clinical Observational Study. *American Journal of Respiratory and Critical Care Medicine*, **203**, 37-53. https://doi.org/10.1164/rccm.201909-1869oc

[62] Ricciardolo, F.L.M., Sorbello, V., Folino, A., Gallo, F., Massaglia, G.M., Favatà, G., *et al*. (2017) Identification of IL-17F/Frequent Exacerbator Endotype in Asthma. *Journal of Allergy and Clinical Immunology*, **140**, 395-406. https://doi.org/10.1016/j.jaci.2016.10.034

[63] Samitas, K., Zervas, E. and Gaga, M. (2017) T2-Low Asthma: Current Approach to Diagnosis and Therapy. *Current Opinion in Pulmonary Medicine*, **23**, 48-55. https://doi.org/10.1097/mcp.0000000000000342

[64] Hammad, H. and Lambrecht, B.N. (2021) The Basic Immunology of Asthma. *Cell*, **184**, 1469-1485. https://doi.org/10.1016/j.cell.2021.02.016

[65] Tliba, O. and Panettieri, R.A. (2019) Paucigranulocytic Asthma: Uncoupling of Airway Obstruction from Inflammation.

Journal of Allergy and Clinical Immunology, **143**, 1287-1294. https://doi.org/10.1016/j.jaci.2018.06.008

[66] Alam, R., Good, J., Rollins, D., Verma, M., Chu, H., Pham, T., *et al*. (2017) Airway and Serum Biochemical Correlates of Refractory Neutrophilic Asthma. *Journal of Allergy and Clinical Immunology*, **140**, 1004-1014.E13. https://doi.org/10.1016/j.jaci.2016.12.963

[67] Grunwell, J.R., Stephenson, S.T., Tirouvanziam, R., Brown, L.A.S., Brown, M.R. and Fitzpatrick, A.M. (2019) Children with Neutrophil-Predominant Severe Asthma Have Proinflammatory Neutrophils with Enhanced Survival and Impaired Clearance. *The Journal of Allergy and Clinical Immunology*: *In Practice*, **7**, 516-525.E6. https://doi.org/10.1016/j.jaip.2018.08.024

[68] Su, M.-W., Lin, W.-C., Tsai, C.-H., Chiang, B.-L., Yang, Y.-H., Lin, Y.-T., *et al*. (2018) Childhood Asthma Clusters Reveal Neutrophil-Predominant Phenotype with Distinct Gene Expression. *Allergy*, **73**, 2024-2032. https://doi.org/10.1111/all.13439

[69] Seys, S.F., Lokwani, R., Simpson, J.L. and Bullens, D.M.A. (2019) New Insights in Neutrophilic Asthma. *Current Opinion in Pulmonary Medicine*, **25**, 113-120. https://doi.org/10.1097/mcp.0000000000000543

[70] Sutherland, T.E. (2018) Chitinase-Like Proteins as Regulators of Innate Immunity and Tissue Repair: Helpful Lessons for Asthma? *Biochemical Society Transactions*, **46**, 141-151. https://doi.org/10.1042/bst20170108

[71] Liu, L., Zhang, X., Liu, Y., Zhang, L., Zheng, J., Wang, J., *et al*. (2019) Chitinase-Like Protein YKL-40 Correlates with Inflammatory Phenotypes, Anti-Asthma Responsiveness and Future Exacerbations. *Respiratory Research*, **20**, Article No. 95. https://doi.org/10.1186/s12931-019-1051-9

[72] Guvenir, H., Buyuktiryaki, B., Kulhas Celik, I., Civelek, E., Kilic Suloglu, A., Karaaslan, C., *et al*. (2020) Can Serum Periostin, YKL-40, and Osteopontin Levels in Pre-School Children with Recurrent Wheezing Predict Later Development of Asthma? *Pediatric Allergy and Immunology*, **32**, 77-85. https://doi.org/10.1111/pai.13329

[73] Basu, S. (2010) Bioactive Eicosanoids: Role of Prostaglandin F2α and F2-Isoprostanes in Inflammation and Oxidative Stress Related Pathology. *Molecules and Cells*, **30**, 383-392. https://doi.org/10.1007/s10059-010-0157-1

[74] Woo, S., Park, H.S., Yang, E., Ban, G. and Park, H. (2024) 8-Iso-Prostaglandin F2α as a Biomarker of Type 2 Low Airway Inflammation and Remodeling in Adult Asthma. *Annals of Allergy*, *Asthma & Immunology*, **133**, 73-80.E2. https://doi.org/10.1016/j.anai.2024.04.007

[75] Rodrigo-Muñoz, J.M., Gil-Martínez, M., Lorente-Sorolla, C., García-Latorre, R., Valverde-Monge, M., Quirce, S., *et al*. (2022) MiR-144-3p Is a Biomarker Related to Severe Corticosteroid-Dependent Asthma. *Frontiers in Immunology*, **13**, Article 858722. https://doi.org/10.3389/fimmu.2022.858722

[76] Xu, L., Yi, M., Tan, Y., Yi, Z. and Zhang, Y. (2020) A Comprehensive Analysis of MicroRNAs as Diagnostic Biomarkers for Asthma. *Therapeutic Advances in Respiratory Disease*, **14**. https://doi.org/10.1177/1753466620981863

[77] Vázquez-Mera, S., Martelo-Vidal, L., Miguéns-Suárez, P., Saavedra-Nieves, P., Arias, P., González-Fernández, C., *et al*. (2022) Serum Exosome inflamma-mirs Are Surrogate Biomarkers for Asthma Phenotype and Severity. *Allergy*, **78**, 141-155. https://doi.org/10.1111/all.15480

