

doi: 10.13241/j.cnki.pmb.2018.10.039

· 专论与综述 ·

细胞因子在重症哮喘发病机制中的研究进展 *

彭玲玲 段婷婷 陈艳焦 王 宇 徐玉东 杨永清[△] 尹磊森[△]

(上海中医药大学 上海市针灸经络研究所 上海 201203)

摘要 重症哮喘是指在过去一年中超过 50 %的时间需要给予高剂量糖皮质激素联合长效 β_2 -受体激动剂和白三烯调节剂或全身激素治疗,才能维持哮喘控制或即使在上述治疗下仍不能有效控制症状的疾病。重症哮喘发病机制复杂,危险因素多,治疗困难,是临床热点和难点问题。免疫介导的炎症反应在重症哮喘疾病发生中处于重要地位,多种炎症细胞和前炎症因子介导的免疫应答均参与了重症哮喘的发生和发展。本综述对细胞因子的表达与重症哮喘炎症病理改变做了分析,有助于深入研究重症哮喘发病机制,以期临床诊断和寻找更为有效的靶向治疗药物提供新的理论依据和策略。

关键词 重症哮喘;细胞因子;中性粒细胞;治疗

中图分类号 R-33 R392 R562.25 文献标识码 A 文章编号 1673-6273(2018)10-1990-06

The Progress of Cytokines in the Pathogenesis of Severe Asthma*

PENG Ling-ling, DUAN Ting-ting, CHEN Yan-jiao, WANG Yu, XU Yu-dong, YANG Yong-qing[△], YIN Lei-miao[△]

(Shanghai University of Traditional Chinese Medicine, Shanghai Research Institute of Acupuncture and Meridian, Shanghai, 201203, China)

ABSTRACT: Severe asthma refers to more than six months in one year, high-dose glucocorticoid combined with long-acting β_2 -agonists and leukotriene modulators or systemic corticosteroid therapy are given to control asthma, or still could not control effectively with the above treatment. It is a clinical hot and difficult issues due to its complex pathogenesis, multiple risk factors, difficult treatment. Inflammatory cells and pro-inflammatory factors involve in the occurrence and development of severe asthma, as a result, immune-mediated inflammatory injury plays an important role in the severe asthma. The expression levels of cytokines in the severe asthma and its pathological changes are analyzed in this review, which will be beneficial to further study the pathogenesis with the purpose of providing new theoretical basis and strategy for clinical diagnosis and more effective targeted therapy drugs.

Key words: Severe asthma; Cytokines; Neutrophil; Treatment

Chinese Library Classification(CLC): R-33; R392; R562.25 Document code: A

Article ID: 1673-6273(2018)10-1990-06

前言

重症哮喘(severe asthma, SA),又称难治性哮喘(refractory asthma)、难控制性哮喘(difficult-to-control asthma)、激素抵抗型哮喘(steroid-resistant asthma)等,是指患者在现有药物治疗下仍会反复发作,主要表现为给予高剂量皮质激素仍出现气喘、呼吸困难等状况^[1]。重症哮喘患者虽然只占全部哮喘人数 5-10 %^[2],其急诊率和住院率分别是轻、中度哮喘患者的 15 倍和 20 倍^[3],每年直接的治疗费用是常规哮喘患者 10 倍,消耗了 50 %以上的医疗资源^[4,5]。在全球范围内,重症哮喘给社会和家庭带来的负担愈发沉重,已成为当前重要的公共卫生问题^[6]。

重症哮喘病理生理机制复杂,存在一定争议^[7]。1999 年欧洲呼吸协会(ERS)首次定义重症哮喘为给予高剂量吸入性/系统性皮质激素仍然不能有效控制症状的哮喘^[8]。ERS 和 2000 年

美国胸科协会(ATS)的专家及全球哮喘防治指南(GINA)对重症哮喘临床治疗反应特性的定义的核心是强调其重症^[9]。虽然在 2010 年世界卫生组织(WHO)根据对高剂量激素反应性和临床症状也给出了重症哮喘定义^[10],但医学界仍没有形成重症哮喘的统一定义^[9]。重症哮喘区别常规哮喘的三个明显特征如下:给予高剂量皮质激素仍然出现哮喘症状;病理生理机制由中性粒细胞介导;哮喘表型包含 $T_H1/T_H2/T_H17$ 等不同免疫特征^[11]。

重症哮喘的治疗方面,高剂量皮质激素合并长效 β_2 -受体激动剂等药物仍是目前临床应对方案^[12]。而针对重症哮喘皮质激素耐受情况,新的替代治疗策略不断出现^[3]。IgE 单克隆抗体奥马佐(Omalizumab)可干预 IgE 介导的超敏反应炎症通路控制重症哮喘临床症状^[13],降低约 30 %哮喘急性加重,但有效拮抗血清高浓度 IgE 必须使用超高剂量和昂贵费用限制了该药推广^[14]。利用 CXCR₂ 受体拮抗剂 SCH527123 来阻断中性粒细胞

* 基金项目:国家自然科学基金项目(81473760;81574058);上海市人才发展基金项目(201610)

作者简介:彭玲玲(1990-),硕士研究生,主要研究方向:针灸防治哮喘临床与基础研究,电话:021-54592134, E-mail: plingling1007@163.com

