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视黄酸在哮喘气道炎症中的研究进展

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摘　要

哮喘是一种慢性气道炎症性疾病，其特征为可逆性的气流受限和呼吸道高反应性。当前哮喘治疗仍以吸入性糖皮质激素(ICS)和长效β2受体激动剂(LABA)联合疗法为主，开发低毒性的辅助治疗策略对于临床哮喘防治至关重要。视黄酸(Retinoic acid, RA)是维生素A的主要生物活性代谢产物，通过促进T细胞增殖和延长其存活时间等，在哮喘中起核心作用。在此，本文就RA与支气管哮喘关系的研究进展进行综述。

关键词

视黄酸，儿童，哮喘，气道炎症

Advances in the Research of Retinoic Acid in Asthmatic Airway Inflammation

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Abstract

Asthma is a chronic airway inflammatory disease characterized by reversible airflow limitation and airway hyperresponsiveness. Current therapeutic regimens primarily rely on combined therapy with inhaled corticosteroids (ICS) and long-acting β2-agonists (LABAs). The development of low-toxicity adjuvant therapeutic strategies is therefore critical for clinical asthma management. Retinoic acid (RA), the primary biologically active metabolite of vitamin A, plays a central role in asthma by promoting T cell proliferation, prolonging T cell survival, and modulating immune responses.

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This review summarizes recent advances in understanding the relationship between RA and bronchial asthma.

Keywords

Retinoic Acid, Children, Asthma, Airway Inflammation

1. 引言

近年来，哮喘的发病率在许多国家持续上升，尤其在儿童和青少年中更为显著[1]。当前约 5.2%青少年和 3.9%的儿童合并重度哮喘，对常规治疗反应不佳，严重影响了未成年人健康与生活质量[2]，因此寻求新的哮喘的治疗方法非常重要。哮喘的发病机制复杂，其免疫机制涉及以 Th2 细胞为主的适应性免疫反应和以固有淋巴细胞(ILCs)为主的先天性免疫反应[3]。维生素 A (Vitamin A, VA)是一组在人类膳食中极易获取的重要微量营养素，通过饮食中的动物性食物或植物性胡萝卜素在肠道中转化后吸收。视黄酸(Retinoic acid, RA)是 VA 的主要生物活性代谢产物，RA 缺乏时，气道黏膜防御能力下降，炎症因子的释放增多，从而为哮喘炎症的发生与加重提供了条件。在此，本文从视黄酸的生物学调节基础、视黄酸水平与哮喘的相关性、视黄酸减轻哮喘炎症的作用机制方面进行综述。

2. 视黄酸的生物学调节基础

VA 是指所有含有不饱和脂环的动物、植物来源或化学合成的类视黄醇相关化合物，以及基于由四个异戊二烯单元和五个共轭双键组成的不饱和类异戊二烯链的结构[4]，对身体健康以及免疫系统的正常功能必不可少。它由视黄醇和 600 多种类胡萝卜素组成，包括 β-胡萝卜素、β-隐黄质、叶黄素–玉米黄素和番茄红素等。RA 是 VA 的主要生物活性代谢产物，具有全反式维甲酸(All-trans-retinoic acid, ATRA)、9-顺式视黄酸、13-顺式视黄酸、其他异构体等多种异构体，通过结合并激活细胞核中的视黄酸受体(Retinoic acid receptors, RAR)、类 VAX 受体(Retinoid X receptors, RXRs)和 PPAR-$\beta/\delta/\gamma$ 等发挥生物作用，介导了发育、神经系统功能、免疫反应、细胞增殖和分化等多种全身效应，可促进多个靶基因的转录[5]。RA-RAR/RXR 通路可直接结合 DNA 上的视黄酸反应元件(Retinoic acid response elements, RAREs)，激活抗炎基因(如 FoxP3、IL-10)或抑制促炎基因(如 GATA3、RORγt) [6] [7]；也可通过浓度和时间依赖性协同增强细胞中 NF-κB 和 Toll 样受体活性，调节 IL-6、TNF-α 等细胞因子的释放[8]。

