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·综述·

尘螨过敏原调控气道上皮细胞相关致敏机制研究进展*

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【摘要】 尘螨是最常见的吸入性过敏原之一,是引起过敏性哮喘、过敏性鼻炎、特应性皮炎等过敏性疾病的重要因素。尘螨过敏已被世界卫生组织(WHO)视为全球性卫生问题之一,但迄今尚无尘螨诱发的过敏性疾病的有效治疗方案。作为气道抵抗过敏原、病毒、细菌、环境污染物等炎症刺激和抗原的第一道防线,气道上皮细胞构筑了肺组织与外环境间的第一道屏障,在多种急慢性肺部炎症性疾病发病机制中发挥了关键作用。尘螨过敏原刺激后,气道上皮细胞参与过敏原致敏及气道炎症反应过程,在呼吸系统天然免疫功能中发挥重要作用。本文主要就尘螨过敏原及其调控气道上皮细胞炎症反应致过敏机制研究进展作一综述。

【关键词】 尘螨;过敏原;气道上皮细胞;致敏机制;综述

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Progress of researches on dust mites-modulated airway epithelial cells-associated sensitization mechanisms

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【Abstract】 As one the most common inhaled allergens, dust mites are major contributors to allergenic diseases, including allergenic asthma, allergic rhinitis and atopic dermatitis. Dust mite allergy has been considered as one of global health problems by the World Health Organization (WHO); however, there is no cure for dust mites-induced allergenic diseases. As the first-line defense against inflammatory stimuli and antigens in the airway, including allergens, viruses, bacteria and environmental pollutants, airway epithelial cells form the first barrier between the lung and external environments, and play a critical role in the pathogenesis of multiple acute and chronic lung disorders. Following allergen stimulation, airway epithelial cells are involved in allergen sensitization and inflammatory reactions, which play an important role in natural immune functions of the respiratory system. This review summarizes the advances in dust mite allergens and airway epithelial cells-associated sensitization mechanisms.

【Key words】 dust mite; allergen; airway epithelial cell; sensitization mechanism; review

***尘螨属节肢动物门、蜘蛛纲、真螨目、蜱螨科,呈世界性分布,在温热潮湿地区孳生密度最高[1]。尘螨主要孳生于床上用品、软垫家具、地毯等处,通常以这些纺织品上的有机残留物(人类或动物脱落的皮屑、头发或指甲碎片等)和微生物为食物来源[2]。既往研究表明,尘螨是人类最常见的吸入性过敏原之一,是引起过敏性哮喘、过敏性鼻炎、特应性皮炎等过敏性疾病的重要因素[3-4]。屋尘螨(house dust mite, HDM)是最常见和最重要的气源性过敏原之一[5],全球有6500万~1.3亿人患HDM相关过敏性疾病[6]。鉴于尘螨过敏患者数量众多、过敏性疾病患者生活质量极大受损、医疗成本高、社会经济负担重,尘螨过敏已被世界卫生组织(WHO)视为全球性卫生问题之一[7]。但迄今尚无尘螨诱发的过敏性疾病的有效治疗方案[8-9]。

作为气道和肺部抵抗过敏原、病毒、细菌、环境污染物等炎症刺激和抗原的第一道防线,气道上皮细胞构筑了肺组织与外环境间的第一道屏障,在多种急慢性肺部疾病发病机制中发挥了关键作用[10]。气道上皮被视为调控宿主炎症、免疫和再生反应的不可或缺的控制器,从而抵抗过敏原、病毒和环境污染物入侵[11]。在暴露于过敏原刺激后,气道上皮细胞参与过敏原致敏及炎症反应过程,在气道和肺部天然免疫功能中发挥重要作用[12-13]。本文主要就尘螨过敏原及其调控气道上皮细胞相关致敏机制研究进展作一综述。

1 尘螨过敏原

在日常尘螨环境中,人们主要以吸入携带尘螨过敏原颗粒

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物的形式致尘螨过敏[14]。HDM不仅自身可以产生过敏原，还可以携带转运其他微生物及其相关致敏物质[5]。尘螨过敏原主要存在于粪便颗粒、外骨骼以及尸体碎片中，其生存环境灰尘中含有大量脂多糖和细菌[1]。