[△]通讯作者:尹磊森,博士,副研究员, E-mail: collegeym@shutcm.edu.cn;

杨永清,博士,研究员, E-mail: yyq@shutcm.edu.cn

(收稿日期:2017-12-26 接受日期:2018-01-23)

趋化因子白介素 8 (interleutin-8, IL-8, 又称 CXCL8) 效应, 结果发现重症哮喘病人症状评分有改善且痰液中中性粒细胞数量显著下降 36.3%, 发作次数显著降低^[15]。但使用肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α) 单克隆抗体无法显著改善重症患者一秒用力呼气容积 (forced expiratory volume in one second, FEV1) 等呼吸功能和发作次数^[16]。临床观察到三磷酸腺苷 (简称 ATP) 在哮喘病人肺泡灌洗液 (bronchoalveolar lavage fluid, BALF) 中高表达, 而屏蔽肺组织 ATP 受体 P2Rs 或中和 ATP 均可显著降低哮喘发作, 机制研究确定 ATP 可通过激活髓样树突状细胞增强 T_H2 型炎症^[17]。在重症哮喘机制研究中, 嘌呤代谢过程产物 ATP、一磷酸腺苷 (AMP) 和腺苷等和中性粒细胞气道炎症密切相关^[18], P1、P2 等特异性嘌呤受体也被认为是可能是潜在的哮喘药物靶标^[19,20]。目前研究揭示使用针对某些炎症因子的阻断剂可以较好的控制重症哮喘症状, 但对于治疗其它部分细胞因子介导的炎症反应还是不能得到有效改善。

重症哮喘发病机制复杂, 其中免疫介导的炎症损伤在疾病发生中处于重要地位, 病理过程中分泌的促炎症因子对疾病的发生发展也起到关键作用。本综述将从 IL-8、IL-17、TGF- β 1 (转化因子 β 1) 和 TNF- α 等关键炎症因子在重症哮喘发病机制中所起的作用进行论述, 有助于为临床诊断和开发有效的相应靶点药物提供新的理论依据。

1 白介素 8 (IL-8) 与重症哮喘的关系

IL-8 又称趋化因子 CXCL8, 是一种炎性趋化性因子, 能够特异性地趋化中性粒细胞进入炎症组织, 促使炎症细胞释放游离中性粒细胞弹性蛋白酶 (neutrophil elastase, NE) 等炎症介质^[21], 是近年来发现的重要的中性粒细胞趋化因子。

IL-8 在重症哮喘急性炎症的中性粒细胞浸润中起关键作用。哮喘发生过程中, 气道上皮细胞在受到脂多糖 (LPS) 刺激后快速地产生大量的 IL-8, 中性粒细胞通过 Toll 样受体 (toll-like receptor, TLR) 和 G 蛋白耦联受体 CXCR1/CXCR2 能检测到 IL-8、LPS 和 TNF 等成分而上调自身的迁移活性并向气道炎症部位聚集^[22], 释放 NE 等毒性介质, 造成支气管损伤以加重哮喘。研究发现在重症哮喘患者支气管黏膜中, 表皮生长因子受体 (epithelial growth factor receptor, EGFR) 及 IL-8 mRNA 表达明显升高, 伴中性粒细胞浸润, 且 EGFR 和 IL-8 表达呈正相关, 认为重症哮喘患者的上皮细胞损伤与 IL-8 分泌水平升高至中性粒细胞浸润密切相关^[23]。有研究报道, IL-8 受体 CXCR1 和 CXCR2 在重症哮喘患者痰液中中性粒细胞的表达明显低于外周血, 外周血与痰中受体 CXCR1 和 CXCR2 表达呈负相关, 表明体内中性粒细胞是通过受体 CXCR1 和 CXCR2 检测到气道中分泌的 IL-8, 从而促使自身从外周血迁移至气道中, 引起气道中中性粒细胞浸润^[24]。口服皮质类固醇可引起 IL-8 的上皮表达显著增加, 表明皮质类固醇本身可能会导致持续气道中性粒细胞增多, 且 IL-8 的浓度和痰中中性粒细胞的百分比呈正相关, 可看出 IL-8 与重症哮喘之间关系密切^[25]。

另外, IL-8 也是一种嗜酸粒细胞趋化因子。IL-8 刺激的中性粒细胞可能通过释放超氧阴离子 O_2^{-} ^[26]、基质金属蛋白酶 (matrix metalloproteinase, MMP-9)^[27]、白三烯 B4 (leukotriene B4, LTB4) 和血小板活化因子 (platelet-activating factor, PAF)^[28], 导

致重症哮喘气道中嗜酸性粒细胞的募集, 引起气管平滑肌收缩、黏膜水肿、血管通透性增高和气道重塑。

2 白介素 17 (IL-17) 与重症哮喘的关系

过去十年的研究均证实 T_H17 细胞和中性粒细胞在重症哮喘炎症机制中扮演着重要角色^[29], 因而 IL-17 作为 T_H17 细胞分泌的特征型细胞因子也备受关注。IL-17 又名细胞毒性 T 淋巴细胞相关抗原 8 (cytotoxic T-lymphocyte-associated antigen 8, CTLA-8), 是由嗜酸性粒细胞和 CD4⁺T 淋巴细胞等分泌的一种前炎性因子^[30]。