RA 给药能抑制 Th17 并促进促进 Foxp3 调节性 T 细胞分化分化，减轻气道炎症[9] [10]；能减少免疫球蛋白 IgA 的产生，作为调节信号在黏膜免疫反应中发挥关键作用[11]。此外，RA 还诱导先天免疫细胞归巢，如先天性淋巴细胞(ILC) [12]。在类风湿性关节炎模型中，ATRA 治疗还抑制 Th17 细胞分化，同时促进 Treg 细胞分化，从而减轻肠道炎症、滑膜炎症和关节炎[13]。此外，RA 会影响各种免疫细胞，包括 B 细胞迁移和归巢、T 细胞分化及诱导树突状细胞免疫耐受表型[5] [14] [15]。以上研究说明，RA 还具有抗炎作用，在免疫细胞和免疫反应中起着广泛的作用，可以平衡免疫应答、诱导耐受。

3. 视黄酸水平与哮喘的相关性

研究表明，RA 水平与哮喘状态及其加重风险有关。Son 等人[16]发现哮喘患者的血清 VA 浓度明显

低于正常人群。Luo 等人[17]也指出，哮喘的严重程度与血清 VA 水平高度负相关。并且 VA 可以通过降低炎症反应的程度来缓解过敏性鼻炎和哮喘的发生[18] [19]。VA 缺乏通过增强炎症细胞浸润和 2 型细胞因子白细胞介素 5 (Interleukin-5, IL-5)和白细胞介素 13 (Interleukin-13, IL-13)的水平，加剧哮喘肺部炎症[20]。而 RA 在气道中幼稚 T 细胞分化为 FOXP3+ Treg 细胞中起关键作用，其浓度与血清中 IL-10 和 TGF-β 水平呈正相关[21]。

RA 作为一种抗氧化剂，其摄入量减少与哮喘和过敏性疾病患病率增加有关[22]，其发挥抗过敏作用的机制是通过诱导 Treg 细胞和抑制 Th2 反应来实现的[5]。与正常人和对照组小鼠相比，哮喘患者和屋尘螨(House dust mite, HDM)诱导的哮喘小鼠肺组织中 RA 和视黄醇水平显著降低；哮喘肺组织中 RA 的代谢减弱，通过使用 ATRA 或 RARγ 激动剂增加 RAR 的信号传导可缓解哮喘气道重塑[23]。在过敏原暴露下连续摄入 RA 可改善食物过敏小鼠模型中食物过敏的严重程度，降低血浆中卵清蛋白特异性 IgE、IgA 和 IgG1 水平[24]。Chen 等人的一项研究表明，使用 ATRA 可减轻哮喘小鼠肺组织气道炎症和平滑肌细胞增殖[25]。Sakamoto H 等人[26]将 ATRA 与 OVA 同时注射到支气管哮喘小鼠模型中，发现小鼠气道高反应性、嗜酸性粒细胞增多、BALF 中细胞因子水平升高和杯状细胞化生水平均显著降低。

但也有研究指出，RA 水平与哮喘呈负相关，Schuster 等人发现 VA 缺乏会降低哮喘模型的严重程度，而高剂量 VA 摄入则加剧了哮喘症状[27]。Checkley 等人[28]观察到，慢性 VA 缺乏症地区补充 VA 不能降低哮喘风险。而 Hu 等人发现哮喘患者血清 VA 水平确实低于健康对照者，但是怀孕期间 VA 摄入量增高于 7 岁时哮喘患病风险增加有关，而 VA 摄入量与儿童哮喘风险之间没有显着相关性[15]。以上研究的不一致性可能与不同研究采用的检测技术的灵敏度与标准化不足有关；也可能与血清 RA 无法准确反映视黄酸水平有关，VA 主要储存在肝脏中，肝脏密切调节循环视黄醇水平，血清 RA 水平不会下降，直到肝脏几乎耗尽[29]。但更多研究倾向于使用 RA 作为哮喘和过敏的辅助治疗。

