

· 综述 ·

趋化因子配体13在常见感染性病原体感染中的表达及意义

陈芝慧¹, 谭英征², 龙云铸² (1. 吉首大学医学院, 湖南 吉首 416000; 2. 中南大学湘雅医学院附属株洲医院感染内科, 湖南 株洲 412000)

【摘要】趋化因子配体13 (C-X-C motif chemokine ligand 13, CXCL13) 又称B细胞吸引趋化因子1或B淋巴细胞趋化因子, 通过与B细胞、辅助T细胞上的G蛋白偶联趋化因子受体结合, 诱导其向生发中心运输, 促进B细胞成熟和抗体应答, 从而实现对病毒清除以及炎症的快速控制。然而, 目前相关研究表明CXCL13水平过高可能导致免疫反应受损, 促进疾病进展。CXCL13水平变化可作为反映疾病进展、抗病毒疗效有效指标, 并且对疫苗研发有所帮助。因此, 本文主要对CXCL13在常见感染性病原体感染如人类免疫缺陷病毒感染、乙型肝炎病毒感染、结核分枝杆菌感染以及SARS-CoV-2感染中的表达及其意义进行综述。

【关键词】趋化因子配体13; 人类免疫缺陷病毒; 乙型肝炎病毒; 结核分枝杆菌

DOI: 10.19871/j.cnki.xfcrbzz.2023.05.015

【中图分类号】R51; R446.1

Expression and significance of C-X-C motif chemokine ligand 13 in common infectious pathogens infection

Chen Zhihui¹, Tan Yingzheng², Long Yunzhu² (1. Jishou University school of Medicine, Hunan Jishou 416000, China; 2. Department of Infectious Diseases, Zhuzhou Hospital Affiliated to Xiangya School of Medicine, Central South University, Hunan Zhuzhou 412000, China)

【Abstract】 C-X-C motif chemokine ligand 13 (CXCL13) can promote B cell maturation and antibody response by binding to G protein-coupled chemokine receptor (CXCR5) that locating on B cells and Tfh cells. Consequently, the inhibition of virus replication, even the elimination of virus, can be realized, which conclusively facilitating to the rapid control of inflammation. However, it should be noted that excessive increase of CXCL13 may lead to impaired immune response and further deterioration of infection. In view of these important effects, the change of CXCL13 concentration is likely to become an effective index for evaluation of disease progression and antiviral efficacy, and will be helpful for future vaccine development. In summary, the paper mainly reviews the expression and significance of CXCL13 in common infectious pathogens such as human immunodeficiency virus, hepatitis B virus infection, tuberculosis and SARS-CoV-2.

【Key words】 C-X-C motif chemokine ligand 13; Human immunodeficiency virus; Hepatitis B virus; Mycobacterium tuberculosis

趋化因子配体13 (C-X-C motif chemokine ligand 13, CXCL13), 又称B细胞吸引趋化因子1或B淋巴细胞趋化因子, 是G蛋白偶联趋化因子受体 (G protein-coupled chemokine receptor five, CXCR5) 的配体, 由位于4号染色体 (4q21) 的CXCL13基因编码^[1-3]。CXCL13主要存在于肝脏、脾脏、淋巴结、阑尾和胃中, 由滤泡树突状细胞 (dendritic cell, DC) 和滤泡辅助T细胞 (follicular helper T cells, Tfh) 分泌^[4-5]。同时, 巨噬细胞等髓系细

胞也被报道在激活时可分泌CXCL13^[6]。CXCL13的受体CXCR5在B细胞、Tfh和DC上表达^[4, 7]。CXCL13与B细胞、Tfh细胞上的CXCR5结合, 诱导其向生发中心 (germinal center, GC) 运输, 从而导致B细胞向浆细胞和记忆B细胞的分化, 在自身免疫性疾病和炎症反应中发挥重要作用^[4, 8-9]。在感染性病原体感染过程中, 血清CXCL13水平可能显著升高^[1], 通过GC反应可产生高亲和力抗体, 有利于炎症控制。本文主要对CXCL13在常见感染性疾病, 如HIV感染、乙型肝炎

