

肥大细胞在肺部感染性疾病中的作用

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【摘要】肺部肥大细胞主要分布于肺部血管周围, 支气管以及粘膜组织。病原体入侵时, 肥大细胞通过胞吞作用直接摄取病原体, 同时通过激活自身受体促进下游细胞介质的释放, 增强炎性细胞的募集, 直接和间接杀伤病原体。此外, 肺部肥大细胞参与病原体的抗原递呈, 介导细胞和体液免疫。肥大细胞对肺部病原体感染具有重要的保护功能。

【关键词】肥大细胞; 肺; 感染; 免疫

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The role of mast cells in pulmonary infectious diseases

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【Abstract】 Pulmonary mast cells are mainly distributed in the surrounding of pulmonary vessels, bronchi, and mucosa. When pathogens invade, they are directly phagocytosed by mast cells through endocytosis. In addition, pulmonary mast cells participate in the antigen presentation of pathogens, and then mediate cellular and humoral immunity. In conclusion, mast cells play an important role in protecting lung from pathogen infection.

【Keywords】 Mast cell; Lung; Infection; Immunity

前言

肥大细胞主要位于呼吸、消化、泌尿及皮肤等多个器官和组织中, 其作为宿主免疫细胞与巨噬细胞、树突状细胞、自然杀伤细胞等共同构成了机体抵抗外界病原体的第一道防线^[1], 肥大细胞可以分泌多种细胞介质, 包括炎症因子、蛋白酶、抗肥大细胞菌肽、趋化因子及花生四烯酸等, 参与机体的多种病理生理过程^[2, 3]。

随着对肥大细胞研究的进一步深入, 近年来许多学者发现, 除参与过敏性疾病以外^[4, 5], 肥大细胞在机体抵抗外界病原体入侵过程中同样发挥了重要的免疫作用。肥大细胞表面可表达多种受体, 感受多种病原体的刺激, 并且与多种炎性细胞以及细胞

外基质相互作用, 发挥相应的免疫功能^[6]。外来病原体入侵呼吸道时, 肥大细胞可以通过介导固有免疫和适应性免疫维护肺部稳态^[7]。当前, 有证据表明, 肥大细胞参与到结核杆菌、支原体、衣原体、铜绿假单胞菌以及H5N1禽流感病毒等肺部感染的发病过程中。本文对近年来肺部肥大细胞在抵抗病原体入侵方面的研究进展作一综述, 以探讨肥大细胞的反应过程和作用机制。

1 肥大细胞的分类和肺内分布

肥大细胞作为一种多功能祖细胞, 来源于骨髓, 刚进入外周血时处于不成熟状态, 当前体细胞迁徙到特定组织和器官时才能分化和成熟^[8]。已有研

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究发现,干细胞因子(Stem Cell Factor, SCF)、白细胞介素(Interleukin, IL)、肿瘤坏死因子(Tumor Necrosis Factor, TNF)^[9]等不同的调节因子可以促进未成熟的肥大细胞分化成不同类型的细胞亚群。同时,肥大细胞也是具有异质性的细胞群。不同的个体以及同种个体不同部位的肥大细胞对外界刺激的反应程度也有很大不同^[10]。Schwartz根据肥大细胞是否分泌胰蛋白酶和胃促胰酶,将其分为MC_T和MC_{TC}两类。这两类细胞的数量会根据所在组织和器官的病理生理过程发生相应的变化。例如,在非小细胞肺癌中,MC_T和MC_{TC}数量均增加^[11],在过敏性疾病中MC_T明显增加^[12],而在溃疡性膀胱炎中,MC_{TC}数量明显增加^[13]。MC_T主要发挥宿主防御的功能,而MC_{TC}则参与血管生成和组织重构^[14]。

肥大细胞有相当一部分定植于肺部,每克肺组织大约有数百万个肥大细胞^[15],肺组织的肥大细胞主要位于肺血管和支气管周围。根据肥大细胞的表型及发育特征,可以将其分为结缔组织型和粘膜组织型。前者主要分布于肺静脉周围,后者主要位于气道黏膜上皮^[16]。