4. 视黄酸减轻哮喘炎症的作用机制

哮喘作为一种慢性气道炎症，Th2/Th1/Treg 等免疫细胞动态平衡、气道上皮的屏障功能损伤、气道重塑以及局部氧化应激都可能是疾病进展的关键。

4.1. RA 与哮喘气道免疫反应

RA 是呼吸道黏液层的组成部分，通过促进黏蛋白分泌改善呼吸道的抗原非特异性免疫功能[30]。Th1/Th2 免疫失调是哮喘发生、发展的重要机制，其中 Th2 细胞过度表达在哮喘发病中起主要促进作用。RA 同时以高度特异性的方式调节机体的免疫反应，通过下调过敏相关的 Th2 途径和促炎性 Th17 途径，调节炎症介质，减轻气道的炎症反应[31]。在维生素 A 存在的情况下，IL-2 水平升高，刺激 T 细胞分化为调节性 T 细胞(Treg)，促进 Treg 细胞的增殖分化，维持免疫耐受并调节自身免疫反应[32]。RA 作为细胞因子转化生长因子-β (TGF-β)依赖性免疫反应的关键调节剂，能够抑制 IL-6 驱动的幼稚 T 细胞向促炎性 Th17 细胞的转化，并促进抗炎性 Treg 细胞分化[33]。

维生素 A 缺乏会损害免疫系统对感染的防御，如果维生素 A 水平不能迅速恢复，这些情况的严重程度和持续时间会延长[34]。动物研究中报道，维生素 A 缺乏症减少了实验性哮喘的发展，表明维生素 A 缺乏症可能偏向于 Th1 细胞介导的反应，而远离诱导哮喘的 Th2 细胞介导的反应[27]。但人类研究表明，怀孕期间补充维生素 A 会增加 Th1 细胞介导的反应，并降低 Th2 细胞介导的反应，这表明子宫环境中的偏斜可以降低儿童患哮喘的风险[35]。同时，Tian 等[36]发现新生儿肺炎链球菌感染后血清维生素 A 有短期和持续下降，感染后补充维生素 A 可显著促进 Th1 细胞的产生，降低 Th2 细胞表达，减轻气道高反应性和炎症细胞浸润。这表明感染后补充维生素 A 可通过改变 CD4+ T 细胞亚群抑制哮喘的进展。

4.2. RA 与哮喘气道上皮功能损伤

维生素 A 能维持气道上皮细胞、黏膜纤毛及平滑肌正常表型结构完整性[37]。维生素 A 通过促进角质形成细胞向成熟表皮细胞的分化，维持正常上皮细胞的动态平衡。

在哮喘发病过程中，许多哮喘过敏原可以破坏上皮紧密连接[38]，肥大细胞和 T2 固有淋巴细胞的活化分别促进组胺和 IL-13 等介质的释放，这可以进一步破坏连接复合物并增加上皮通透性[39]。上皮损伤促进细胞因子的释放如 TSLP、IL-1β、IFN-γ、TNF、IL-4、IL-13，它们可以降低连接蛋白的表达，从而形成上皮损伤、气道重塑和炎症反应的循环[40]。目前的研究认为，哮喘等疾病的启动环节与气道上皮结构完整性的破坏或功能紊乱相关[41]。

维生素 A 缺乏引起肺上皮内层结构改变，肺泡基底膜增厚和 I 型胶原异位沉积，肺泡间隔减少，导致呼吸道上皮鳞状化生和角化，纤毛上皮细胞被鳞状上皮取代，导致黏液产生减少，易于感染[29]。维生素 A 缺乏导致的坏死性气管支气管炎和鳞状上皮化生在维生素 A 水平恢复后可以逆转[32]。Aggarwal 等[42]发现在卵清蛋白致敏过程中补充全反式维甲酸可减少杯状细胞化生，参与调节黏液生成。

4.3. RA 与哮喘气道高反应性

气道平滑肌的收缩主要受毒蕈碱受体(M2, M3)受体的调控。目前认为，哮喘患者气道高反应性(Airway hyperresponsiveness, AHR)与 M2 受体功能异常，引起乙酰胆碱释放增加，M3 受体过度激活有关。研究表明维生素 A 缺乏的大鼠的支气管组织中的 M2 受体表达降低，M2 受体介导的支气管收缩抑制的能力降低，故 AHR 增加。一项研究显示于 VAD 大鼠的上皮下支气管弹性纤维较对照组明显减少，且在补充维生素 A 后可明显恢复[43]。

