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ω-3脂肪酸在儿童哮喘治疗研究中的进展

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摘　要

哮喘是一种广泛存在的呼吸系统疾病，在全球范围内具有相当大的影响力，其影响遍及不同地域，在不同人群中的发病率从1%到18%不等。从一系列观察性和干预性研究中收集到的数据表明了n-3脂肪酸在改善炎症方面的潜在治疗能力，这与哮喘发病机制密切相关。因此，ω-3多不饱和脂肪酸(ω-3 PUFAs)已成为目前研究的一个焦点，是一种前景广阔治疗哮喘的辅助疗法，其治疗效果的机制是多方面的，特点是复杂的相互作用，包括两种直接方式，如将花生四烯酸置换为二十碳五烯酸的底物，并随后调节其代谢，以及还有涉及炎症基因转录激活调控变化的间接途径。此外，ω-3 PUFAs还能产生一系列专门的炎症相关介质，即消退素，它们在抑制炎症过程进展方面发挥着协同作用。重要的是，膳食中补充ω-3脂肪酸或其生物活性衍生物对健康的影响微乎其微。因此，通过补充ω-3脂肪酸这一非药物干预策略，有可能为哮喘的治疗带来益处。

关键词

支气管哮喘，ω-3多不饱和脂肪酸，治疗，综述，儿童

Advancements in the Research on Omega-3 Fatty Acids for the Treatment of Asthma in Children

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Abstract

Asthma epitomizes a widespread respiratory ailment of considerable global significance, exerting its impact across varied geographical landscapes, with prevalence rates ranging from 1% to 18% across different population cohorts. A synthesis of evidence gleaned from an array of observational and interventional investigations collectively underscores the potential therapeutic prowess of n-3 fatty acids in ameliorating inflammatory cascades, particularly those intricately linked with the pathogenesis of asthma. Consequently, omega-3 polyunsaturated fatty acids (*ω*-3 PUFAs) have emerged as a focal point of inquiry, representing a promising adjunctive therapeutic avenue in the management of asthma. The mechanistic orchestration underlying the therapeutic effects of *ω*-3 PUFAs is multifaceted, characterized by intricate interplays encompassing both direct modalities, such as the displacement of arachidonic acid as a substrate for eicosanoid biosynthesis and subsequent modulation of their metabolism, and indirect pathways involving regulatory alterations in the transcriptional activation of inflammatory genes. Furthermore, *ω*-3 PUFAs engender a repertoire of specialized pro-resolving mediators, notably resolvins, which exert concerted efforts in attenuating the progression of inflammatory processes. Importantly, dietary supplementation with *ω*-3 fatty acids or their bioactive derivatives has been correlated with negligible adversities on pivotal health indices. Consequently, the burgeoning interest in *ω*-3 fatty acid supplementation represents a compelling non-pharmacological intervention strategy with the potential to confer therapeutic dividends in the management paradigm of asthma.

Keywords

Bronchial Asthma, *ω*-3 Polyunsaturated Fatty Acids, Treatment, Review, Child

1. 引言

支气管哮喘(简称哮喘)是一种气道慢性炎症为特征的异质性疾病，其典型特征包括不同程度的可逆性气道阻塞和不同程度的呼气气流受限，临床上常表现为咳嗽、气促、胸闷和哮鸣等症状[1]。总体而言，儿童哮喘的患病率呈逐年上升趋势，给患儿家庭和社会带来了重大的经济负担[2]，尽管在美国采用吸入性糖皮质激素(Inhaled corticosteroid, ICS)联合支气管扩张剂进行治疗，但仍有大约 5%~10%的患者未能有效缓解症状或病情持续恶化[3]，相较于其他轻症患者，这部分患者的治疗成本高出六到七倍，占到了美国哮喘相关支出的 40%以上[4]。在韩国，儿童哮喘的治疗支出位列所有年龄段之首[5]。近 20 年来，我国城市儿童哮喘的患病率逐年递增，且患儿的年龄逐渐降低，尤其以学龄前儿童最为常见，这严重影响了患儿的生活质量[6]。目前，哮喘的治疗策略主要以药物控制为主，包括 β2-受体激动剂、糖皮质激素、抗胆碱能药物、白三烯调节剂等。然而，一项相关研究指出，在中国，有 20%的哮喘患儿在接受药物治疗后病情控制不佳，44%的患儿依从性较差，治疗时间较长，费用较高[7]。欧米伽-3 多不饱和脂肪酸(Omega-3 fatty acids, Omega-3 polyunsaturated fatty acids, ω-3 PUFAs)又称 n-3 脂肪酸，是人体健康至关重要的脂肪酸之一，包括 α-亚麻酸(α-Linolenic acid, ALA)、二十碳五烯酸(Eicosapentaenoic acid, EPA)和二十二碳六烯酸(Docosahexaenoic acid, DHA)。这些脂肪酸不能由人体内部自行合成，必须通过饮食摄入，