2 肥大细胞的活化

病原体作用于肥大细胞会促使其胞内炎症及抗菌介质的释放发挥相应的免疫保护功能^[17,18]。肥大细胞的胞内介质包括已经存储的和刺激后新合成的介质^[19],这两类介质可以调控肺内的防御系统,以应对外来病原体的入侵。肥大细胞受到外界病原体刺激后,可以通过胞吐过程,释放生物活性物质^[20]。而胞吐过程可能与细菌膜上表达的调理素有关^[21]。有学者指出,当细菌刺激肥大细胞后会诱导其胞吐过程,但这一过程是渐进性的,且释放的介质质量与细菌数量成正比^[22]。

不同的动物肺部感染模型会刺激肥大细胞释放不同的介质。铜绿假单胞菌和流感嗜血杆菌可以刺激肺内肥大细胞释放组织胺^[23,24],脂多糖诱导的肺损伤中,肥大细胞表达IL-1 β 增高^[25],铜绿假单胞菌肺炎中,激活的肥大细胞可以释放TNF- α 、IL-1 β 、IL-6^[26]。作为重要的血管活性物质,组织胺可以增强血管的通透性^[27],在病原体感染时,可以促进炎症细胞到达感染部位。TNF- α 在感染时可以增强中性粒细胞及巨噬细胞的招募,以清除病原菌。此外,肥大细胞也可以释放肝素、多巴胺、5-羟色胺、胃促胰酶和类胰蛋白酶等。其中,肥大细胞来源的胃促胰酶和类胰蛋白酶可以通过降解P物质和

血管活性肠肽,影响气道粘液糖蛋白的分泌,从而在增强肺部防御功能中发挥作用^[28]。肥大细胞通过分泌以上活性物质而发挥对外来病原体的防御作用,参与到肺部疾病的发生和发展之中。同样,在支气管哮喘中,肥大细胞作为最主要的效应细胞,被激活后可以释放组织胺、白三烯等细胞介质,参与气道收缩等病理生理过程^[29]。

识别外来病原体的特殊信号,是肥大细胞发生防御反应进而激活并释放一系列炎性介质的前提。肥大细胞主要依靠自身受体来完成对外来病原体的识别。肥大细胞主要表达趋化因子受体、凋亡受体、免疫球蛋白Fc部分c末端的受体以及c-kit受体^[30]。肥大细胞表面趋化因子受体被趋化因子激活后,下游的钙离子通道、蛋白激酶等相应活化,引起肥大细胞重构^[31]。凋亡受体主要包括Fas和肿瘤坏死因子相关凋亡诱导配体(TNF-Related Apoptosis Inducing Ligand, TRAIL)两类,两者结构类型均为I型跨膜蛋白^[32]。Fas与配体结合后,可以招募衔接蛋白,进而激活含半胱氨酸的天冬氨酸蛋白水解酶(Caspase)途径,启动级联反应,转导细胞的凋亡信号^[33]。除了介导凋亡,Fas还参与到调控肥大细胞的生长发育之中。Fas被敲除后肥大细胞胞内递质水平降低,脱颗粒程度下降,IL以及TNF表达降低^[34]。TRAIL包括死亡受体和诱骗受体,其中介导细胞凋亡的是死亡受体,而诱骗受体发挥细胞保护功能^[35]。有研究发现,根据免疫方式的不同,TRAIL介导的肥大细胞凋亡率也是各有差异,在某些病理条件下可以抑制肥大细胞的过度增殖,进而保护机体^[36]。Fc γ 受体中Fc ϵ RI是肥大细胞的刺激型受体,其 β 链和 γ 链上的免疫受体酪氨酸激活基序磷酸化后可以激活脾酪氨酸激酶,进而激活下游的磷脂酰肌醇激酶(Phosphatidylinositol 3-kinase, PI3K)等,引起细胞的脱颗粒现象^[37]。Fc γ R II B是肥大细胞的抑制型受体,当Fc ϵ RI与其配体结合后,Fc γ R II B会发挥抑制功能,其胞内ITIM通过磷酸化过程切断PI3K介导的下游通路,进而抑制肥大细胞的激活^[38]。c-kit受体属于酪氨酸激酶受体家族,胞外有5个免疫球蛋白样的结构域,其配体为SCF,主要由成纤维细胞、上皮细胞等分泌^[39-40]。c-kit与SCF结合后,形成二聚体,通过下游的磷酸肌醇依赖性蛋白激酶-1(Phosphoinositide Dependent Protein Kinase-1, PDK-1)、磷脂酶C γ -1(Phospholipase C γ -1, PLC γ -1)、Ras等信号分子传递信息,促使肥大细胞进入生长分化期^[41]。肥