McGowan 等发现膳食中缺乏维生素 A 的成年大鼠具有较高的 AHR [44]。一项研究发现，在卵清蛋白诱导哮喘模型中，类维生素 A 受体的部分激动剂的应用几乎降低了哮喘的所有病理改变，包括 AHR，气道炎症细胞聚集，肺泡灌洗液中的促炎细胞因子的水平以及杯状细胞化生[45]。同样的，Sahamoto 等人[26]发现在小鼠卵清蛋白诱导模型中，应用全反式维甲酸 A 后，观察到 AHR 的降低以及其他哮喘症状的缓解。由此得出，维生素 A 在调节 AHR 和维持正常的支气管上皮方面是必不可少的。

4.4. RA 减轻哮喘气道氧化应激水平

维生素 A 是一种抗氧化剂，能清除氧分子和过氧自由基等活性氧并抑制促炎性细胞因子[46]。根据既往研究，哮喘患者维生素 A 水平的降低可能是由于在过量自由基存在的情况下抗氧化剂维生素 A 的利用增加引起的。慢性疾病如哮喘常常既是维生素缺乏症的原因又是结果。在哮喘患者中氧化应激增加导致抗氧化剂维生素(如维生素 A)的消耗增加，而维生素 A 的降低可能会促进氧化应激。既往研究显示哮喘患者常伴有维生素水平降低。在哮喘的发病中常合并其他病理生理改变例如肺部感染或气道炎症，故哮喘发生风险与维生素 A 含量之间的负相关可以通过炎症导致血清维生素 A 水平降低来解释。目前尚不清楚维生素 A 水平低是与哮喘病症发病机制相关的主要原因，还是由哮喘炎症过程引起的继发事件。

哮喘的特征是以全身自由基产生增加为特征的气道炎症[47]。氧化应激通过促进 T 细胞分化向 Th2 表型导致炎症的发展，氧化应激增加在诱导哮喘等过敏性气道炎症中起着关键作用[48]。可能通过生理性猝灭单线态氧和抑制自由基链反应，避免哮喘炎症反应加重[49]。一项研究表明由于饮食改变导致抗氧化剂摄入量减少会导致肺部抗氧化防御减弱，并增加对气道炎症和哮喘的易感性[50]。

综上所述，RA 对于调节哮喘有关键作用，补充 RA 可通过调节免疫、维持气道上皮完整性、降低气道高反应性、防止气道重塑及下调氧化应激等作用控制哮喘症状。RA 还可以通过连接到其核受体(包括 RAR、RXR 和 PPAR-β/δ)来影响翻译或刺激表观遗传效应，从而改变局部微环境与炎症因子水平。由此，

RA 对哮喘和过敏的有益治疗作用，可将 RA 作为治疗这些疾病的新型且有前途的辅助治疗剂引入。由于在临床研究中考虑到药物的潜在毒性，目前在哮喘患者补充 RA 等方面研究中尚无随机对照试验，尚需要安全的临床研究以及更全面的基础研究进一步阐明 RA 是否可以防治哮喘。

参考文献

[1] Yang, C., Lv, J., Li, X., Yang, X. and Yin, M. (2024) Global Burden of Asthma in Young Adults in 204 Countries and Territories, 1990-2019: Systematic Analysis of the Global Burden of Disease Study 2019. *Preventive Medicine Reports*, **37**, Article ID: 102531. https://doi.org/10.1016/j.pmedr.2023.102531

[2] GBD 2019 Chronic Respiratory Diseases Collaborators (2023) Global Burden of Chronic Respiratory Diseases and Risk Factors, 1990-2019: An Update from the Global Burden of Disease Study 2019. *EClinicalMedicine*, **59**, Article ID: 101936.