基金项目: 湖南省新发传染病临床医学技术示范基地建设项目基金 (2021SK4038)

通信作者: 龙云铸, Email: 2863454482@qq.com

引用格式: 陈芝慧, 谭英征, 龙云铸. 趋化因子配体13在常见感染性病原体感染中的表达及意义[J/CD]. 新发传染病电子杂志, 2023, 8 (5): 80-84. Chen Zhihui, Tan Yingzheng, Long Yunzhu. Expression and significance of C-X-C motif chemokine ligand 13 in common infectious pathogens infection[J/CD]. Electronic Journal of Emerging Infectious Diseases, 2023, 8(5): 80-84.

病毒 (hepatitis B virus, HBV) 感染、结核分枝杆菌 (mycobacterium tuberculosis, MTB) 感染以及 SARS-CoV-2 感染中的表达及其意义进行综述。

1 趋化因子配体13水平与人类免疫缺陷病毒

艾滋病主要是HIV感染引起的机体免疫功能缺陷疾病^[10]。HIV感染的主要标志是人体CD4⁺T淋巴细胞的逐渐丧失和CD4⁺T淋巴细胞稳态失衡, 导致免疫功能的逐渐损害^[11]。Tfh是CD4⁺T淋巴细胞的一个特殊亚群, 可以促进B细胞成熟并分化为浆细胞、记忆B细胞, 在分泌抗体方面起重要作用^[12-14]。HIV感染期间, CXCL13主要由GC中表达CXCR5的Tfh (CXCR5⁺Tfh) 和B细胞滤泡中的DC分泌^[4-5, 8]。Cagigi等^[15]研究发现HIV-1感染者GC中CXCL13 mRNA水平较高, 而B细胞中CXCR5分子mRNA表达没有降低, 但B细胞表达CXCR5水平下降。随着HIV感染疾病进展, 患者血浆CXCL13水平逐渐升高, CXCR5水平下降, 可能会导致CXCR5受体内化和内吞, 从而可能会使CXCR5⁺B细胞的数量减少^[16]。而CXCR5⁺B细胞的数量减少能促进GC内CXCR5⁺Tfh的扩增, 扩增的CXCR5⁺Tfh可以产生更多CXCL13, 引起B细胞分化受干扰, 导致B细胞功能障碍^[12, 17-18]。同时CXCL13水平过高可能会使GC过早和不恰当地释放激活的B细胞, B细胞过度激活最终形成艾滋病淋巴瘤^[15-16]。Mehraj等^[19]研究发现随着HIV感染疾病进展, CXCL13水平逐渐的升高与CD4⁺T淋巴细胞计数和CD4⁺/CD8⁺比值呈负相关。由此可见, CXCL13在HIV感染疾病进展中发挥了一定作用。血浆过高的GC反应是由抗原特异性B细胞通过其受体进行亲和成熟的体细胞超突变 (somatic hypermutation, SHM) 的过程, SHM是HIV感染产生广泛中和抗体 (broadly neutralizing antibody, BnAbs) 的必要条件^[20-21], 同时其产生与HIV载量、多样性等有关^[22-23]。HIV感染者的纵向队列研究发现血浆CXCL13水平升高与抗HIV的BnAbs的产生相关, 能够产生HIV BnAbs的个体可能具有更好的GC反应^[8, 24]。因此, 检测血浆CXCL13在人体疫苗试验研究中是指示GC活性潜在的观察指标。抗反转录病毒疗法 (antiretroviral treatment, ART) 能有效地抑制了HIV-1的复制, ART期间, 升高的血浆CXCL13也逐渐下降, 但ART治疗中断后, HIV-1迅速反弹, 表明CXCL13可作为ART有效性的评价指标^[25]。最近研究发现, HIV-1感染过程中CXCR5⁺NK细胞不断积累, CXCR5⁺NK细胞数量与CXCL13的表达强度呈正相关, 而与HIV-1 DNA/RNA水平呈负相关^[26], 说明该亚群可能对HIV-1具有抑制作用。总之, 在HIV感染疾病进展中, CXCL13水平逐渐