在重症哮喘发病机制中, IL-17 具有强大的招募中性粒细胞的能力。IL-17 作为 T_H17 细胞关键的促炎因子, 可直接通过分泌 IL-8 引起肺中中性粒细胞募集和活化^[31], 或间接诱导气道上皮细胞、气管平滑肌细胞和支气管纤维母细胞活化, 刺激这些细胞高表达中性粒细胞趋化因子 CXCL1 和 IL-8, 趋化中性粒细胞在气道局部浸润增殖, 参与重症哮喘中性粒细胞气道炎症反应、气道高反应性和气道重塑过程^[32]。 T_H17 细胞也可以通过表达信号传导与转录激活因子 3 (signal transducer and activator of transcription 3, STAT3), 驱动和释放除 IL-17 以外的细胞因子诱导中性粒细胞趋化反应^[33]。

在重症哮喘患者诱导痰、支气管活检及外周血中 IL-17 水平含量高表达, 且 IL-17 水平和由 IL-17 诱生得 3 型固有淋巴细胞 (innate lymphoid cells, ILC3) 数量与哮喘严重程度呈明显正相关^[34-35]。另有研究报道, IL-17 会导致小鼠气管环和人支气管组织的平滑肌细胞强烈收缩, 引起气道高反应性, 这种作用是由 IL-17 诱导地气管平滑肌细胞中 RhoA-ROCK 途径的激活介导的, 是平滑肌收缩过程中肌球蛋白轻链 (myosin light chain, MLC) 磷酸化的两个关键调节剂^[37]。且 IL-17 能协同加强 IL-4 和 TGF- β 产生, 以促进支气管上皮细胞增殖及间叶细胞标记物表达形态学变化^[38]。

在治疗方面, 布罗达单抗 (Brodalumab, AMG827) 作为人抗 IL-17RA 免疫球蛋白 G2 (IgG2) 单克隆抗体之一, 可高亲和力结合 IL-17RA, 特异性阻断 IL-17, 在治疗银屑病、类风湿性关节炎和克罗恩氏病方面均取得良好疗效^[39,40]。但将 Brodalumab 运用于重症哮喘的临床研究却发现, 在哮喘控制测试评分、无症状持续时间以及 FEV1 肺功能等方面指标均无改善, 仅在气道高可逆性亚组中观察到哮喘控制测试评分的微小改善, 且不受血液中性粒细胞或嗜酸性粒细胞的影响, 表明抑制 IL-17 并没有起到重症哮喘有效治疗的效果^[41]。故针对 Brodalumab 治疗重症哮喘还需作进一步的临床研究, 从而制定和实施更有效的治疗策略。

在重症哮喘疾病中产生 IL-17 的细胞不再局限于 T_H17 细胞^[29], 在炎症反应过程中先天免疫细胞 (如 B 淋巴细胞、中性粒细胞、T 细胞、自然杀伤细胞和髓系细胞等) 也会产生大量的 IL-17^[42]。研究发现 IL-23 可以促进记忆性 CD4⁺T 淋巴细胞分泌 IL-17^[43], 随后在重组激活基因 (RAG) 缺陷小鼠 (缺少 T、B 淋巴细胞) 的实验研究中, 观察到 IL-23 仍能诱导 IL-17 的表达, 表明是 IL-23 诱导先天免疫细胞产生了 IL-17, 从而为 IL-17 的先天免疫细胞来源提供了证据^[44]。几乎所有产生 IL-17 的先天免疫细胞都表达 IL-23 受体 (IL-23R), 而且介导的免疫信号通

路也能够通过影响巨噬细胞和树突状细胞放大重症哮喘炎症反应^[43]。

3 转化生长因子- β (TGF- β)与重症哮喘的关系

TGF- β 由上皮细胞、嗜酸性粒细胞、巨噬细胞和成纤维细胞等产生,是一种能使正常成纤维细胞的表型发生转化的多功能细胞因子,在重症哮喘中参与上皮转化、上皮纤维化、气道平滑肌(ASM)重塑、微血管变化和粘液产生^[45]。

在不同细胞类型和其它细胞因子存在的条件下,TGF- β 表现出多向性和多效性。在单核细胞、淋巴细胞和上皮细胞中,TGF- β 能抑制细胞增殖和细胞因子分泌,而在成纤维细胞和气管平滑肌细胞中,TGF- β 可诱导细胞增殖和促纤维素及促炎症因子的释放^[46]。

在抑制免疫反应机制层面,TGF- β 通过抑制炎症细胞功能和促进调节性T淋巴细胞(regulatory cells, Treg)产生来抑制哮喘症状与免疫应答,同时抑制树突状细胞活化^[47]。其机制是将未成熟的CD25⁺T细胞转变为调节性CD25⁺细胞,并调节Treg细胞抑制功能,而体内阻断TGF- β 会使CD25⁺Foxp3⁺Treg细胞数量减少及功能不足^[48],促使Treg增殖、活化,该靶向的分子机制将可能为重症哮喘提供潜在的治疗靶点。