大细胞的生长发育依赖于c-kit的调控,其主要表达于祖细胞的分化早期^[42]。而在 $Kit^{W-sh/W-sh}$ 小鼠中,由于c-kit基因表达异常,而表现为肥大细胞缺陷,在回输骨髓来源的肥大细胞后,可以恢复肥大细胞的抗菌功能^[43]。尽管c-kit受体可以激活下游的PLC γ 、PI3K等分子,但是单独作用时无法触发肥大细胞的脱颗粒过程,必须依赖Fc γ 受体的激活。在此过程中c-kit增强了Fc γ 引起的细胞脱颗粒以及分泌细胞介质的能力^[44]。Halova等人发现c-kit可以激活胞内的人第10号染色体缺失的磷酸酶及张力蛋白同源的基因(Phosphatase and Tensin Homolog Deleted on Chromosome Ten, PTEN)和SH2结构的5'肌醇磷酸酶-1(SHIP-1),对肥大细胞起到趋化作用^[45]。Malaviya等人也发现肥大细胞可以表达一种甘露糖化的受体,与肺炎克雷伯杆菌结合,使细菌的粘附素基因FimH失活^[46, 47]。另外,肥大细胞并非需与病原体紧密接触才可以激活,其也可以被病原体的颗粒或可溶性成分所激活^[48, 49]。如肺部感染百日咳时,百日咳鲍特菌可产生毒素抑制肥大细胞的活性,进而对肺部造成损伤^[50]。

3 肺部肥大细胞对病原体的清除

肥大细胞主要依靠识别、吞噬和清除的方式在抵御多种病原体感染中发挥作用。活化的肥大细胞可以通过多种方式释放活性介质,较常见的有组织胺、TNF、白三烯、IL等。

肺部是结核分支杆菌感染人体的主要靶器官,也是诱导免疫反应的主要部位^[51]。体外实验表明在结核分支杆菌感染中,肥大细胞可以通过激活CD48增强对结核分支杆菌的摄取,同时可以分泌趋化因子募集相应的炎症细胞,参与对结核杆菌的清除^[52, 53]。Carlos等人构建了小鼠结核分枝杆菌肺部感染模型,发现肺部肥大细胞活化后可以分泌相应的趋化因子增强炎症细胞的募集,参与肺部抵御结核分支杆菌感染^[54]。肥大细胞表达的Toll样受体(Toll-like Receptor, TLR)也参与此过程。给TLR2缺陷鼠回输肥大细胞后,肺部IL-1 β , IL-6, TNF- α 的表达上调,辅助性T细胞应答增强,肺部感染局部CD8⁺T细胞募集增多,可见肥大细胞补偿了缺陷鼠的肺部抗菌功能缺陷^[55]。

在小鼠克雷伯杆菌肺炎模型中,与正常小鼠相比,肥大细胞缺陷小鼠在感染6 h后肺细菌载量更高,是正常小鼠的10倍以上。向缺陷鼠体内回输肥大细胞后,肺组织的抗菌能力增强^[56],这表明肥

大细胞的缺失削弱了小鼠清除细菌的能力。同时,对肺泡灌洗液中细胞及炎症因子检测发现,与正常小鼠和肥大细胞重构小鼠相比,缺陷组小鼠中性粒细胞数量更少, TNF的表达下降,而TNF是招募中性粒细胞的关键因子^[57]。除了TNF, Rachel等人也发现, IL-6缺陷的小鼠肺部抵抗克雷伯杆菌的功能下降。小鼠肥大细胞特异性敲除IL-6后,肺损伤加重,中性粒细胞浸润降低,这表明肥大细胞来源的IL-6也可以通过募集中性粒细胞,来增强机体对克雷伯杆菌的杀伤作用^[58]。综上,肥大细胞缺陷鼠肺部对克雷伯杆菌的清除能力与中性粒细胞浸润密切相关,而肥大细胞可以增强中性粒细胞在感染部位的募集。

