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儿童过敏性哮喘变应原研究进展

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摘 要

过敏性哮喘是一种常见的呼吸系统慢性疾病，严重影响患儿的生活质量。吸入性变应原在哮喘发生和发展的过程中起到至关重要的作用。本文通过对哮喘相关吸入性变应原的研究文献进行综述，以期对哮喘的防止提供新的思路。

关键词

哮喘，曲霉，尘螨，蟑螂，花粉

Advances in Allergens for Children's Allergic Asthma

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Abstract

Allergic asthma is a common chronic respiratory disease that seriously affects the quality of life of children. Inhalational allergens play a crucial role in the occurrence and development of asthma. This article reviews the research literature on inhaled allergens related to asthma, in order to provide new ideas for the prevention of asthma.

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Keywords

Asthma, *Aspergillus*, Dust Mites, Cockroaches, Pollen

1. 引言

哮喘是一种慢性呼吸系统疾病，通过遗传和环境影响的复杂相互作用而发展，影响着全世界至少 3 亿人。几十年来，哮喘的患病率一直在稳步上升，由于直接间接成本，它仍是一个主要的公共卫生问题和全球经济负担[1]，影响着几乎全年龄段的个体。哮喘、过敏性鼻炎和湿疹已经成为世界范围内儿童最常见的慢性疾病[2] [3]；过敏性哮喘是一种由变应原诱发的以气流受限、气道高反应性、IgE 升高、气道慢性炎症为特征的疾病[4]，被定义为以气道阻塞、粘液产生和支气管痉挛为特征的慢性非均质炎症性疾病[5]。气道黏膜对环境因素的在过敏性哮喘中起重要作用，吸入过敏原、烟雾暴露、室内和室外空气污染是哮喘的常见诱因，临床症状表现为胸闷、咳嗽、喘息和呼吸困难，最终影响生活质量[6]。即使大多数哮喘患者的症状使用低剂量抗炎药就能得到很好的控制，仍有约 10%的患者出现严重症状，严重影响生活质量，甚至危及生命[7]。在我国，过敏性疾病患者的数量正在增加，2020 年，我国儿童哮喘的患病率已增长至约 3%，较 30 年前升高了 150% [8]，不同地区的患病率差异很大[9]。气道平滑肌收缩和对外界刺激的过度敏感是哮喘的主要特征。哮喘的病理特征包括粘液分泌过多引起的气流阻塞、纤毛功能丧失、支气管高反应性、炎症和气道重塑[10]，多种复杂的免疫反应参与了过敏性哮喘的发生和发展。过敏原目前，过敏性疾病涉及三种免疫机制：免疫球蛋白 E(IgE)介导、混合(IgE/非 IgE)和非 IgE 介导的过敏[11]。过敏性疾病往往在接触致敏原后迅速发病，例如：接触猫会在几分钟内引起打喷嚏、眼睛瘙痒和喘息；被黄蜂蜇伤可在 15 分钟内引起全身荨麻疹；吃花生可在 20 分钟内引起全面过敏反应。因此，对致敏原的特点及致敏机制的研究有助于指导过敏性疾病的治疗和预防。

2. 过敏性哮喘变应原研究进展

过敏性疾病的致敏原主要来源于尘螨、花粉、蟑螂、动物皮屑和真菌。在我国，支气管哮喘和(或)过敏性鼻炎最常见的过敏原是室内尘螨，其次是蟑螂、花粉和霉菌；过敏原的区域分布因气候不同而不同[12] [13]；例如在华南地区，最常见尘螨和真菌，华北地区最常见花粉和尘螨。随着食物结构的丰富和多样化，食物过敏的比例也逐渐增加，食物过敏的症状往往出现在摄入食物后的几分钟至数小时，表现在多个器官，包括：口腔黏膜、皮肤、胃肠道、呼吸道以及心血管系统。急性荨麻疹是食物过敏最常见的皮肤表现。由于与吸入过敏原存在交叉致敏作用，食物过敏原的诊断更为复杂[14]。例如水果和蔬菜与各种形式的花粉有交叉致敏作用，虾和蟹对尘螨和蟑螂过敏原有交叉致敏作用。