在促进免疫应答反应层面上,TGF- β 可引起重症哮喘患者气道炎症反应、高反应性和气道重构。TGF- β 家族中以TGF- β_1 活性最强,其以自分泌或旁分泌的形式通过细胞表面的信号转导途径来调节细胞的增殖、分化和凋亡,对细胞外基质蛋白的合成、创伤修复及免疫功能等有重要作用。在重症哮喘患者中,TGF- β_1 可通过Smad2或3途径和激活MAPK信号通路^[49],分别介导气道上皮细胞产生抗凋亡和促凋亡作用^[50]。同时,TGF- β_1 会随着表面上皮损伤加重而造成气道上皮细胞脱落和上皮-间质转化(epithelial-mesenchymal transition, EMT)^[51],最终引起重症哮喘患者气道高反应性加剧。TGF- β_1 也是重症哮喘气道重构的主要调控因子。使用原位杂交和免疫组化技术,已证实重症哮喘患者的支气管黏膜中TGF- β_1 水平较轻度哮喘患者显著升高,且TGF- β_1 表达水平与基底膜厚度和哮喘严重程度呈正相关^[52]。研究发现,用抗泛素化TGF- β 抗体阻断TGF- β 会阻止哮喘小鼠模型气道重塑的发展^[53]。

TGF- β_1 作为促纤维化的关键炎症因子,参与上皮纤维化形成,使气管平滑肌细胞和杯状细胞肥大增生,增加胶原和纤维连接蛋白(简称纤连蛋白)合成,并促进气道胶原沉积、基底膜增厚和结缔组织蛋白合成,从而导致管腔狭窄和不可逆肺功能改变^[54]。重症哮喘患者中TGF- β_1 水平含量明显升高,研究结果显示,重症哮喘儿童血清及BALF中TGF- β_1 水平明显高于轻度哮喘儿童,表明TGF- β_1 水平高低与哮喘疾病严重程度呈显著正相关,且重症哮喘儿童可能存在不同程度的气道重构^[55]。在治疗方面,奥马佐作为人源性的抗IgE单克隆抗体,可减少过敏性哮喘模型中TGF- β 产生,表明该药物可通过影响哮喘气道中TGF- β 的水平来抑制肺部器官组织纤维化,通过逆转肺器官组织纤维化以达到治愈哮喘的目的^[56]。

4 肿瘤坏死因子- α (TNF- α)与重症哮喘的关系

TNF- α 由活化得单核-巨噬细胞、T淋巴细胞和自然杀伤

细胞等合成和分泌,是重要的炎症反应诱导剂和免疫调节剂^[57],在重症哮喘气道慢性炎症机制中起关键作用^[58]。

TNF- α 是重症哮喘炎症过程中重要的启动因子。TNF- α 可诱导气道上皮细胞分泌细胞因子[如IL-5、IL-6、IL-8、粒细胞集落刺激因子(G-CSF)和粒细胞-巨噬细胞集落刺激因子(GM-CSF)]、趋化因子[如嗜酸性粒细胞趋化因子(Eotaxin)、单核细胞趋化蛋白-1(MCP-1)和调节活化正常T细胞表达与分泌的趋化因子CCL5(RANTES)]、粘附分子如E-选择素(E-selectin)、血管-细胞间粘附分子(VCAM-1)和细胞间粘附分子(ICAM-1),促使中性粒细胞和嗜酸性粒细胞的迁移,最终导致慢性炎症和不可逆性气道重构^[59]。此外,TNF- α 能通过增强钙信号通路使气道平滑肌细胞高度收缩,从而导致严重的气道高反应性^[60]。TNF- α 在重症哮喘患者中表达明显升高,参与重症哮喘发作。实验研究显示,吸入或者静脉注射TNF- α 可引起大鼠气道阻力增加和气道高反应性,并伴有支气管中嗜酸性粒细胞浸润,诱发重症哮喘^[61]。临床研究发现,与轻度哮喘患者相比,重症哮喘患者BALF中TNF- α 浓度以及支气管活检样本中TNF- α 蛋白和mRNA水平均明显升高^[62]。

在重症哮喘治疗方面,糖皮质激素并不能降低重症哮喘患者的TNF- α 水平,故直接针对TNF- α 异常的靶向治疗受到越来越多的关注。实验研究发现,将抗TNF- α 中和抗体应用于由屋尘螨过敏原诱发的小鼠哮喘模型,可减轻哮喘小鼠肺部炎症和引起病理改善^[63]。临床研究结果显示,与轻中度哮喘组相比,重症哮喘持续状态患者的外周血单核细胞上膜结合的TNF- α 、TNFR1及TNF- α 转化酶的表达明显增多,经过10周可溶性的TNF- α 受体结合蛋白依那西普(etanercept)治疗后,可以改善重症哮喘的症状、肺功能及气道高反应性^[64]。而后另一项临床研究观察到依那西普不能显著改善重症哮喘的症状、肺功能及气道高反应性^[65]。以上研究提示,抗TNF- α 治疗只能使小部分特殊表型的重症哮喘患者临床获益。而目前针对抗TNF- α 治疗其副作用较大,如发生严重感染、肿瘤,甚至个别死亡的报告,故对于重症哮喘患者的抗TNF- α 治疗,还有待进一步优化改进。