尤其是从含量丰富的食物，如鱼类、亚麻籽和核桃中获取。Omega-3 脂肪酸在多个生物学过程中发挥着关键作用，包括细胞膜的结构和功能、炎症调节以及神经系统的发育和功能等。近年来，一些研究表明 ω-3 脂肪酸具有抗炎作用，并能降低气道高反应性[8] [9] [10] [11]。现对国内外 ω-3 脂肪酸治疗哮喘的研究进展进行综述。

2. 哮喘的发病机制

哮喘的发病机制尚未完全阐明；然而，近年来对哮喘的持续研究已经证实，哮喘具有多基因遗传背景，并受到遗传和环境因素的共同调控[12]。由于发病机制、基因组、生理学、组织学、生物标志物、临床表现以及治疗反应各异，哮喘在不同患者身上表现出一定的异质性。近年来，人们对哮喘的遗传表型和内型进行了详尽的研究。根据不同的分类标准，哮喘可分为多种表型，而哮喘内型的研究尚未达成统一的标准，但哮喘的表型与内型之间的密切相关已得到广泛认可。此外，表观遗传调控也参与了哮喘的发病机制，包括 DNA 甲基化、组蛋白修饰和非编码 RNA 的调控[13]。目前，哮喘的发病机制主要涉及气道炎症、气道高反应性和气道重塑。

1) 气道炎症

不同类型的哮喘最终表现出不同程度的炎症、气道反应性、粘液分泌和气道重塑，这一差异可能受到上皮细胞和免疫细胞等介导的影响[14]。在典型的过敏性或 IgE 介导的哮喘模型中，不同的环境刺激会诱发气道上皮细胞和树突状细胞之间的相互作用，从而引发免疫反应。气道上皮细胞通过模式识别受体识别过敏原或具有蛋白酶活性的微生物，导致大量细胞因子、核苷酸和脂肪酸代谢产物的表达，并向负责招募 Th1 或 Th2 细胞因子、中性粒细胞和嗜酸性粒细胞的免疫细胞发出信号[15]。树突状细胞则处理这些环境因子的抗原，并将其呈现给 T 细胞，从而引发 Th2 淋巴细胞的克隆扩增，导致 IL-4、IL-13 和 IL-5 的产生，以及 B 细胞的分化和转换，从而产生 IgE。此外，Th2 细胞因子还会调节肥大细胞和嗜酸性粒细胞的增殖，活化的肥大细胞和嗜酸性粒细胞会产生更多的 Th2 细胞因子，从而导致炎症的发生。Th2 细胞因子的存在维持气道炎症。支气管活检结果显示，哮喘患者的支气管内存在嗜酸性粒细胞、活化的肥大细胞和主要由 Th2 细胞组成的 T 淋巴细胞浸润。这些细胞的增殖和肥大导致气道上皮细胞结构的变化，包括上皮下胶原沉积和气道平滑肌增厚，以及新生血管增多和粘液增生。