蛋白酶活性是花粉、动物皮屑和蜂毒等过敏原的共同特征[15]，HDMs及其粪便颗粒中含有几种蛋白水解酶[16]。根据过敏原发现时间和序列同源性，WHO和国际免疫学会联合会(International Union of Immunological Societies)过敏原命名小组委员会(Allergen Nomenclature Sub-committee)已对40种粉尘螨(*Dermatophagoides farinae*，DFA)过敏原、40种屋尘螨(*Dermatophagoides pteronyssinus*，DPT)过敏原进行了标准化命名，其中以屋尘螨Ⅰ类变应原(Der p1)和粉尘螨Ⅰ类变应原(Der f1)和Der p2/f2致敏率最高[4]。半胱氨酸蛋白酶Der p1/f1及丝氨酸蛋白酶Der p3/f3、p6/f6和p9主要存在于尘螨粪便颗粒中[15]；两种蛋白酶在作为过敏原的同时，还可以直接作用于上皮细胞产生特异性效应[17-18]。Der p2与淋巴细胞抗原96(LY96，又称MD-2)结构同源，可以替代MD-2重建脂多糖(LPS)驱动的Toll样受体4(TLR4)信号通路[19]。Der p10是一种原肌球蛋白，作为HDM肌肉蛋白介导过敏反应[20]，且与虾、蟹等甲壳纲动物来源的原肌球蛋白间存在交叉反应[21]。Der p11是一种含874个氨基酸的副肌球蛋白，推算分子量为100 kDa，与螨、蜱及其他无脊椎动物副肌球蛋白高度同源，存在于螨体而非粪便中，是特应性皮炎中的一种重要过敏原[22]。

尘螨颗粒中还存在几丁质、尘螨DNA、细菌DNA、内毒素和多糖等成分，这些成分被称为病原相关分子模式(pathogen-associated molecular patterns，PAMPs)，能够为先天免疫细胞表面的模式识别受体(pattern recognition receptor，PRR)所识别，调节先天免疫[23]。几丁质是一种以葡萄糖胺为基础的聚合物，是形成螨外骨骼和真菌细胞壁的主要成分[24]。未甲基化的尘螨和细菌DNA，可以作为PAMPs激活TLR9[25]。螨虫粪便中的内毒素在Der p2帮助下激活TLR4，导致气道炎症和支气管高反应性[26]。此外，尘螨提取物中存在的细菌信号肽[27]可作为PAMPs通过甲酰肽受体(FPR)和FPR样1激活人嗜酸性粒细胞[28]。

2 气道上皮细胞相关尘螨致敏机制

尘螨过敏原本身和过敏原源或环境中存在的危险信号可以直接激活上皮细胞上的蛋白酶激活受体(protein-activated receptors，PARs)和PRRs，释放大量气道上皮细胞因子，促进Th2型免疫反应增强，从而参与过敏性炎症反应的发生与发展[29]。吸入的尘螨过敏原活化上皮细胞和树突状细胞(dendritic cells，DCs)的PRR，破坏上皮细胞间的紧密连接，使得DCs接触到过敏原[30]。部分过敏原可以活化上皮细胞和DCs的核因子κB(nuclear factor kappa-B，NF-κB)信号；上皮细胞活化后，产生尿酸、ATP、脂蛋白A(LPA)等内源性危险信号，以及粒细胞-巨噬细胞集落刺激因子(GM-CSF)、胸腺基质淋巴细胞生成素(TSLP)等细胞因子[31]。同时上皮细胞也产生趋化因子配体2(CCL2)和CCL20，募集DCs至肺脏[32]。在这些信号的共同作用下，DCs迁移至纵膈淋巴结，DCs的MHC Ⅱ分子递呈抗原肽段并与T细胞表面受体相互作用，促进T细胞向Th2细胞极化，从而导致Th1/Th2失衡[33]。Th2细胞可产生包括白细胞介素4(IL-4)、IL-5、IL-13在内的大量细胞因子，IL-4和IL-13可以促进趋化因子产生，进一步促进炎性细胞浸润；同时作用于B细胞，促进B细胞分化为浆细胞，分泌IgE抗体[34]。IL-5促进嗜酸性粒细胞增殖分化，同时募集嗜酸性粒细胞。肥大细胞结合B细胞分泌的IgE抗体，在IL-9作用下进一步活化，脱颗粒并释放组胺等物质，作用于支气管、血管、腺体等，从而引起支气管哮喘、鼻炎、皮炎等变应性疾病[35]。