[3] Kool, M., Willart, M.A.M., van Nimwegen, M., Bergen, I., Pouliot, P., Virchow, J.C., *et al*. (2011) An Unexpected Role for Uric Acid as an Inducer of T Helper 2 Cell Immunity to Inhaled Antigens and Inflammatory Mediator of Allergic Asthma. *Immunity*, **34**, 527-540. https://doi.org/10.1016/j.immuni.2011.03.015

[4] Schmieder, H., Leischner, C., Piotrowsky, A., Marongiu, L., Venturelli, S. and Burkard, M. (2025) Exploring the Link between Fat-Soluble Vitamins and Aging-Associated Immune System Status: A Literature Review. *Immunity & Ageing*, **22**, Article No. 8. https://doi.org/10.1186/s12979-025-00501-3

[5] Lotfi, R. (2024) Retinoic Acid (RA): A Critical Immunoregulatory Molecule in Asthma and Allergies. *Immunity, Inflammation and Disease*, **12**, e70051. https://doi.org/10.1002/iid3.70051

[6] Bi, G., Liang, J., Bian, Y., Shan, G., Besskaya, V., Wang, Q., *et al*. (2022) The Immunomodulatory Role of All-Trans Retinoic Acid in Tumor Microenvironment. *Clinical and Experimental Medicine*, **23**, 591-606. https://doi.org/10.1007/s10238-022-00860-x

[7] Trinh, T., Hoang, T.X. and Kim, J.Y. (2020) All-Trans Retinoic Acid Increases NF-κB Activity in PMA-Stimulated THP-1 Cells Upon Unmethylated CPG Challenge by Enhancing Cell Surface TLR9 Expression. *Molecular and Cellular Biochemistry*, **473**, 167-177. https://doi.org/10.1007/s11010-020-03817-4

[8] Wu, J., Zhang, Y., Liu, Q., Zhong, W. and Xia, Z. (2013) All-Trans Retinoic Acid Attenuates Airway Inflammation by Inhibiting Th2 and Th17 Response in Experimental Allergic Asthma. *BMC Immunology*, **14**, Article No. 28. https://doi.org/10.1186/1471-2172-14-28

[9] Sun, C., Hall, J.A., Blank, R.B., Bouladoux, N., Oukka, M., Mora, J.R., *et al*. (2007) Small Intestine Lamina Propria Dendritic Cells Promote De Novo Generation of Foxp3 T Reg Cells via Retinoic Acid. *The Journal of Experimental Medicine*, **204**, 1775-1785. https://doi.org/10.1084/jem.20070602

[10] Surman, S.L., Jones, B.G., Sealy, R.E., Rudraraju, R. and Hurwitz, J.L. (2014) Oral Retinyl Palmitate or Retinoic Acid Corrects Mucosal IgA Responses toward an Intranasal Influenza Virus Vaccine in Vitamin A Deficient Mice. *Vaccine*, **32**, 2521-2524. https://doi.org/10.1016/j.vaccine.2014.03.025

[11] Kim, M.H., Taparowsky, E.J. and Kim, C.H. (2015) Retinoic Acid Differentially Regulates the Migration of Innate Lymphoid Cell Subsets to the Gut. *Immunity*, **43**, 107-119. https://doi.org/10.1016/j.immuni.2015.06.009

[12] Zhang, Y., Luo, Y., Shi, J., Xie, Y., Shao, H. and Li, Y. (2024) All-Trans Retinoic Acid Alleviates Collagen-Induced Arthritis and Promotes Intestinal Homeostasis. *Scientific Reports*, **14**, Article No. 1811. https://doi.org/10.1038/s41598-024-52322-x

[13] Ramanarayanan, P., Heine, G. and Worm, M. (2023) Vitamin A and Vitamin D Induced Nuclear Hormone Receptor Activation and Its Impact on B Cell Differentiation and Immunoglobulin Production. *Immunology Letters*, **263**, 80-86. https://doi.org/10.1016/j.imlet.2023.08.006

[14] Nagy, N.A., Hafkamp, F.M.J., Sparrius, R., Bas, R., Lozano Vigario, F., van Capel, T.M.M., *et al*. (2024) Retinoic Acid-loaded Liposomes Induce Human Mucosal CD103+ Dendritic Cells That Inhibit Th17 Cells and Drive Regulatory T-Cell Development *in Vitro*. *European Journal of Immunology*, **54**, e2350839. https://doi.org/10.1002/eji.202350839