5 结语与展望

近年来,随着对重症哮喘中生物学和免疫细胞信号通路认识的不断提高,催生了众多生物制剂如抗IL-8、IL-17、TNF- α 和IgE单克隆抗体的研发,在医学界也已经引起了广泛关注。上述细胞因子在重症哮喘组、轻度哮喘组或健康对照组中的表达水平见表1。不同于抗炎药物和支气管舒张剂缓解症状,抗体靶标药物是针对那些致使哮喘发作加重的免疫信号通路进行治疗,直接通过攻击重症哮喘的致病根源以达到治疗作用,更具有特异性和针对性。其中重症哮喘发病机制及对应的生物制剂见图1。

然而,目前针对重症哮喘治疗的免疫靶向药物还处于早期临床试验阶段,且现阶段治疗药物在临床应用中还存在着种种不足和问题。随着对重症哮喘病理机制研究的深入了解,相信接下来将不断有新型生物制剂被研发上市,这不仅能加速推进精准医疗的发展,而且能达到治疗或辅助治疗哮喘疾病的目的,以逐步满足重症哮喘病患群体的医疗需求和提高重症哮喘患者的生活质量至为重要。

表 1 重症哮喘组、轻度哮喘组和健康对照组中细胞因子的表达水平

Table 1 The expression levels of cytokines in severe asthma group, mild asthma group and health control group (Mean± SEM)

Cytokine chemokine	Detection substance	HC	Mild asthma	Severe asthma	References
IL-8 (pg/mL)	sputum	14.6± 6.2	11.0± 5.9	59.6± 19.8	[66]
IL-8 (pg/mL)	ASM		2.5± 0.4	5.7± 0.7	[67]
IL-8 (pg/mL)	epithelium		2.2± 1.1	3.8± 1.3	[68]
	subepithelium		9.7± 4.8	17.9± 6.6	
IL-17 (pg/mL)	serum	7.58	74.09	103.89	[69]
TGF-β1 (pg/mL)	Bronchial biopsies	3.5± 0.8	7.8± 1.5	18.5± 3.1	[52]
TNF-α (pg/mL)	serum		8.9± 0.6	12.0± 1.2	[70]
TNF-α (fg/mL)	BALF	117 (median)	111 (median)	160 (median)	[62]

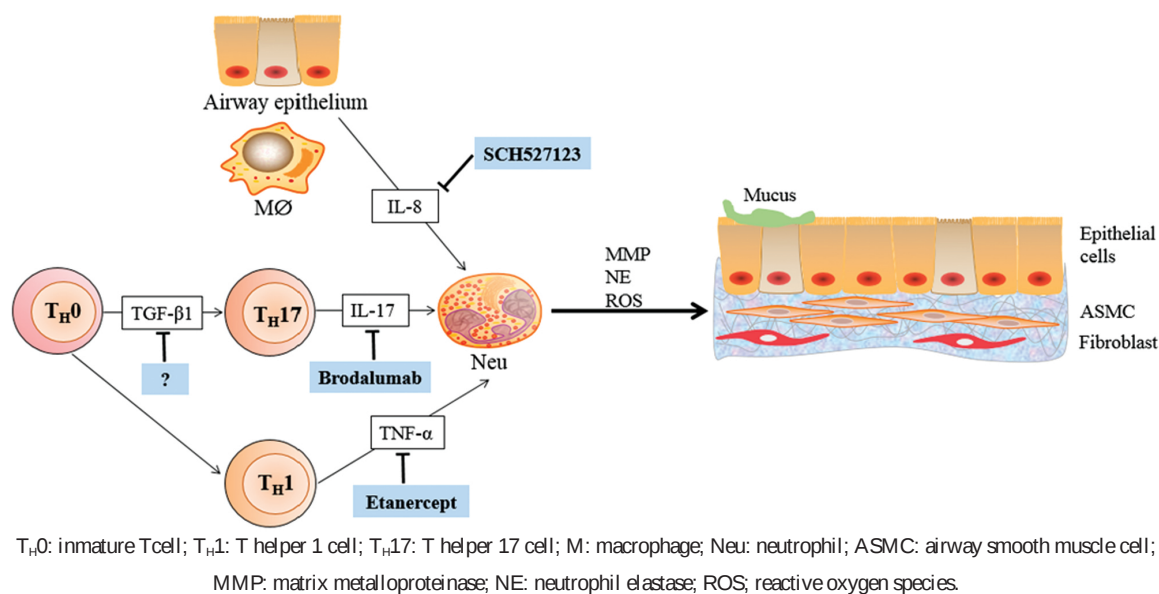


图 1 重症哮喘发病机制及抗体靶标药物治疗

Fig.1 Severe asthma pathogenesis and antibody target drug therapy

参考文献 (References)