1) 曲霉

烟曲霉可以在室内和室外生长，成年人每天可吸入数百个孢子，由于其体积较小，因此更容易到达下呼吸道[15]。曲霉孢子的萌发和生长过程中会产生许多分子，一些可作为过敏原介导或加重哮喘症状。由曲霉引起的肺部疾病大致可分为腐生性(曲霉瘤)、变应性(烟曲霉相关哮喘)、过敏性(支气管肺曲霉病)和侵袭性(侵袭性肺曲霉病) [16]。曲霉引起的哮喘往往较为严重[16]，通常进展为过敏性支气管肺曲霉病，

其在气道中定殖后不易被炎症细胞清除，能在很长一段时间内持续释放过敏原和其他产物[15]，对患者的肺组织及肺功能产生不可逆的损害。具有蛋白酶活性的烟曲霉变应原可能引起在破坏上皮完整性、驱动粘蛋白产生、上皮下纤维化和平滑肌细胞过度活跃方面尤为重要。有研究发现，在一组严重哮喘患者中，约 19%的患者出现支气管扩张，合并肺功能差并出现频繁加重；并与烟曲霉特异性致敏和痰培养阳性密切相关[17]；另一项研究结果表明，35%的严重哮喘患者出现支气管扩张，并与烟曲霉致敏/痰培养阳性高度相关[18]。过敏性曲霉病是一种复杂的肺部疾病，是由针对哮喘和囊性纤维化患者气道中的烟曲霉定殖的免疫反应引起[19]，早在 1978 年，就有研究发现真菌和哮喘之间的联系[20]。真菌致敏的潜在机制尚不明确，其产生的蛋白酶被认为占主要作用，烟曲霉被证明具有致敏作用的 20 余种蛋白质其中许多是蛋白酶，并且其产生的过敏反应可以被蛋白酶抑制剂减弱，真菌蛋白酶被认为是真菌气道感染引起变应性肺病的关键因素[21] [22]。烟曲霉和气道上皮的相互作用是随后气道炎症和损伤修复的关键[23]。在哮喘环境下，富含黏蛋白、暴露的气道基质成分和血浆蛋白的环境为吸入气道的曲霉提供了理想的生长条件。在烟曲霉的萌发过程中，能直接产生多种具有蛋白酶活性的过敏原和代谢副产物，直接破坏上皮的完整，引发促炎细胞因子和纤维化生长因子的产生。随后，免疫细胞的募集和血浆蛋白的进一步泄露将引起炎症、纤维蛋白沉积和结构变化的恶性循环发展。

综上所述，真菌致敏的哮喘症状及病理损害均较重，对其损伤机制仍需要进一步更深入的研究。同时，不同真菌直接也存在相互作用；例如，有研究发现，针对曲霉的特定 IgE 水平升高，其他真菌菌落如枝胞熟、青霉属和裂藻属同样可以被观察到[24]；在其他患者队列中观察到，真菌致敏的哮喘患者也常见交替菌和枝孢子菌[25]。真菌的致敏及损伤机制及相关作用仍需要更深入的基础和临床研究。