2.1 HDM过敏原与PARs 上皮细胞上的G蛋白偶联PARs，可以识别HDM丝氨酸蛋白酶过敏原；丝氨酸蛋白酶将细胞外N端水解后，PARs被激活，Der p3/f3和Der p9能够激活气道上皮细胞上的PAR-2和PAR-4，释放IL-6、IL-8等促炎细胞因子和GM-CSF等趋化因子[36-39]。半胱氨酸蛋白酶Der p1作为凝血酶原，激活气道上皮细胞上的PAR-1和PAR-4，诱导ATP释放，通过P_2X_7嘌呤感受器激活途径间接活化TLR-4，产生细胞内活性氧(ROS)，调节IL-33释放和促炎基因表达[40-41]。有研究发现，PAR-1可识别Der f3/p3，刺激肺肥大细胞中PAR-4依赖性Ca^{2+}流入，使其迁移和激活[42]。HDM丝氨酸蛋白酶过敏原可以触发气道上皮细胞中瞬时受体电位香草酸1(TRPV1)激活，与PAR-2共同促进ATP释放和P2YR2依赖性信号传导，导致上皮细胞中IL-33释放[43]。

2.2 HDM过敏原与PRRs 作为PAMPs，尘螨颗粒中的多种成分可以与上皮细胞和抗原呈递细胞上的PRRs结合，诱导Th2型免疫反应[22]。目前，尘螨粪便和体内已知PAMPs包括几丁质、尘螨DNA、细菌DNA、内毒素和多糖[44]。迄今为止，至少已发现4种类型PRRs：① TLRs，位于细胞表面或内体中；② NOD样受体(NLRs)，位于细胞质中；③ RIG-I样受体(RLRs)，位于细胞内；④ C型凝集素受体(CLRs)，可识别碳水化合物结构的细胞表面受体[45]。在PRRs识别PAMPs后，PRRs触发NF-κB、丝裂原活化蛋白激酶(MAPK)和Ⅰ型干扰素等下游信号通路，从而诱导炎性介质大量产生[46]。

气道上皮暴露于低剂量LPS、长链饱和脂肪酸(SFAs)、单独或与具有脂质/脂肪酸结合能力的HDM过敏原时，可激活TLR2和TLR4[47]。这些受体激活将触发NF-κB信号通路，导致IL-33、TSLP、IL-25、GM-CSF和IL-1α等细胞因子产生[48]。高迁移率族蛋白1(HMGB1)释放可以增加促炎因子产生，这种慢性炎症介质不仅促进Ⅱ型DC_s募集和活化、还刺激Ⅱ型固有淋巴细胞(ILC2s)，导致IL-5和IL-13释放[49]。此外，内毒素可降低激活DCs的内皮细胞因子表达，从而抑制HDM的Th2型免疫反应；因而，长期暴露于低水平内毒素或农场灰尘可保护小鼠发生HDM诱导性哮喘[50]。

Der p2与MD-2结构同源，可以替代MD-2重建LPS驱动的TLR4信号通路，TLR4激活会募集接头蛋白髓样分化因子88(MyD88)或含有TIR结构域的接头蛋白(TRIF)[19]。MyD88募集会导致TNF受体相关因子6(TRAF6)激活，触发NF-κB易位到细胞核，还触发MAPK级联反应，导致AP-1激活，从而调控细胞因子基因表达[51]。TRIF激活NF-κB和干扰素调节因子3(IRF3)，诱导促炎细胞因子基因和Ⅰ型干扰素的表达[52]。Der f35有一个与MD-2相关的脂质识别结构域，与Ⅱ类过敏原类似，但其是否对TLR4激活起作用仍有待进一步研究[53]。几丁质可通过TLR-2/Dectin-1/MR信号通路刺激IL-33、TSLP和IL-25等细胞因子释放[54]，而β-葡聚糖介导的