- [1] Heaney LG, Djukanovic R, Woodcock A, et al. Research in progress: Medical Research Council United Kingdom Refractory Asthma Stratification Programme (RASP-UK)[J]. Thorax, 2016, 71(2): 187-189
- [2] Campo P, Rodriguez F, Sanchez-Garcia S, et al. Phenotypes and endotypes of uncontrolled severe asthma: new treatments[J]. J Invest Allergol Clin Immunol, 2013, 23(2): 76-88
- [3] Fajt ML, Wenzel SE. Development of New Therapies for Severe Asthma [J]. Allergy Asthma Immunol Res, 2017, 9(1): 3-14
- [4] Kerkhof M, Tran TN, Soriano JB, et al. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population[J]. Thorax, 2017, 0: 1-9
- [5] Hekking PP, Wener RR, Amelink M, et al. The prevalence of severe refractory asthma[J]. J Allergy Clin Immunol, 2015, 135(4): 896-902
- [6] Canonica GW, Senna G, Mitchell PD, et al. Therapeutic interventions in severe asthma[J]. World Allergy Organ J, 2016, 9(1): 40
- [7] Bourdin A, Molinari N, Vachier I, et al. Prognostic value of cluster analysis of severe asthma phenotypes [J]. J Allergy Clin Immunol, 2014, 134(5): 1043-1050
- [8] Chung KF, Godard P, Adelroth E, et al. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy-Resistant Asthma. European Respiratory Society [J]. Eur Respir J, 1999, 13 (5): 1198-1208
- [9] Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma[J]. Eur Respir J, 2014, 43(2): 343-373
- [10] Bousquet J, Mantzouranis E, Cruz AA, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma [J]. J Allergy Clin Immunol, 2010, 126(5): 926-938
- [11] Liu W, Liu S, Verma M, et al. Mechanism of TH2/TH17-predominant and neutrophilic TH2/TH17-low subtypes of asthma[J]. J Allergy Clin Immunol, 2017, 139(5): 1548-1558
- [12] Wener RR, Bel EH. Severe refractory asthma: an update [J]. Eur Respir Rev, 2013, 22(129): 227-235
- [13] Samitas K, Delimpoura V, Zervas E, et al. Anti-IgE treatment, airway inflammation and remodelling in severe allergic asthma: current knowledge and future perspectives[J]. Eur Respir Rev, 2015, 24(138): 1-10