除了细菌的肺部感染,也有学者构建了支原体肺部感染模型。发现与野生鼠相比,肥大细胞缺陷的WBB6F1/J- Kit^W/Kit^{W-v} 小鼠肺部清除支原体的能力减弱,而回输正常肥大细胞和特异性敲除IL-6的肥大细胞后,肺组织的支原体载量均降低^[59],这表明尽管肥大细胞来源的IL-6并不参与对支原体的杀伤,但肥大细胞本身或许可以通过直接或间接的作用参与肺部对支原体的保护性免疫活动。Xu等人选择用另一种肥大细胞缺陷鼠 Kit^{W-sh}/Kit^{W-sh} 构建支原体肺炎模型,得到相同的结论,相比于野生鼠, Kit^{W-sh}/Kit^{W-sh} 小鼠在感染后体重下降,生存期更短,肺部支原体负荷也增加^[60]。

4 小结

肺部肥大细胞主要分布于血管周围、支气管、粘膜等深部组织。肥大细胞可以通过多种方式识别外来病原体并对其进行杀灭。肥大细胞既可以通过胞吞作用摄取侵入的病原体,也可以通过胞内炎症介质等产物的释放,发挥直接和间接免疫保护功能。肥大细胞来源的炎症因子,如IL-6和TNF- α 等除自身具有的促炎作用外,还可以将中性粒细胞等炎症细胞大量招募到感染局部,发挥相应的功能。另外,肥大细胞也可以将病原体抗原递呈给相应的免疫细胞,通过介导上皮细胞的增殖等方式,调控肺部宿主防御体系^[61]。当前,对肥大细胞在肺部病原体感染中的作用及其机制的研究日趋深入,这不仅为感染免疫学研究开辟了新领域,而且也为相关疾病的诊治提供新的理论依据。