Th2极化依赖于Dectin-1表达下调和Der p10相互作用[55]。Der p5/f5和Der p21/f21激活气道上皮细胞中TLR2/NF-κB/MAPK信号通路[56]；而Der f31可以激活气道上皮细胞TLR2/TLR4，释放TSLP和IL-33，激活肺组织中的ILC2s[57]。

哮喘患者暴露于HDM后，气道中还可以产生尿酸和ATP，两者被称为损伤相关分子模式(DAMPs)，是提示免疫系统组织损伤的重要危险信号[58-59]。尿酸通过触发CLR信号激活Syk/PI3K依赖性DCs，诱导Th2型免疫反应[59]。有研究认为，HDM通过NLR途径激活先天性免疫反应，HDM提取物刺激人角质细胞可激活caspase-1，上调NLRP3炎症小体、分泌IL-1b和IL-18[60]。

2.3 其他机制

2.3.1 HDM过敏原破坏上皮完整性 除了作为过敏原外，半胱氨酸蛋白酶Der p1和丝氨酸蛋白酶Der p3、p6和p9在特应性反应中直接作用于上皮细胞[61]。来自HDM粪便颗粒的丝氨酸蛋白酶过敏原Der p1可破坏胞内紧密连接；在气道上皮细胞内，Der p1可导致紧密连接蛋白occludin断裂，推测Der p1切割位点位于occludin蛋白胞外结构域肽及claudin-1蛋白；而紧密连接破坏可非特异性提高上皮细胞通透性，从而促进Der p1穿透上皮细胞屏障[62]。既往曾认为蛋白酶对上皮细胞的作用仅限于破坏上皮细胞间的紧密连接蛋白，现在认识到这些蛋白酶还有其他作用[63]。在特应性皮炎中，蛋白酶可减弱皮肤屏障功能[64]；激活表皮角质形成细胞和真皮神经中的PAR-2，导致非组胺介导的瘙痒[65]。HDM的丝氨酸蛋白酶活性可诱导IL-8和GM-CSF释放，提示HDM的丝氨酸蛋白酶活性通过PAR-2激活活化角质形成细胞而导致特异性皮炎发生[66]。此外，具有蛋白酶活性的HDM过敏原可通过PAR-2活化影响表皮通透性屏障稳态及后续皮肤中钙离子调控[67]。在过敏性哮喘中，Der p1可通过活化MAPK信号通路诱导气道平滑肌反应性变化，而Der p1诱导的促哮喘效果与ERK1/2通路活化有关[68]。HDM上皮刺激可选择性促进哮喘支气管平滑肌细胞增殖[69]，而哮喘严重程度、气道平滑肌肿大与PAR-2及其配体表达相关[70]。

2.3.2 尘螨过敏原是其他致敏物质的促进剂 尘螨中的佐剂不仅促进对尘螨本身过敏原致敏，而且促进对其他潜在过敏原致敏。Der p1的蛋白水解活性增加了小鼠对卵清蛋白(OVA)及其他环境中过敏原的IgE抗体反应[71]。BALB/C小鼠鼻内给予HDM提取物随后立即给予OVA雾化会诱导肺部产生强烈的嗜酸粒细胞性炎症反应，这与支气管高反应增加、血清OVA特异性IGE和IgG1抗体水平升高以及IL-4、IL-5、IL-13等Th2型细胞因子水平上升有关[72]。此外，HDM来源几丁质会通过TLR2依赖性通路增加OVA诱导的气道高反应性，而几丁质诱导的肿瘤坏死因子α(TNF-α)是对引入性过敏原产生Th2型细胞反应的关键介质[73]。

3 结语

上皮屏障完整性受损促进了DCs和上皮细胞对过敏原的摄取，而基于抗蛋白酶防御的下调则增强了组织损伤和免疫激活。PARs特异性裂解以及TLRs和CLRs等PRRs激活，调控促炎和促Th2型细胞因子/趋化因子上调，这些细胞因子/趋化因子释放不仅可以募集和激活炎症细胞，还可以诱导Th2分化。HDM过敏原共存于由脂质或多糖成分组成的混合基质中，可能来源于螨虫本身、内共生体、外共生体或其他环境。推测这些成分本身可能与真菌微生物群相互作用，从而影响过敏；深入阐明这些成分构成有助于进一步了解过敏机制，从而为寻找HDM诱发的过敏性疾病预防与治疗靶点提供参考依据。

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