- 594-601
- [14] Martinez FD, Vercelli D. Asthma [J]. *Lancet*, 2013, 382 (9901): 1360-1372
- [15] Nair P, Gaga M, Zervas E, et al. Safety and efficacy of a CXCR2 antagonist in patients with severe asthma and sputum neutrophils: a randomized, placebo-controlled clinical trial [J]. *Clin Exp Allergy*, 2012, 42(7): 1097-1103
- [16] Déjager L, Dendoncker K, Eggermont M, et al. Neutralizing TNF α restores glucocorticoid sensitivity in a mouse model of neutrophilic airway inflammation [J]. *Mucosal Immunol*, 2015, 8(6): 1212-1225
- [17] Idzko M, Hammad H, van Nimwegen M, et al. Extracellular ATP triggers and maintains asthmatic airway inflammation by activating dendritic cells [J]. *Nat Med*, 2007, 13(8): 913-919
- [18] Gao YD, Cao J, Li P, et al. Th2 cytokine-primed airway smooth muscle cells induce mast cell chemotaxis via secretion of ATP [J]. *J Asthma*, 2014, 51(10): 997-1003
- [19] Sevigny J, Martin-Satue M, Pintor J. Purinergic Signalling in Immune System Regulation in Health and Disease [J]. *Mediators Inflamm*, 2015, 2015: 106863
- [20] Wright A, Mahaut-Smith M, Symon F, et al. Impaired P2X1 Receptor-Mediated Adhesion in Eosinophils from Asthmatic Patients [J]. *J Immunol*, 2016, 196(12): 4877-4884
- [21] Hosoki K, Ying S, Corrigan C, et al. Analysis of a Panel of 48 Cytokines in BAL Fluids Specifically Identifies IL-8 Levels as the Only Cytokine that Distinguishes Controlled Asthma from Uncontrolled Asthma, and Correlates Inversely with FEV1 [J]. *PLoS One*, 2015, 10 (5): e0126035
- [22] Tang FS, Van Ly D, Spann K, et al. Differential neutrophil activation in viral infections: Enhanced TLR-7/8-mediated CXCL8 release in asthma [J]. *Respirology*, 2016, 21(1): 172-179
- [23] Hamilton LM, Torres-Lozano C, Puddicombe SM, et al. The role of the epidermal growth factor receptor in sustaining neutrophil inflammation in severe asthma [J]. *Clin Exp Allergy*, 2003, 33(2): 233-240
- [24] Todd CM, Salter BM, Murphy DM, et al. The effects of a CXCR1/CXCR2 antagonist on neutrophil migration in mild atopic asthmatic subjects [J]. *Pulm Pharmacol Ther*, 2016, 41: 34-39
- [25] Fukakusa M, Bergeron C, Tulic MK, et al. Oral corticosteroids decrease eosinophil and CC chemokine expression but increase neutrophil, IL-8, and IFN- γ -inducible protein 10 expression in asthmatic airway mucosa [J]. *J Allergy Clin Immunol*, 2005, 115 (2): 280-286
- [26] Nakagome K, Matsushita S, Nagata M. Neutrophilic inflammation in severe asthma [J]. *Int Arch Allergy Immunol*, 2012, 158 (Suppl 1): 96-102
- [27] Turkeli A, Yilmaz O, Taneli F, et al. IL-5, IL-8 and MMP-9 levels in exhaled breath condensate of atopic and nonatopic asthmatic children [J]. *Respir Med*, 2015, 109(6): 680-688
- [28] Koga H, Miyahara N, Fuchimoto Y, et al. Inhibition of neutrophil elastase attenuates airway hyperresponsiveness and inflammation in a mouse model of secondary allergen challenge: neutrophil elastase inhibition attenuates allergic airway responses [J]. *Respir Res*, 2013, 14 (1): 8
- [29] Chesné J, Braza F, Mahay G, et al. IL-17 in severe asthma. Where do we stand? [J]. *Am J Respir Crit Care Med*, 2014, 190(10): 1094-1101
- [30] Beringer A, Noack M, Miossec P. IL-17 in Chronic Inflammation: From Discovery to Targeting [J]. *Trends Mol Med*, 2016, 22 (3): 230-241
- [31] Carlos RV, Cristina CE, Leopoldo GB, et al. IL-17-producing peripheral blood CD177+neutrophils increase in allergic asthmatic subjects [J]. *Allergy Asthma Clin Immunol*, 2013, 9(1): 23
- [32] Alramli W, Préfontaine D, Chouiali F, et al. T (H)17-associated cytokines (IL-17A and IL-17F) in severe asthma [J]. *J Allergy Clin Immunol*, 2009, 123(5): 1185-1187
- [33] Nguyen PM, Putoczki TL, Ernst M. STAT3-Activating Cytokines: A Therapeutic Opportunity for Inflammatory Bowel Disease? [J]. *J Interferon Cytokine Res*, 2015, 35(5): 340-350
- [34] Kim HY, Lee HJ, Chang YJ, et al. Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity [J]. *Nat Med*, 2014, 20(1): 54-61
- [35] Irvin C, Zafar I, Good J, et al. Increased frequency of dual-positive TH2/TH17 cells in bronchoalveolar lavage fluid characterizes a population of patients with severe asthma [J]. *J Allergy Clin Immunol*, 2014, 134(5): 1175-1186
- [36] Alyasin S, Karimi MH, Amin R, et al. Interleukin-17 gene expression and serum levels in children with severe asthma [J]. *Iran J Immunol*, 2013, 10(3): 177-185
- [37] Kudo M, Melton AC, Chen C, et al. IL-17A produced by α beta T cells drives airway hyper-responsiveness in mice and enhances mouse and human airway smooth muscle contraction [J]. *Nat Med*, 2012, 18 (4): 547-554
- [38] Ji X, Li J, Xu L, et al. IL4 and IL-17A provide a Th2/Th17-polarized inflammatory milieu in favor of TGF- β 1 to induce bronchial epithelial-mesenchymal transition (EMT) [J]. *Int J Clin Exp Pathol*, 2013, 6(8): 1481-1492
- [39] Targan SR, Feagan BG, Vermeire S, et al. A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of AMG 827 in Subjects With Moderate to Severe Crohn's Disease [J]. *Gastroenterology*, 2012, 143(3): e26
- [40] Lebwohl M, Strober B, Menter A, et al. Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis [J]. *N Engl J Med*, 2015, 373(14): 1318-1328
- [41] Busse WW, Holgate S, Kerwin E, et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma [J]. *Am J Respir Crit Care Med*, 2013, 188(11): 1294-1302
- [42] Cua DJ, Tato CM. Innate IL-17-producing cells: the sentinels of the immune system [J]. *Nat Rev Immunol*, 2010, 10(7): 479-489
- [43] Halwani R, Sultana A, Vazquez-Tello A, et al. Th-17 regulatory cytokines IL-21, IL-23, and IL-6 enhance neutrophil production of IL-17 cytokines during asthma [J]. *J Asthma*, 2017, 54(9): 893-904
- [44] Chognard G, Bellemare L, Pelletier AN, et al. The dichotomous pattern of IL-12 α and IL-23R expression elucidates the role of IL-12 and IL-23 in inflammation [J]. *PLoS One*, 2014, 9(2): e89092
- [45] Alalawi M, Hassan T, Chotirmall SH. Transforming growth factor β and severe asthma: A perfect storm [J]. *Respir Med*, 2014, 108(10): 1409-1423