升高一方面导致免疫功能逐渐损害, 另一方面与抗HIV BnAbs产生相关, 表明血浆CXCL13未来可以作为HIV感染疾病进展、抗病毒疗效有效评估指标, 并有助于疫苗的研发。近期对CXCR5⁺NK细胞研究发现, 血浆CXCL13水平越高, CXCR5⁺细胞亚群比例越高^[26]。对CXCR5⁺亚群的研究将会成为热点, CXCR5⁺NK细胞可能是HIV-1感染免疫控制的关键治疗靶点, 将会是HIV感染免疫治疗方面的一个重大突破。

2 趋化因子配体13与乙型肝炎病毒

慢性HBV感染者自发消除HBV的概率小于1%。开发新的抗病毒策略以实现HBV感染功能性治愈 (血清HBsAg和HBV DNA持续检测不到, HBeAg阴转, 伴或不伴HBsAg血清学转换) 至关重要^[27-29]。Publicover等^[30]报道, 在HBV感染小鼠模型中, HBV清除主要归因于肝巨噬细胞CXCL13的表达。CXCL13在肝巨噬细胞中以年龄依赖性的方式表达, 通过与B细胞和Tfh细胞膜上CXCR5受体结合, 促进B细胞和Tfh细胞共同迁移到肝组织的B细胞滤泡和生发中心内, 产生高亲和力的记忆B细胞和浆细胞^[31-32], 分泌HBV特异性抗体, 从而发挥抗病毒作用。在急性、慢性HBV感染期间, 免疫介导肝细胞破坏并伴有T细胞和B细胞聚集的炎症反应可使血清ALT水平升高^[33]。Widney等^[16]观察到HBV感染者血浆CXCL13与炎症标志物和CD4⁺T淋巴细胞计数呈正相关。病例对照研究显示, 急性HBV感染期患者血浆CXCL13升高水平与ALT峰值以及HBV DNA水平呈正相关^[34]。Li等^[35]通过转录组测序技术发现肝内CXCL13的mRNA表达水平与血浆CXCL13的表达水平相一致; 同时肝内CXCL13的mRNA表达与血清中的ALT水平呈正相关。用酶联免疫吸附试验检测不同免疫阶段的慢性HBV感染者CXCL13浓度, 在免疫激活阶段患者血清CXCL13明显升高^[32], 升高的CXCL13促进慢性HBV感染者肝内CXCR5⁺淋巴细胞 (CXCR5⁺CD4⁺T细胞) 归巢和异常B细胞免疫应答^[36], CXCR5⁺CD4⁺T细胞通过分泌白介素-21协助B细胞分泌HBV相关抗体并与HBsAg血清转阴相关^[32, 37]。一项研究发现^[35], 慢性HBV感染者高水平CXCL13促进了肝内CXCR5⁺CD8⁺T淋巴细胞的募集到肝脏, 可以产生高水平的HBV特异性干扰素- γ 、IL-21。IL-21水平升高有助于提高CD8⁺T淋巴细胞抗病毒作用, 并且可以促使乙肝表面抗体 (抗-HBs) 产生。Wan等^[38]研究发现, 慢性HBV感染母亲体内CXCL13中的rs355687位点被发现与降低HBV宫内传播风险相关, 该序列可能通过上调CXCL13基因表达, 发挥抗病毒作用阻断HBV从母体向新生儿的传播。接受替比夫定治疗55例HBeAg阳性的患者, 治疗52周后, 实现病毒抑