2)尘螨

屋尘螨致敏是世界上最常见的呼吸道过敏原因之一[26]，室内尘螨属于节肢动物，喜生长于潮湿的室内环境，广泛存在于室内灰尘、床垫、床单等，以人类的皮肤碎片为食。大量流行病学研究表明，尘螨是我国中东部、西部及一些北方城市哮喘/鼻炎的主要吸入性过敏原[27] [28] [29] [30]。有研究表明，过敏性疾病患者中约 59.0%、57.6%的患者分别对粉螨和翼螨过敏[13]，尘螨致敏和暴露与哮喘症状的严重程度和支气管高反应性有关，是哮喘后续发展的重要决定因素。螨虫的过敏原同样具有酶活性；在混合粉尘中，可检测出胰蛋白酶、凝乳蛋白酶、胶原酶、淀粉酶、几丁质酶等酶的活性，这些蛋白质水解酶的活性可能有助于增强尘螨和粉尘的致病作用[31]。尘螨过敏原的蛋白水解活性可能会破坏肺部微环境的稳定性，使其成为原过敏性环境，并有可能利于过敏性炎症。因此，避免接触尘螨可能对其他空气致敏原引起的过敏和其自身引起的过敏反应有重要调节作用，这种猜测仍需要进一步的研究来证实。对尘螨敏感的哮喘患者，其症状往往与家中尘螨过敏原的水平相关，在接触尘螨后支气管痉挛和气道高反应加重，在无尘螨的环境中症状减轻[32]。此外，螨虫暴露和呼吸道病毒感染之间的协同作用进一步加重原有的气道症状，是急性喘息或住院的主要原因。因此，减少尘螨接触是控制尘螨过敏哮喘患者最有效的手段。吸入是接触尘螨的主要途径，其次，口服及皮肤破损同样可以引起尘螨致敏的发生。尤其在婴幼儿，经常将手和玩具放入手中可能出现尘螨的口服途径吸收。尘螨的特异性致敏与哮喘发展的关系是复杂的，家中尘螨过敏原的水平往往与哮喘患者症状严重程度密切相关；即使在螨虫生长旺盛的潮湿地区，应用严格的除螨措施也能明显降低室内的过敏原水平。减少尘螨的暴露往往可以改善患者的临床症状。由有机织物制成的孔径约 6 μm 的织物可以对尘螨产生很好的抑制作用[33]，使用防尘螨床上用品作为干预措施已多次被证实是减少床上用品表面回收尘螨过敏原数量的有效措施[34] [35] [36]。此外，经常清洗床上用品、避免使用地毯、使用除螨剂、控制室内湿度等均能起到一定的除螨作用；实际上，由于支出增加、生活方式改变甚至缺乏配偶的支持，这些措施往往难以长期坚持。

3) 花粉

花粉引起的季节性过敏性哮喘是哮喘最重要的亚型之一，影响着全世界数百万人[37]；是变应性鼻炎发生和恶化的主要危险因素之一，现有研究发现，同样也影响着过敏性哮喘[38]。在我国北方地区，除尘螨之外，花粉是另一个非常重要的吸入性过敏原，春季以桦树花粉为主，秋季则以蒿和葎草花粉为主[37]，空气中花粉浓度往往与季节性过敏性哮喘的严重程度密切相关；在城镇地区，景观树如柏树、白蜡树、桦树、橄榄树等的花粉同样是导致哮喘发作的重要因素。近年来，花粉过敏发病率逐年上升，许多因素导致这一结果，如气候变化、城市化、生物多样性丧失等[39]。气候变化会影响植物分布及植物生理，使植物释放出更多的过敏性花粉。当花粉被吸入鼻腔后，会释放引起过敏反应的蛋白质，引起过敏性鼻炎[40]；这些蛋白质可以以气溶胶的形式被运送至下呼吸道，从而导致过敏的发生。此外，花粉还会释放大量低分子量化合物促进人体对致敏蛋白的免疫反应。花粉过敏原、空气污染物和环境因素是影响过敏原浓度和哮喘严重程度的关键因素[41] [42]。花粉中过敏原的释放也可能发生在特定的气候条件，如雷暴天气。雷暴哮喘的发生在全球多处地方有被发现并描述[43]，包括我国的内蒙古地区；在雷暴开始时，过敏发作的患者数量迅速增加，部分患者往往出现严重症状。在雷暴天气的作用下，花粉被破坏产生更小的、容易吸入的微粒并形成气溶胶，使得空气中的致敏微粒浓度大幅升高，这些微粒可以被吸入下呼吸道引起花粉过敏患者的哮喘发作[44]。尽管雷暴天气导致哮喘发作并不频繁，但是其发作往往引起急诊患者迅速增加，对医疗系统产生较大冲击；因此，进行有效的预警和预防可以产生更重要的作用[45] [46]。花粉过敏的治疗及预防主要包含避免接触过敏原、药物管理以及过敏原的免疫治疗。在花粉季节减少外出、做好个人防护；应用抗过敏药物及吸入糖皮质激素可以有效减少哮喘的急性发作。新型生物制剂如特异性抗体的应用有可能有助于减少季节性哮喘的发作，但其临床价值仍需进一步研究。