2) 气道过度反应

气道过度反应的特点在于在各种刺激下，气道呈现过度或过早的收缩，这是哮喘发病的一个重要因素。Nassenstein 等人[16]认为，神经生长因子可能是调节哮喘的神经内分泌－免疫网络失衡机制的启动因子。神经生长因子由炎症部位的细胞产生，诱导平滑肌收缩，调节白细胞产生促炎分子，导致气道感觉神经的过度增殖和敏感化。此外，最近的研究发现了一些与气道高反应性相关的产物，如 p22phox [17]和 IL-33 [18]等。

3) 气道重塑

气道重塑的特征包括各种结构变化，如粘液趋化、层状网状增厚、血管生成增加、上皮下纤维化以及平滑肌肥大和增生，这些结构变化由各种免疫介质或细胞机制引发。在 Naveed SU 等人的研究[19]中发现，哮喘患者气道平滑肌细胞产生的基质金属蛋白酶(Matrix metalloproteinase-1, MMP-1)，是对照组及健康人的 5.4 倍($P = 0.002$)，而 MMP-1 的活性增加，与 FEV1 下降和哮喘症状恶化有关。与气道重塑相关的主要细胞包括 T 淋巴细胞、嗜酸性粒细胞、肥大细胞、成纤维细胞和其他上皮细胞。最近的研究表明，气道上皮细胞在气道重塑中发挥着重要作用[20]。上皮－间质营养单位是位于上皮细胞和间质细胞之间的一层成纤维细胞。这些成纤维细胞在一系列局部刺激下分化为肌成纤维细胞，并分泌多种细胞介质和蛋白质，影响上皮细胞、平滑肌细胞、血管和神经末梢的动态结构。支气管的上皮－间质转化可能因

上皮－间质营养单位的不同激活而导致不同的哮喘表型，从而使治疗方法更具针对性[21]。

3. ω-3 脂肪酸的合成、代谢和生物学功能

ω-3 脂肪酸中结构最简单的为 α-亚麻酸(α-Linolenic acid, ALA)，在人体内，ALA 通过 Δ6-去饱和酶(Δ6-desaturase)的作用下形成十八(烷)酸(硬脂酸，stearidonic，SDA，C18:4n-3)，二十碳四烯酸(eicosatetraenic acid, C20:4n-3)是在延伸酶的作用下，SDA 增加 2 个碳原子形成的；二十碳四烯酸在 Δ5-去饱和酶 (Δ5-desaturase)作用下增加 1 个双键形成二十碳五稀酸(EPA, C20:5n-3)，EPA 进行 2 个延长步骤产生二十二碳五稀酸(DPA, C22:5n-3)，二十二碳五烯酸经过一系列伸长步骤、Δ6-去饱和酶和 β-氧化形成二十二碳六烯酸(DHA, C22:6n-3)。以上合成过程主要在人体肝脏内完成，少量在大脑中进行。DHA 在大脑、精子、视神经和视网膜中含量最高，而 EPA 由于在代谢分解和提供氧化能量方面的作用，在各种组织中含量较低。一些相关研究[22] [23]表明，增加 ALA 的摄入量并不会显著提高人体内 EPA、DPA 和 DHA 的含量，这表明 ALA 在人体内合成 EPA 和 DHA 的能力有限。在人体摄入的食物中，EPA 和 DHA 在动物性食物中的含量通常高于植物性食物，其中主要分布在水产类、禽肉类、蛋奶类、畜肉类食物中[24]。

ω-3 多不饱和脂肪酸的生物功能包括参与生物膜的形成、提供氧化能、调节炎症、免疫反应、脂质代谢以及维持大脑的发育和功能，在多种慢性疾病的发病过程中发挥着积极作用。近年来，许多研究报告称，ω-3 多不饱和脂肪酸可能影响多种参与炎症的细胞的功能，并可能参与调节它们产生的化学介质，从而控制炎症。