制且HBeAg发生血清学转化患者的血清CXCL13水平更高^[32]。一项通过核苷(酸)类似物治疗慢性乙型肝炎停药后在96周随访期内,复发患者血浆CXCL13的水平显著低于未复发患者^[35]。相对于HIV感染者,HBV感染者肝内CXCL13表达水平升高介导免疫反应,产生HBV特异性抗体发挥抗病毒作用;并且在接受抗病毒治疗停药后患者中,未复发患者血浆CXCL13水平较高。因此,CXCL13水平不仅可用于跟踪抗病毒治疗的疗效反应和预后,还可能为今后抗HBV感染靶点治疗提供依据,有助于HBV感染的功能性治愈。同时慢性HBV感染母亲携带CXCL13 rs355687位点的CT基因型,CXCL13表达水平升高,阻断HBV传向新生儿,说明CXCL13分子在HBV宫内感染中的功能意义可能为开发新的预防和治疗提供依据。

3 趋化因子配体13与结核病

结核病是由MTB感染引起的,目前结核病的诊断及治疗存在很多困难,同时耐药肺结核成为治疗的一大难题^[39-40]。近年来,研究发现CXCL13可作为特发性肺纤维化的预后进展标志物^[41],但其在肺结核的诊断及预后的预测等方面的作用有待深入研究。先天淋巴样细胞(innate lymphoid cells, ILCs)是一组异质性的免疫细胞,免疫应答功能与T细胞相似,主要存在于胃肠道和呼吸道黏膜屏障部位^[42-44]。第3组先天淋巴样细胞(group 3 innate lymphoid cells, ILC3s)是ILCs中的1个亚型,主要分泌IL-17、IL-22等细胞因子,发挥阻断细菌感染作用^[45-46]。Ardain等^[47]研究发现,ILC3s在早期肺结核中起保护作用。MTB感染小鼠肺部,CXCL13水平上调,通过受体CXCR5招募ILC3到肺部病灶,分泌IL-17和IL-22促进淋巴滤泡的肉芽肿形成,从而增强早期抗结核作用^[48-49]。IL-17/IL-22双敲除小鼠的肺中ILC3和CXCR5数量减少以及CXCL13 mRNA表达减少,导致小鼠早期肺MTB负荷增加^[47]。Jiang等^[50]研究发现结核性胸膜炎患者胸腔积液的程序性死亡受体1(programmed death 1, PD-1)阳性(PD-1⁺)和PD-1黏膜相关恒定T细胞中,CXCL13是差异表达最显著的基因,在MTB感染的发生中发挥作用。总之,CXCL13及受体CXCR5在控制MTB感染中发挥一定作用。CXCL13可能成为未来研究结核病免疫反应、诊断、治疗反应的潜在观察指标以及研究抗结核药物治疗靶点提供依据。

4 趋化因子配体13与新型冠状病毒感染

COVID-19是由SARS-CoV-2感染引起^[51-52]。大多数感染者无症状或症状轻微,但仍有15%~30%的感染者发展为重型肺炎^[53]。一些假设认为COVID-19的严重

程度是由过度的炎症/免疫反应引起^[54-56],而炎症/免疫反应的本质是细胞因子和趋化因子过度释放^[57]。CXCL13作为趋化B细胞到生化中心发挥重要作用的细胞因子,其水平在SARS-CoV-2感染者中增加^[54,58]。Horspool等^[58]研究发现SARS-CoV-2感染死亡患者血清CXCL13水平显著增高。另一项研究发现,CXCL13在区分COVID-19患者收住重症监护室的敏感度和特异度分别为88.6%和79.6%^[59]。COVID-19患者血浆CXCL13水平升高,可能反映其自身免疫应答作用,然而CXCL13显著升高可能会加剧炎症反应和促进肺纤维化^[59]。由此可见,CXCL13将可能作为评估COVID-19患者严重程度的标志物以及收住重症监护室的预测指标。