4) 蟑螂

蟑螂暴露是哮喘发展的主要危险因素，常见于在中国南方，尤其是农村地区。有研究发现，接触蟑螂过敏原对哮喘发病率的影响似乎比尘螨对患儿的影响更大，蟑螂过敏已被确定为低收入城市人口哮喘发展的最强危险因素之一[47]。流行病学调查表明，中国鼻炎和/或哮喘患者对美洲大蠊和德国小蠊的致敏率分别是 26.34%和 19.37%。蟑螂暴露与蟑螂致敏和呼吸道过敏症状密切相关，其粪便、唾液、卵和脱落角质层中提取的蛋白质被认为是致敏的主要原因，其致敏性已通过皮肤实验、支气管激发实验在人体中得到证实[48]，接触蟑螂过敏原是导致对其致敏的重要原因，杀灭居住环境中的蟑螂能有效减少过敏及哮喘的发作。由于蟑螂的过敏原存在于其排泄物中，即使在短时间内杀灭蟑螂，其残留的致敏原仍会在较长的时间内持续使人致敏，因此症状缓解往往需要数月。在蟑螂过敏原点刺试验阳性及卧室蟑螂过敏原水平较高的儿童装中，哮喘的住院率升高了 3.4 倍[49]；与点刺试验阴性的患儿相比，阳性患儿去就医次数更多、喘息更明显、缺课频率更多[50]。蟑螂过敏原的复杂性和多样性诱导了多方面的免疫反应，涉及免疫系统的内在途径和适应性途径，这些途径由酶蛋白酶活性和肺表面黏膜识别受体的适配激活[51] [52]。多糖的免疫原性与特定的结构特征之间存在潜在联系。蟑螂过敏原中的聚糖可能是其免疫原性的主要决定因素[53]。了解和研究蟑螂的致敏机制有助于新的治疗干预措施的发展，这将在未来治疗哮喘和其他过敏性疾病中发挥作用。

3. 不足与展望

过敏原、免疫反应和气道疾病之间的相互作用非常复杂，其背后的机制仍未完全阐明。治疗过敏性疾病的最佳策略是多种方法的结合，包括避免过敏原、患者教育、适当的药物治疗和过敏原的免疫治疗。过敏原的检测是预防和治疗过敏性疾病的核心，减少过敏原暴露能有效改善过敏性哮喘的症状和生活质量。过敏性鼻炎与哮喘密切相关，约 40%的过敏性鼻炎患者患有哮喘。早期诊断和治疗可以有效控制疾

病的进展，减轻患者痛苦和经济负担。过敏原的分布随气候变化而变化，因此，建立基于当地流行过敏原谱对改善区域特异性过敏性疾病的诊断和治疗具有重要意义。此外，有研究表明，多摄入水果和蔬菜对哮喘的控制可能存在积极的影响；尤其在儿童[54]，增加水果和蔬菜的摄入可以降低哮喘的风险[55]。综上所述，过敏原谱的构建和院外饮食、运动干预可能是改善哮喘预后的有效措施，其有效性可能需要更进一步的临床研究来证明；减少过敏原的接触是最有效的措施，其执行仍存在阻碍。

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