1) ω-3 PUFAs 可减少白细胞趋化作用：能够降低白细胞的趋化性：趋化性指的是白细胞在化学物质(特别是来源于花生四烯酸的花生四烯酸)的作用下向炎症部位移动的过程。对健康志愿者进行鱼油补充的研究表明，每日摄入 3~15 克 EPA + DHA 可以减少中性粒细胞和单核细胞对不同趋化因子(如 LTB4、细菌肽和人类血清)的趋化反应[25] [26] [27] [28] [29]。Schmidt 等人[30]等人的一项剂量反应研究显示，每日摄入 1.3 克 EPA + DHA 的 ω-3 PUFA 能够抑制趋化，其机制尚不完全清楚，但可能与化学感受器的表达减少或拮抗作用有关。

2) PUFA ω-3 能够减少粘附分子的表达，从而削弱白细胞与内皮细胞之间的相互作用：粘附分子是内皮细胞和白细胞表面的蛋白质，它们通过形成配体来促进不同细胞之间的相互作用。由于这些相互作用，血液中的白细胞与血管壁相互作用，并离开血液进入炎症活动场所。通过细胞培养[27]-[34]和动物实验[30] [31] [32] [34] [35] [36]，相关研究表明，在暴露于 n-3-PUFA 因子后，单核细胞[33]、巨噬细胞[35]、淋巴细胞[36]以及内皮细胞[31]表面某些粘附分子的表达会减少，因此在某些情况下导致了白细胞和内皮细胞之间的黏附减少[31] [34] [36]。对健康志愿者进行鱼油补充的研究表明，每天摄入约 1.5 克 EPA + DHA 可以降低受干扰素-γ 刺激的离体单核细胞表面细胞间粘附分子(ICAM)-1 的表达水平[37]。在外周血管疾病患者中，每天摄入 1.8 克 EPA + DHA 可减少其单核细胞与培养的内皮单层之间的粘附相互作用[38]。另外，EPA (1.8 g/天)可降低代谢综合征患者血流中可溶性 ICAM-1 和可溶性 VCAM-1 的浓度[34]。

3) n-3 PUFAs 和消退素：在过去二十多年中，已确认 n-3 PUFA 产生的新脂质介质家族，包括由 EPA(E 系列)和 DHA(D 系列)产生的苦味素以及由 DHA 产生的保护素(在神经组织中也称为神经保护素)。COX 和 LOX 途径参与了消退素和保护素的合成，并根据阿司匹林的存在与否形成不同的异构体[39] [40] [41] [42]。研究表明，实验室啮齿动物摄入富含鱼油的食物会增加这些动物体内阿巴西林素的合成[43]。消退素和保护素的生物学效应已经在细胞培养和炎症动物模型中被广泛地证实，表明它们具有抗炎和消炎的作用。例如，消退素 E1、D1 和保护素 D1 均能抑制中性粒细胞的跨内皮迁移，防止中性粒细胞浸润炎症部位；消退素 D1 抑制 IL-1β 的产生；保护素 D1 抑制肿瘤坏死因子(TNF)-α 和 IL-1β 的产生[39] [40] [41] [42]。消退素的生物活性是由特定的 G 蛋白偶联受体介导。消退素 E1 是 LTB_4 受体 BLT_1 [44]的部分激动

剂，可与 LTB_4 竞争并拮抗其趋化作用。

4) n-3 PUFA 与炎症细胞因子的关系：早期研究表明，EPA 和 DHA 可抑制体外培养的人内皮细胞在内毒素刺激下产生 IL-6 和 IL-8 [45] [46]，而 EPA 或鱼油可抑制培养的单核细胞在内毒素诱导下产生的 TNF-α [47] [48] [49] [50]。给予小鼠鱼油摄入可减少巨噬细胞在内毒素刺激下产生的 TNF-α、IL-1β 和 IL-6 [46] [51] [52]，注射内毒素的小鼠体内 TNF-α、IL-1β 和 IL-6 的循环浓度也有所降低[53]。一些关于健康受试者服用鱼油补充剂的研究显示，受内毒素刺激的单核细胞或分离的有核细胞产生的 TNF-α、IL-1β 和 IL-6 有所减少[26] [54] [55]，但并非所有研究都证实了这一效果[9]。一些研究未能显示 n-3 PUFAs 对细胞因子产生的影响，这些研究每天提供的 EPA + DHA 小于 2 g，上述结果可能由于剂量不足造成的。