5 总结

CXCL13作为B细胞的关键调节因子之一,在不同的常见感染性病原体感染中,起到作用也不同。CXCL13与B细胞、Tfh上的G蛋白偶联趋化因子受体CXCR5结合,促进B细胞成熟和抗体应答,从而实现对病毒复制和病毒清除的快速控制。在HBV感染患者体内,CXCL13则通过向慢性HBV感染患者肝脏募集CXCR5⁺CD4⁺T淋巴细胞及CXCR5⁺CD8⁺T淋巴细胞,实现对病毒控制作用。然而CXCL13的过表达在许多疾病中会引起免疫失衡,在HIV感染、SARS-CoV-2感染中,CXCL13水平过高,引起免疫功能损害。在某些自身免疫性疾病中,CXCL13水平可作为疾病诊断、病情进展、治疗反应及预后评估的标志物^[60-62]。Duan等^[9]通过检测HBV相关肝细胞癌患者血清CXCL13浓度发现,CXCL13水平升高($P=0.016$),且与无复发生存率相关。这些已发表的研究表明血清以及血浆CXCL13的测定在常见感染性病原体感染中起重大作用,可将CXCL13作为一种额外的、潜在的治疗反应及预后指示指标,并且CXCL13趋化作用可能成为未来治愈这些疾病的潜在免疫治疗靶点。未来需要更多的研究来确定趋化因子CXCL13及其受体在临床疾病中的应用,为临床治疗研究注入新的能量。

参考文献

- [1] KAZANIETZ MG, DURANDO M, COOKE M. CXCL13 and Its Receptor CXCR5 in Cancer: Inflammation, Immune Response, and Beyond[J]. Front Endocrinol, 2019, 10: 471.
- [2] SHI K, HAYASHIDA K, KANEKO M, et al. Lymphoid chemokine B cell-attracting chemokine-1 (CXCL13) is expressed in germinal center of ectopic lymphoid follicles within the synovium of chronic arthritis patients[J]. J Immunol, 2001, 166(1): 650-655.
- [3] DAVID BA, KUBES P. Exploring the complex role of chemokines and chemoattractants in vivo on leukocyte