[15] Hu, J., Sang, J., Hao, F. and Liu, L. (2023) Association between Vitamin A and Asthma: A Meta-Analysis with Trial Sequential Analysis. *Frontiers in Pharmacology*, **14**, Article ID: 1100002. https://doi.org/10.3389/fphar.2023.1100002

[16] Son, H., Park, H., Park, Y. and Kim, S. (2015) Effect of Retinoic Acid in a Mouse Model of Allergic Rhinitis. *Allergy, Asthma & Immunology Research*, **7**, 590-598. https://doi.org/10.4168/aair.2015.7.6.590

[17] Luo, Z., Liu, E., Luo, J., Li, F., Li, S., Zeng, F., *et al*. (2010) Vitamin a Deficiency and Wheezing. *World Journal of Pediatrics*, **6**, 81-84. https://doi.org/10.1007/s12519-010-0012-7

[18] Feng, L., Sun, F., Chen, Y., Athari, S.S. and Chen, X. (2021) Studying the Effects of Vitamin A on the Severity of Allergic Rhinitis and Asthma. *Iranian Journal of Allergy, Asthma and Immunology*, **20**, 648-692.

https://doi.org/10.18502/ijaai.v20i6.8018

[19] Rezaeianpour, R., Lotfi, R., Mortazavi, S.H., Karaji, A.G., Rezaiemanesh, A. and Salari, F. (2024) Evaluating the Serum Levels of CCL17, CCL22, and CCL28 Chemokines and the Gene Expression of A4β1 and A4β7 Integrins in Patients with Allergic Rhinitis. *Acta Medica Iranica*, **61**, 459-467. https://doi.org/10.18502/acta.v61i8.14903

[20] Zhang, W., Dai, W., Xie, Y., Chen, X., Zhang, P. and Cui, W. (2025) Retinoic Acid Regulates Allergic Inflammation via Limiting Mast Cell Activation. *Food Science & Nutrition*, **13**, e4727. https://doi.org/10.1002/fsn3.4727

[21] Davoodi, A., Lotfi, R., Mortazavi, S.H., *et al*. (2021) Retinoic Acid Correlates with Reduced Serum IL-10 and TGF-β in Allergic Rhinitis. *Reports of Biochemistry and Molecular Biology*, **9**, 399-407.

[22] Golebski, K., Layhadi, J.A., Sahiner, U., Steveling-Klein, E.H., Lenormand, M.M., Li, R.C.Y., *et al*. (2021) Induction of IL-10-Producing Type 2 Innate Lymphoid Cells by Allergen Immunotherapy Is Associated with Clinical Response. *Immunity*, **54**, 291-307.e7. https://doi.org/10.1016/j.immuni.2020.12.013

[23] Defnet, A.E., Shah, S.D., Huang, W., Shapiro, P., Deshpande, D.A. and Kane, M.A. (2021) Dysregulated Retinoic Acid Signaling in Airway Smooth Muscle Cells in Asthma. *The FASEB Journal*, **35**, e22016. https://doi.org/10.1096/fj.202100835r

[24] Maeta, A., Matsushima, M., Katahira, R. and Takahashi, K. (2020) Retinoic Acid Ameliorates the Severity of Food Allergy under Allergen Exposure in a Mouse Model with Food Allergy. *Journal of Nutritional Science and Vitaminology*, **66**, 375-380. https://doi.org/10.3177/jnsv.66.375

[25] Chen, F., Shao, F., Hinds, A., Yao, S., Ram-Mohan, S., Norman, T.A., *et al*. (2018) Retinoic Acid Signaling Is Essential for Airway Smooth Muscle Homeostasis. *JCI Insight*, **3**, e120398. https://doi.org/10.1172/jci.insight.120398

[26] Sakamoto, H., Koya, T., Tsukioka, K., Shima, K., Watanabe, S., Kagamu, H., *et al*. (2015) The Effects of All-Trans Retinoic Acid on the Induction of Oral Tolerance in a Murine Model of Bronchial Asthma. *International Archives of Allergy and Immunology*, **167**, 167-176. https://doi.org/10.1159/000437326

[27] Schuster, G.U., Kenyon, N.J. and Stephensen, C.B. (2008) Vitamin A Deficiency Decreases and High Dietary Vitamin A Increases Disease Severity in the Mouse Model of Asthma. *The Journal of Immunology*, **180**, 1834-1842. https://doi.org/10.4049/jimmunol.180.3.1834