5) n-3 PUFAs 与 T 细胞反应性的关系：在细胞培养中，EPA 和 DHA 可抑制 T 细胞的增殖[56] [57] [58] [59]和 IL-2 [57] [58] [59]的产生。对于接受高剂量鱼油、EPA 或 DHA 的动物的研究也显示，有价值的 T 细胞反应会减少[60] [61] [62]。尽管一些研究表明，增加 n-3 PUFAs 的摄入会降低人类 T 细胞的增殖[54] [63]和 IL-2 的产生[54]，但目前的人体研究结果并不一致。这可能是由于某些研究中提供的 n-3 PUFA 剂量不足所致。

4. ω-3 脂肪酸在治疗哮喘中的作用

EPA 或鱼油能够抑制内毒素诱导的培养单核细胞产生 TNF-α，这可能与 ω-3 PUFAs 抑制气道上皮细胞中核因子激活 B 细胞 κ 轻链增强子(NF-κB)的活性有关[49]。Flesher 等人的研究[64]发现，在慢性过敏性哮喘急性加重的小鼠模型中，RvE1 可促进炎症细胞数量、灌洗液中细胞因子浓度和巨噬细胞细胞因子 mRNA 表达的减少，这表明 RvE1 可能有利于临床气道炎症的消退。Levy 等人的研究[65]表明，在小鼠气道炎症模型中，PD1 可减少气道嗜酸性粒细胞和 T 淋巴细胞在气道募集，气道粘液、IL-13、半胱氨酰白三烯和 PGD(2)水平以及气道对吸入乙酰胆碱的高反应性也有所降低。在徐雨婷等人的研究[66]中，加入 n-3 PUFAs 后，暴露于紫外线下的 SKH-1 小鼠表皮或真皮中 IL-1β、IL-6 和 TNF-α 的表达均有所下降。

20 世纪 90 年代，一项随访 16 年的随机对照实验[67]显示，每天食用鱼油的孕妇的子女患哮喘的风险明显低于孕期食用橄榄油或不食用鱼油的孕妇的后代(P = 0.01)。在 Gürdeniz 等人[68]的 COPSAC 队列研究中，通过为期 6 年的双盲随机安慰剂对照试验，追踪补充鱼油的孕妇，得到 387 名新生儿血液质谱代谢组学的结果，发现补充鱼油的孕妇的后代，其代谢组学特征以及生物标志物 3-羧基-4-甲基-5-丙基-2-呋喃丙酸(CMPF)与 6 岁时哮喘的风险呈负相关别为(HR = 0.89，p = 0.002 和 HR = 0.67，p = 0.005)，表明鱼油补充剂和 CMPF 水平可能在降低儿童哮喘及相关呼吸问题的风险中发挥着潜在的保护作用。在一项为期 3 个月的横断面研究[11]中，通过每天补充含 180 mg EPA 和 120 mg DHA 的鱼油胶囊，检测干预前后哮喘患儿和健康受试者肺功能、血清 Th1、Th2、Th9、Th17 和 Th22 细胞因子的情况，发现患儿肺功能 FEV_1/FVC 明显改善(p = 0.044)，IL-17A 和 TNF-α 显著降低(p < 0.0001)。然而，并非所有临床研究都表明 ω-3 脂肪酸减轻哮喘有效，在一项为期 6 个月的随机、平行、单中心对照试验[69]中，在轻度哮喘患儿的饮食中每周添加 2 餐含有 150 克油性鱼类的地中海饮食，结果实验组呼出的一氧化氮(FeNO)浓度降低，提示对抗炎治疗有效率提高，然而在肺功能、哮喘控制和生活质量评分方面未观察到明显差异。

总之，ω-3 脂肪酸可减轻在体外可减轻细胞培养物中炎症因子的产生，在体内可减少小鼠体内炎症细胞因子表达，但相关临床研究的结果尚未达成共识，因此需要进一步的临床研究来证实 ω-3 脂肪酸对哮喘具有缓解作用。

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