- dynamics [J]. *Immunol Rev*, 2019, 289(1): 9-30.
- [4] BEKELE FY, CHIODI F, SUI Y, et al. The Role of CXCL13 in Antibody Responses to HIV-1 Infection and Vaccination[J]. *Front Immunol*, 2021, 12: 638872.
 - [5] WANG B, WANG M, AO D, et al. CXCL13-CXCR5 axis: Regulation in inflammatory diseases and cancer[J]. *Biochim Biophys Acta Rev Cancer*, 2022, 1877(5): 188799.
 - [6] CARLSEN HS, BAEKKEVOLD ES, MORTON HC, et al. Monocyte-like and mature macrophages produce CXCL13 (B cell-attracting chemokine 1) in inflammatory lesions with lymphoid neogenesis[J]. *Blood*, 2004, 104(10): 3021-3027.
 - [7] SCHAEERLI P, LOETSCHER P, MOSER B. Cutting edge: induction of follicular homing precedes effector Th cell development[J]. *J Immunol*, 2001, 167(11): 6082-6086.
 - [8] HAVENAR-DAUGHTON C, LINDQVIST M, HEIT A, et al. CXCL13 is a plasma biomarker of germinal center activity [J]. *Proc Natl Acad Sci U S A*, 2016, 113(10): 2702-2707.
 - [9] DUAN Z, GAO J, ZHANG L, et al. Phenotype and function of CXCR5+CD45RA-CD4⁺T cells were altered in HBV-related hepatocellular carcinoma and elevated serum CXCL13 predicted better prognosis[J]. *Oncotarget*, 2015, 6(42): 44239-44253.
 - [10] LEE JH, CROTTY S. HIV vaccinology: 2021 update[J]. *Semin Immunol*, 2021, 51: 101470.
 - [11] VIDYA VIJAYAN KK, KARTHIGEYAN KP, TRIPATHI SP, et al. Pathophysiology of CD4⁺T-Cell Depletion in HIV-1 and HIV-2 Infections[J]. *Front Immunol*, 2017, 8: 580.
 - [12] CROTTY S. T Follicular Helper Cell Biology: A Decade of Discovery and Diseases[J]. *Immunity*, 2019, 50(5): 1132-1148.
 - [13] KAW S, ANANTH S, TSOPOLIDIS N, et al. HIV-1 infection of CD4 T cells impairs antigen-specific B cell function[J]. *EMBO J*, 2020, 39(24): e105594.
 - [14] OLATUNDE AC, HALE JS, LAMB TJ. Cytokine-skewed Tfh cells: functional consequences for B cell help[J]. *Trends Immunol*, 2021, 42(6): 536-550.
 - [15] CAGIGI A, MOWAFI F, PHUONG DANG LV, et al. Altered expression of the receptor-ligand pair CXCR5/CXCL13 in B cells during chronic HIV-1 infection[J]. *Blood*, 2008, 112(12): 4401-4410.
 - [16] WIDNEY DP, BREEN EC, BOSCARDIN WJ, et al. Serum levels of the homeostatic B cell chemokine, CXCL13, are elevated during HIV infection[J]. *J Interferon Cytokine Res*, 2005, 25(11): 702-706.
 - [17] BARONE F, BOMBARDIERI M, ROSADO MM, et al. CXCL13, CCL21, and CXCL12 expression in salivary glands of patients with Sjogren's syndrome and MALT lymphoma: association with reactive and malignant areas of lymphoid organization [J]. *J Immunol*, 2008, 180(7): 5130-5140.
 - [18] LINDQVIST M, VAN LUNZEN J, SOGHIOIAN DZ, et al. Expansion of HIV-specific T follicular helper cells in chronic HIV infection [J]. *J Clin Invest*, 2012, 122(9): 3271-3280.
 - [19] MEHRAJ V, RAMENDRA R, ISNARD S, et al. CXCL13 as a Biomarker of Immune Activation During Early and Chronic HIV Infection[J]. *Front Immunol*, 2019, 10: 289.