[28] Checkley, W., West, K.P., Wise, R.A., Wu, L., LeClerq, S.C., Khatry, S., *et al*. (2011) Supplementation with Vitamin A Early in Life and Subsequent Risk of Asthma. *European Respiratory Journal*, **38**, 1310-1319. https://doi.org/10.1183/09031936.00006911

[29] Timoneda, J., Rodríguez-Fernández, L., Zaragozá, R., Marín, M., Cabezuelo, M., Torres, L., *et al*. (2018) Vitamin A Deficiency and the Lung. *Nutrients*, **10**, Article No. 1132. https://doi.org/10.3390/nu10091132

[30] McCullough, F.S.W., Northrop-Clewes, C.A. and Thurnham, D.I. (1999) The Effect of Vitamin A on Epithelial Integrity. *Proceedings of the Nutrition Society*, **58**, 289-293. https://doi.org/10.1017/s0029665199000403

[31] Benson, M.J., Pino-Lagos, K., Rosemblatt, M. and Noelle, R.J. (2007) All-Trans Retinoic Acid Mediates Enhanced T Reg Cell Growth, Differentiation, and Gut Homing in the Face of High Levels of Co-Stimulation. *The Journal of Experimental Medicine*, **204**, 1765-1774. https://doi.org/10.1084/jem.20070719

[32] Marquez, H.A. and Cardoso, W.V. (2016) Vitamin A-Retinoid Signaling in Pulmonary Development and Disease. *Molecular and Cellular Pediatrics*, **3**, Article No. 28. https://doi.org/10.1186/s40348-016-0054-6

[33] Mucida, D., Park, Y., Kim, G., Turovskaya, O., Scott, I., Kronenberg, M., *et al*. (2007) Reciprocal Th17 and Regulatory T Cell Differentiation Mediated by Retinoic Acid. *Science*, **317**, 256-260. https://doi.org/10.1126/science.1145697

[34] Huang, Z., Liu, Y., Qi, G., Brand, D. and Zheng, S. (2018) Role of Vitamin A in the Immune System. *Journal of Clinical Medicine*, **7**, Article No. 258. https://doi.org/10.3390/jcm7090258

[35] Cox, S.E., Arthur, P., Kirkwood, B.R., Yeboah-Antwi, K. and Riley, E.M. (2006) Vitamin A Supplementation Increases Ratios of Proinflammatory to Anti-Inflammatory Cytokine Responses in Pregnancy and Lactation. *Clinical and Experimental Immunology*, **144**, 392-400. https://doi.org/10.1111/j.1365-2249.2006.03082.x

[36] Tian, Y., Tian, Q., Wu, Y., Peng, X., Chen, Y., Li, Q., *et al*. (2020) Vitamin A Supplement after Neonatal *Streptococcus pneumoniae* Pneumonia Inhibits the Progression of Experimental Asthma by Altering $CD4^+$T Cell Subsets. *Scientific Reports*, **10**, Article No. 4214. https://doi.org/10.1038/s41598-020-60665-4

[37] Carazo, A., Macáková, K., Matoušová, K., Krčmová, L.K., Protti, M. and Mladěnka, P. (2021) Vitamin A Update: Forms, Sources, Kinetics, Detection, Function, Deficiency, Therapeutic Use and Toxicity. *Nutrients*, **13**, Article No. 1703. https://doi.org/10.3390/nu13051703

[38] Matsumura, Y. (2012) Role of Allergen Source-Derived Proteases in Sensitization via Airway Epithelial Cells. *Journal of Allergy*, **2012**, Article ID: 903659. https://doi.org/10.1155/2012/903659

[39] Sugita, K., Steer, C.A., Martinez-Gonzalez, I., Altunbulakli, C., Morita, H., Castro-Giner, F., *et al*. (2018) Type 2 Innate Lymphoid Cells Disrupt Bronchial Epithelial Barrier Integrity by Targeting Tight Junctions through IL-13 in Asthmatic