- [46] Sanjabi S, Oh SA, Li MO. Regulation of the Immune Response by TGF- β : From Conception to Autoimmunity and Infection[J]. Cold Spring Harb Perspect Biol, 2017, 9(6): 1-34
- [47] Wan YY, Flavell RA. Regulatory T cells, transforming growth factor- β , and immune suppression [J]. Proc Am Thorac Soc, 2007, 4(3): 271-276
- [48] Conte E, Gili E, Fruciano M, et al. Human lung fibroblasts increase CD4(+)CD25(+)Foxp3(+) T cells in co-cultured CD4(+) lymphocytes [J]. Cell Immunol, 2013, 285(1-2): 55-61
- [49] Al-Alawi M, Hassan T, Chotirmall SH. Transforming growth factor beta and severe asthma: a perfect storm [J]. Respir Med, 2014, 108(10): 1409-1423
- [50] Stumm CL, Halcsik E, Landgraf RG, et al. Lung remodeling in a mouse model of asthma involves a balance between TGF- β 1 and BMP-7[J]. PLoS One, 2014, 9(4): e95959
- [51] Johnson JR, Nishioka M, Chakir J, et al. IL-22 contributes to TGF- β 1-mediated epithelial-mesenchymal transition in asthmatic bronchial epithelial cells[J]. Respir Res, 2013, 14(1): 1-12
- [52] Minshall EM, Leung DY, Martin RJ, et al. Eosinophil-associated TGF- β 1 mRNA expression and airways fibrosis in bronchial asthma [J]. Am J Respir Cell Mol Biol, 1997, 17(3): 326-333
- [53] McMillan SJ, Xanthou G, Lloyd CM. Manipulation of allergen-induced airway remodeling by treatment with anti-TGF- β antibody: effect on the Smad signaling pathway [J]. J Immunol, 2005, 174(9): 5774-5780
- [54] Itoigawa Y, Harada N, Harada S, et al. TWEAK enhances TGF- β 1-induced epithelial-mesenchymal transition in human bronchial epithelial cells[J]. Respir Res, 2015, 16(1): 1-15
- [55] Chakir J, Shannon J, Molet S, et al. Airway remodeling-associated mediators in moderate to severe asthma: effect of steroids on TGF- β , IL-11, IL-17, and type I and type III collagen expression[J]. J Allergy Clin Immunol, 2003, 111(6): 1293-1298
- [56] Huang YC, Leyko B, Frieri M. Effects of omalizumab and budesonide on markers of inflammation in human bronchial epithelial cells [J]. Ann Allergy Asthma Immunol, 2005, 95(5): 443-451
- [57] Brown SD, Brown LA, Stephenson S, et al. Characterization of a high TNF- α phenotype in children with moderate-to-severe asthma[J]. J Allergy Clin Immunol, 2015, 135(6): 1651-1654
- [58] Camille T, Claire P, Sylvain M-A, et al. Monoclonal Anti-TNF- α Antibodies for Severe Steroid-Dependent Asthma: A Case Series[J]. Open Respir Med J, 2013, 7(1): 21-25
- [59] Blume C, Reale R, Held M, et al. Cellular crosstalk between airway epithelial and endothelial cells regulates barrier functions during exposure to double-stranded RNA [J]. Immunity, inflammation and disease, 2017, 5(1): 45-56
- [60] Brown SD, Lou AB, Stephenson S, et al. Characterization of a "high" TNF- α phenotype in moderate-to-severe asthmatic children [J]. J Allergy Clin Immunol, 2015, 135(6): 1651-1654
- [61] Kips JC, Tavernier J, Pauwels RA. Tumor necrosis factor causes bronchial hyperresponsiveness in rats [J]. Am Rev Respir Dis, 1992, 145(2 Pt 1): 332-336
- [62] Howarth PH, Babu KS, Arshad HS, et al. Tumour necrosis factor (TNF α) as a novel therapeutic target in symptomatic corticosteroid dependent asthma[J]. Thorax, 2005, 60(12): 1012-1018
- [63] Kim J, McKinley L, Natarajan S, et al. Anti-tumor necrosis factor- α antibody treatment reduces pulmonary inflammation and methacholine hyper-responsiveness in a murine asthma model induced by house dust[J]. Clin Exp Allergy, 2006, 36(1): 122-132
- [64] Berry MA, Hargadon B, Shelley M, et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma[J]. N Engl J Med, 2006, 354(7): 697-708
- [65] Holgate ST, Noonan M, Chaney P, et al. Efficacy and safety of etanercept in moderate-to-severe asthma: a randomised, controlled trial[J]. Eur Respir J, 2011, 37(6): 1352-1359
- [66] Kikuchi S, Kikuchi I, Takaku Y, et al. Neutrophilic inflammation and CXC chemokines in patients with refractory asthma [J]. Int Arch Allergy Immunol, 2009, 149(Suppl 1): 87-93
- [67] Pepe C, Foley S, Shannon J, et al. Differences in airway remodeling between subjects with severe and moderate asthma [J]. J Allergy Clin Immunol, 2005, 116(3): 544-549
- [68] Shannon J, Ernst P, Yamauchi Y, et al. Differences in airway cytokine profile in severe asthma compared to moderate asthma[J]. Chest, 2008, 133(2): 420-426
- [69] Hasegawa T, Uga H, Mori A, et al. Increased serum IL-17A and Th2 cytokine levels in patients with severe uncontrolled asthma [J]. Eur Cytokine Netw, 2017, 28(1): 8-18
- [70] Agache I, Ciobanu C, Agache C, et al. Increased serum IL-17 is an independent risk factor for severe asthma[J]. Respir Med, 2010, 104(8): 1131-1137
- (上接第 1981 页)
- [20] 张奥博,刘良发,路承,等.cN0 期甲状腺乳头状癌颈部中央区淋巴结转移的危险因素分析[J].临床耳鼻咽喉头颈外科杂志, 2017, 31(15): 1141-1145
Zhang Ao-bo, Liu Liang-fa, Lu Cheng, et al. Risk factors of central neck lymph node metastasis in cN0 papillary thyroid carcinoma[J]. Clin Otorhinolaryngol Head Neck Surg (China), 2017, 31(15): 1141-1145
- [21] Ito Y, Miyauchi A, Inoue H, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients [J]. World J Surg, 2010, 34(1): 28-35