 - [20] SOK D, LASERSON U, LASERSON J, et al. The effects of somatic hypermutation on neutralization and binding in the PGT121 family of broadly neutralizing HIV antibodies [J]. *PLoS Pathog*, 2013, 9(11): e1003754.
 - [21] KLEIN F, DISKIN R, SCHEID JF, et al. Somatic mutations of the immunoglobulin framework are generally required for broad and potent HIV-1 neutralization [J]. *Cell*, 2013, 153(1): 126-138.
 - [22] COHEN K, ALTFELD M, ALTER G, et al. Early preservation of CXCR5+ PD-1+ helper T cells and B cell activation predict the breadth of neutralizing antibody responses in chronic HIV-1 infection[J]. *J Virol*, 2014, 88(22): 13310-13321.
 - [23] ABELA IA, KADELKA C, TRKOLA A. Correlates of broadly neutralizing antibody development[J]. *Curr Opin HIV AIDS*, 2019, 14(4): 279-285.
 - [24] BURTON DR, AHMED R, BAROUCH DH, et al. A Blueprint for HIV Vaccine Discovery[J]. *Cell Host Microbe*, 2012, 12(4): 396-407.
 - [25] MABUKA JM, DUGAST AS, MUEMA DM, et al. Plasma CXCL13 but Not B Cell Frequencies in Acute HIV Infection Predicts Emergence of Cross-Neutralizing Antibodies[J]. *Front Immunol*, 2017, 8: 1104.
 - [26] GUO AL, JIAO YM, ZHAO QW, et al. Implications of the accumulation of CXCR5(+) NK cells in lymph nodes of HIV-1 infected patients [J]. *EBio Medicine*, 2022, 75: 103794.
 - [27] ZEISEL MB, LUCIFORA J, MASON WS, et al. Towards an HBV cure: state-of-the-art and unresolved questions-report of the ANRS workshop on HBV cure[J]. *Gut*, 2015, 64(8): 1314-1326.
 - [28] DURANTE D, ZOULIM F. New antiviral targets for innovative treatment concepts for hepatitis B virus and hepatitis delta virus[J]. *J Hepatol*, 2016, 64(1): 117-131.
 - [29] 中华医学会感染病学分会, 中华医学会肝病学会. 慢性乙型肝炎临床治愈(功能性治愈)专家共识[J]. *临床肝胆病杂志*, 2019, 35(8): 1693-1701.
 - [30] PUBLICOVER J, GAGGAR A, NISHIMURA S, et al. Age-dependent hepatic lymphoid organization directs successful immunity to hepatitis B[J]. *J Clin Invest*, 2013, 123(9): 3728-3739.
 - [31] ANSEL KM, NGO VN, HYMAN PL, et al. A chemokine-driven positive feedback loop organizes lymphoid follicles[J]. *Nature*, 2000, 406(6793): 309-314.
 - [32] LIU C, HUANG X, WERNER M, et al. Elevated Expression of Chemokine CXCL13 in Chronic Hepatitis B Patients Links to Immune Control during Antiviral Therapy[J]. *Front Immunol*, 2017, 8: 323.
 - [33] FENG J, LU L, HUA C, et al. High frequency of CD4+ CXCR5+ TFH cells in patients with immune-active chronic hepatitis B [J]. *PLoS one*, 2011, 6(7): e21698.
 - [34] YOSHIO S, MANO Y, DOI H, et al. Cytokine and chemokine signatures associated with hepatitis B surface antigen loss in hepatitis B patients [J]. *JCI insight*, 2018, 3(20): e122268.
 - [35] LI Y, TANG L, GUO L, et al. CXCL13-mediated recruitment of intrahepatic CXCR5(+)CD8(+) T cells favors viral control in chronic HBV infection[J]. *J Hepatol*, 2020, 72(3): 420-430.
 - [36] LI Y, WANG W, TANG L, et al. Chemokine (C-X-C motif) ligand 13 promotes intrahepatic chemokine (C-X-C motif) receptor 5+ lymphocyte homing and aberrant B-cell immune responses in primary biliary cirrhosis [J]. *Hepatology*,