[78] Alhamdan, F., Greulich, T., Daviaud, C., Marsh, L.M., Pedersen, F., Thölken, C., *et al*. (2023) Identification of Extracellular Vesicle MicroRNA Signatures Specifically Linked to Inflammatory and Metabolic Mechanisms in Obesity-associated Low Type-2 Asthma. *Allergy*, **78**, 2944-2958. https://doi.org/10.1111/all.15824

[79] Uguz, A., Berber, Z., Coskun, M., Halide Akbas, S. and Yegin, O. (2005) Mannose-Binding Lectin Levels in Children with Asthma. *Pediatric Allergy and Immunology*, **16**, 231-235. https://doi.org/10.1111/j.1399-3038.2005.00258.x

[80] Borta, S.M., Dumitra, S., Miklos, I., Popetiu, R., Pilat, L., Puşchiță, M., *et al*. (2020) Clinical Relevance of Plasma Concentrations of MBL in Accordance with IgE Levels in Children Diagnosed with Bronchial Asthma. *Medicina*, **56**, Article 594. https://doi.org/10.3390/medicina56110594

[81] Shi, J., Zhu, X., Xie, M., Wang, J., He, Y., Xu, Y., *et al*. (2016) MBL2 Polymorphisms and the Risk of Asthma. *Annals of Allergy*, *Asthma & Immunology*, **117**, 417-422.E1. https://doi.org/10.1016/j.anai.2016.08.001

[82] Elgendy, A. (2024) Assessment of Tenascin C Levels in the Serum of Patients with Bronchial Asthma. *Egyptian Journal of Immunology*, **31**, 20-29. https://doi.org/10.55133/eji.310103

[83] Wang, Z., He, Y., Li, Q., Zhao, Y., Zhang, G. and Luo, Z. (2023) Dysregulation of Iron Homeostasis in Airways Associated with Persistent Preschool Wheezing. *Respiratory Research*, **24**, Article No. 170. https://doi.org/10.1186/s12931-023-02466-7

[84] Abboud, M.M., Al-Rawashde, F.A. and Al-Zayadneh, E.M. (2021) Alterations of Serum and Saliva Oxidative Markers in Patients with Bronchial Asthma. *Journal of Asthma*, **59**, 2154-2161. https://doi.org/10.1080/02770903.2021.2008426

[85] Shimizu, T. (2009) Lipid Mediators in Health and Disease: Enzymes and Receptors as Therapeutic Targets for the Regulation of Immunity and Inflammation. *Annual Review of Pharmacology and Toxicology*, **49**, 123-150. https://doi.org/10.1146/annurev.pharmtox.011008.145616

[86] Wang, S., Tang, K., Lu, Y., Tian, Z., Huang, Z., Wang, M., *et al*. (2021) Revealing the Role of Glycerophospholipid Metabolism in Asthma through Plasma Lipidomics. *Clinica Chimica Acta*, **513**, 34-42. https://doi.org/10.1016/j.cca.2020.11.026

[87] Correnti, S., Preianò, M., Gamboni, F., Stephenson, D., Pelaia, C., Pelaia, G., *et al*. (2024) An Integrated Metabo-Lipidomics Profile of Induced Sputum for the Identification of Novel Biomarkers in the Differential Diagnosis of Asthma and COPD. *Journal of Translational Medicine*, **22**, Article No. 301. https://doi.org/10.1186/s12967-024-05100-2

[88] Gürdeniz, G., Kim, M., Brustad, N., Ernst, M., Russo, F., Stokholm, J., *et al*. (2022) Furan Fatty Acid Metabolite in Newborns Predicts Risk of Asthma. *Allergy*, **78**, 429-438. https://doi.org/10.1111/all.15554

[89] Xu, S., Liu, W., Zhang, L., He, Q., Ma, C., Jiang, J., *et al*. (2023) High Mobility Group Box 1 Levels as Potential Predictors of Asthma Severity. *Chinese Medical Journal*, **136**, 1606-1608. https://doi.org/10.1097/cm9.0000000000002491

[90] Ingram, J.L., Slade, D., Church, T.D., Francisco, D., Heck, K., Sigmon, R.W., *et al*. (2016) Role of Matrix Metalloproteinases-1 and -2 in Interleukin-13-Suppressed Elastin in Airway Fibroblasts in Asthma. *American Journal of Respiratory Cell and Molecular Biology*, **54**, 41-50. https://doi.org/10.1165/rcmb.2014-0290oc

[91] Prabha, A., Lokesh, K.S., Chaya, S.K., Jayaraj, B.S., Malamardi, S., Subbarao, M.V.S.S.T., *et al*. (2021) Pilot Study Investigating Diagnostic Utility of Serum MMP-1 and Tgf-B1 in Asthma in 'Real World' Clinical Practice in India. *Journal of Clinical Pathology*, **75**, 222-225. https://doi.org/10.1136/jclinpath-2020-206821

[92] Naveed, S., Clements, D., Jackson, D.J., Philp, C., Billington, C.K., Soomro, I., *et al*. (2017) Matrix Metalloproteinase-1 Activation Contributes to Airway Smooth Muscle Growth and Asthma Severity. *American Journal of Respiratory and Critical Care Medicine*, **195**, 1000-1009. https://doi.org/10.1164/rccm.201604-0822oc

[93] Chen, F., Liang, Y., Zeng, Z., Du, L., Xu, C., Guo, Y., *et al*. (2022) Association of Increased Basic Salivary Proline-Rich Protein 1 Levels in Induced Sputum with Type 2-High Asthma. *Immunity*, *Inflammation and Disease*, **10**, e602. https://doi.org/10.1002/iid3.602