Patients. *Journal of Allergy and Clinical Immunology*, **141**, 300-310.e11. https://doi.org/10.1016/j.jaci.2017.02.038

[40] Frey, A., Lunding, L.P., Ehlers, J.C., Weckmann, M., Zissler, U.M. and Wegmann, M. (2020) More than Just a Barrier: The Immune Functions of the Airway Epithelium in Asthma Pathogenesis. *Frontiers in Immunology*, **11**, Article No. 761. https://doi.org/10.3389/fimmu.2020.00761

[41] Russell, R.J., Boulet, L., Brightling, C.E., Pavord, I.D., Porsbjerg, C., Dorscheid, D., *et al*. (2024) The Airway Epithelium: An Orchestrator of Inflammation, a Key Structural Barrier and a Therapeutic Target in Severe Asthma. *European Respiratory Journal*, **63**, Article ID: 2301397. https://doi.org/10.1183/13993003.01397-2023

[42] Aggarwal, S., Kim, S., Cheon, K., Tabassam, F.H., Yoon, J. and Koo, J.S. (2006) Nonclassical Action of Retinoic Acid on the Activation of the Camp Response Element-Binding Protein in Normal Human Bronchial Epithelial Cells. *Molecular Biology of the Cell*, **17**, 566-575. https://doi.org/10.1091/mbc.e05-06-0519

[43] McGowan, S.E., Holmes, A.J. and Smith, J. (2004) Retinoic Acid Reverses the Airway Hyperresponsiveness but Not the Parenchymal Defect That Is Associated with Vitamin A Deficiency. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, **286**, L437-L444. https://doi.org/10.1152/ajplung.00158.2003

[44] McGowan, S.E., Smith, J., Holmes, A.J., Smith, L.A., Businga, T.R., Madsen, M.T., *et al*. (2002) Vitamin A Deficiency Promotes Bronchial Hyperreactivity in Rats by Altering Muscarinic M_2 Receptor Function. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, **282**, L1031-L1039. https://doi.org/10.1152/ajplung.00319.2001

[45] Fujii, U., Miyahara, N., Taniguchi, A., Oda, N., Morichika, D., Murakami, E., *et al*. (2017) Effect of a Retinoid X Receptor Partial Agonist on Airway Inflammation and Hyperresponsiveness in a Murine Model of Asthma. *Respiratory Research*, **18**, Article No. 23. https://doi.org/10.1186/s12931-017-0507-z

[46] Milani, A., Basirnejad, M., Shahbazi, S. and Bolhassani, A. (2016) Carotenoids: Biochemistry, Pharmacology and Treatment. *British Journal of Pharmacology*, **174**, 1290-1324. https://doi.org/10.1111/bph.13625

[47] Vural, H., Aksoy, N., Ceylan, E., Gencer, M. and Ozguner, F. (2005) Leukocyte Oxidant and Antioxidant Status in Asthmatic Patients. *Archives of Medical Research*, **36**, 502-506. https://doi.org/10.1016/j.arcmed.2005.02.006

[48] Park, C., Kim, T., Lee, K., Moon, K., Bae, Y., Jang, M.K., *et al*. (2009) Increased Oxidative Stress in the Airway and Development of Allergic Inflammation in a Mouse Model of Asthma. *Annals of Allergy, Asthma & Immunology*, **103**, 238-247. https://doi.org/10.1016/s1081-1206(10)60188-3

[49] Wagner, J.G., Jiang, Q., Harkema, J.R., Ames, B.N., Illek, B., Roubey, R.A., *et al*. (2007) γ-Tocopherol Prevents Airway Eosinophilia and Mucous Cell Hyperplasia in Experimentally Induced Allergic Rhinitis and Asthma. *Clinical & Experimental Allergy*, **38**, 501-511. https://doi.org/10.1111/j.1365-2222.2007.02855.x

[50] Marmsje, K., Rosenlund, H., Kull, I., Haykansson, N., Wickman, M., Pershagen, G., *et al*. (2009) Use of Multivitamin Supplements in Relation to Allergic Disease in 8-Y-Old Children. *The American Journal of Clinical Nutrition*, **90**, 1693-1698. https://doi.org/10.3945/ajcn.2009.27963