- 2015, 61(6): 1998-2007.
- [37] LI Y, MA S, TANG L, et al. Circulating chemokine (C-X-C Motif) receptor 5(+) CD4(+) T cells benefit hepatitis B e antigen seroconversion through IL-21 in patients with chronic hepatitis B virus infection [J]. *Hepatology*, 2013, 58(4): 1277-1286.
- [38] WAN Z, LIN X, LI T, et al. Genetic variant in CXCL13 gene is associated with susceptibility to intrauterine infection of hepatitis B virus [J]. *Sci Rep*, 2016, 6: 26465.
- [39] 宋敏, 陆普选, 方伟军, 等. 2022年WHO全球结核病报告: 全球与中国关键数据分析[J/CD]. *新发传染病电子杂志*, 2023, 8(1): 87-92.
- [40] NATARAJAN A, BEENA PM, DEVNIKAR AV, et al. A systemic review on tuberculosis [J]. *Indian J Tuberc*, 2020, 67(3): 295-311.
- [41] DEPIANTO DJ, CHANDRIANI S, ABBAS AR, et al. Heterogeneous gene expression signatures correspond to distinct lung pathologies and biomarkers of disease severity in idiopathic pulmonary fibrosis[J]. *Thorax*, 2015, 70(1): 48-56.
- [42] IGNACIO A, BREDA CNS, CAMARA NOS. Innate lymphoid cells in tissue homeostasis and diseases[J]. *World J Hepatol*, 2017, 9(23): 979-989.
- [43] PANDA SK, COLONNA M. Innate Lymphoid Cells in Mucosal Immunity [J]. *Front Immunol*, 2019, 10: 861.
- [44] EBERL G, COLONNA M, DI SANTO JP, et al. Innate lymphoid cells. Innate lymphoid cells: a new paradigm in immunology [J]. *Science*, 2015, 348(6237): aaa6566.
- [45] COLONNA M. Innate Lymphoid Cells: Diversity, Plasticity, and Unique Functions in Immunity[J]. *Immunity*, 2018, 48(6): 1104-1117.
- [46] NARINYAN W, POLADIAN N, ORUJYAN D, et al. Immunologic Role of Innate Lymphoid Cells against Mycobacterial tuberculosis Infection[J]. *Biomedicines*, 2022, 10(11):2828.
- [47] ARDAIN A, DOMINGO-GONZALEZ R, DAS S, et al. Group 3 innate lymphoid cells mediate early protective immunity against tuberculosis [J]. *Nature*, 2019, 570(7762): 528-532.
- [48] ZENG B, XING R, DONG C, et al. Commentary: Group 3 innate lymphoid cells mediate early protective immunity against tuberculosis [J]. *Front Immunol*, 2020, 11: 1925.
- [49] SLIGHT SR, RANGEL-MORENO J, GOPAL R, et al. CXCR5 T helper cells mediate protective immunity against tuberculosis [J]. *J Clin Invest*, 2013, 123(2): 712-726.
- [50] JIANG J, CAO Z, QU J, et al. PD-1-expressing MAIT cells from patients with tuberculosis exhibit elevated production of CXCL13[J]. *Scand J Immunol*, 2020, 91(4): e12858.
- [51] AZKUR AK, AKDIS M, AZKUR D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19[J]. *Allergy*, 2020, 75(7): 1564-1581.
- [52] 廖康生, 卢洪洲. 新型冠状病毒奥密克戎变异株的研究进展: 对其科学防控措施的启示[J/CD]. *新发传染病电子杂志*, 2022, 7(1): 1-5.
- [53] WU Z, MCGOOGAN JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention[J]. *Jama*, 2020, 323(13): 1239-1242.
- [54] MEHTA P, MCAULEY DF, BROWN M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression[J]. *Lancet*, 2020, 395(10229): 1033-1034.
- [55] CATANZARO M, FAGIANI F, RACCHI M, et al. Immune response in COVID-19: addressing a pharmacological challenge by targeting pathways triggered by SARS-CoV-2[J]. *Signal Transduct Target Ther*, 2020, 5(1): 84.
- [56] LEISMAN DE, RONNER L, PINOTTI R, et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes[J]. *Lancet Respir Med*, 2020, 8(12): 1233-1244.
- [57] WONG CK, LAM CW, WU AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome [J]. *Clin Exp Immunol*, 2004, 136(1): 95-103.
- [58] HORSPOOL AM, KIEFFER T, RUSS BP, et al. Interplay of Antibody and Cytokine Production Reveals CXCL13 as a Potential Novel Biomarker of Lethal SARS-CoV-2 Infection [J]. *mSphere*, 2021, 6(1): e01324-e01420.
- [59] PERREAU M, SUFFIOTTI M, MARQUES VP, et al. The cytokines HGF and CXCL13 predict the severity and the mortality in COVID-19 patients[J]. *Nat Commun*, 2021, 12(1):4888.
- [60] JONES JD, HAMILTON BJ, CHALLENGER GJ, et al. Serum C-X-C motif chemokine 13 is elevated in early and established rheumatoid arthritis and correlates with rheumatoid factor levels[J]. *Arthritis Res Ther*, 2014, 16(2): R103.
- [61] TRAIANOS EY, LOCKE J, LENDREM D, et al. Serum CXCL13 levels are associated with lymphoma risk and lymphoma occurrence in primary Sjögren's syndrome[J]. *Rheumatol Int*, 2020, 40(4): 541-548.
- [62] FINCH DK, ETTINGER R, KARNELL JL, et al. Effects of CXCL13 inhibition on lymphoid follicles in models of autoimmune disease [J]. *Eur J Clin Invest*, 2013, 43(5): 501-509.

【收稿日期】 2023-02-15