参考文献

- [1] ABRAHAM S N, ST JOHN A L. Mast cell-orchestrated

- immunity to pathogens[J]. *Nat Rev Immunol*, 2010, 10(6): 440-452.
- [2] METCALFE D D, BARAM D, MEKORI Y A. Mast cells[J]. *Physiol Rev*, 1997, 77(4): 1033-1079.
- [3] LI G, DOMENICO J, JIA Y, et al. NF-kappaB-dependent induction of cathelicidin-related antimicrobial peptide in murine mast cells by lipopolysaccharide[J]. *Int Arch Allergy Immunol*, 2009, 150(2): 122-132.
- [4] VERHEIJDEN KIM A T, BRABER S, LEUSINK-MUIS T, et al. The combination therapy of dietary galacto-oligosaccharides with budesonide reduces pulmonary th2 driving mediators and mast cell degranulation in a murine model of house dust mite induced asthma[J]. *Front Immunol*, 2018, 9: 2419.
- [5] KANG B C, KIM M J, LEE S, et al. Nothofagin suppresses mast cell-mediated allergic inflammation[J]. *Chem Biol Interact*, 2018, 298: 1-7.
- [6] CASLIN H L, KIWANUKA K N, HAQUE T T, et al. Controlling mast cell activation and homeostasis: work influenced by bill paul that continues today[J]. *Front Immunol*, 2018, 9: 868.
- [7] ANDERSSON C K, MORI M, BJERMER L, et al. Alterations in lung mast cell populations in patients with chronic obstructive pulmonary disease[J]. *Am J Respir Crit Care Med*, 2010, 181(3): 206-217.
- [8] AUSTEN K F, GURISH M F. Resolution of a human mast cell development conundrum[J]. *Blood*, 2017, 130(16): 1777-1778.
- [9] HU Z Q, ZHAO W H, SHIMAMURA T. Regulation of mast cell development by inflammatory factors[J]. *Curr Med Chem*, 2007, 14(28): 3044-3050.
- [10] THEOHARIDES T C, TSILIONI I, REN H. Recent advances in our understanding of mast cell activation-or should it be mast cell mediator disorders?[J]. *Expert Rev Clin Immunol*, 2019, 15(6): 639-656.
- [11] SHIKOTRA A, OHRI C M, GREEN R H, et al. Mast cell phenotype, TNF α expression and degranulation status in non-small cell lung cancer[J]. *Sci Rep*, 2016, 6: 38352.
- [12] ANDERSSON C, TUFVESSON E, DIAMANT Z, et al. Revisiting the role of the mast cell in asthma[J]. *Curr Opin Pulm Med*, 2016, 22(1): 10-17.
- [13] MALIK S T, BIRCH B R, VOEGELI D, et al. Distribution of mast cell subtypes in interstitial cystitis: implications for novel diagnostic and therapeutic strategies?[J]. *J Clin Pathol*, 2018, 71(9): 840-844.
- [14] CHURCH M K, LEVI-SCHAFFER F. The human mast cell[J]. *J Allergy Clin Immunol*, 1997, 99(2): 155-160.
- [15] BAGHER M, LARSSON-CALLERFELT A K, ROSEMARK O, et al. Mast cells and mast cell tryptase enhance migration of human lung fibroblasts through protease-activated receptor 2[J]. *Cell Commun Signal*, 2018, 16(1): 59.
- [16] BREITLING S, HUI Z, ZABINI D, et al. The mast cell-B cell axis in lung vascular remodeling and pulmonary hypertension[J]. *Am J Physiol Lung Cell Mol Physiol*, 2017, 312(5): L710-L721.
- [17] JOHNSON-WEAVER B, CHOI H W, ABRAHAM S N, et al. Mast cell activators as novel immune regulators[J]. *Curr Opin Pharmacol*, 2018, 41: 89-95.
- [18] LIU C, OUYANG W, XIA J, et al. Tumor necrosis factor- α is required for mast cell mediated host immunity against cutaneous staphylococcus aureus infection[J]. *J Infect Dis*, 2018, 218(1): 64-74.
- [19] CHRIST P, SOWA A S, FROY O, et al. The circadian clock drives mast cell functions in allergic reactions[J]. *Front Immunol*, 2018, 9: 1526.
- [20] ŻELECHOWSKA P, AGIER J, RÓŻALSKA S, et al. Leptin stimulates tissue rat mast cell pro-inflammatory activity and migratory response[J]. *Inflamm Res*, 2018, 67(9): 789-799.
- [21] JOULIA R, GAUDENZIO N, RODRIGUES M, et al. Mast cells form antibody-dependent degranulatory synapse for dedicated secretion and defence[J]. *Nat Commun*, 2015, 6: 6174.
- [22] CLEMENTSEN P, LARSEN FO, MILMAN N, et al. Haemophilus influenza release histamine and enhance histamine release from human bronchoalveolar cells. Examination of patients with chronic bronchitis and controls[J]. *APMIS*, 1995, 103(11): 806-812.
- [23] FRIEDL P, KONING B, KONING W. Effects of mucoid and non-mucoid pseudomonas aeruginosa isolates from cystic fibrosis patients on inflammatory mediator release from human polymorphonuclear granulocytes and rat mast cells[J]. *Immunology*, 1992, 76(1): 86-94.
- [24] CHURCH M K, NORN S, PAO G J, et al. Non-IgE-dependent bacteria induced histamine release from human lung and tonsillar mast cells[J]. *Clin Allergy*, 1987, 17(4): 341-353.
- [25] MONÇÃO-RIBEIRO L C, CAGIDO V R, LIMA-MURAD G, et al. Lipopolysaccharide-induced lung injury: role of P2X7 receptor[J]. *Respir Physiol Neurobiol*, 2011, 179(2/3): 314-325.
- [26] LÊ B V, KHORSI-CAUET H, BACH V, et al. Mast cells mediate pseudomonas aeruginosa lipopolysaccharide-induced lung inflammation in rat[J]. *Eur J Clin Microbiol Infect Dis*. 2012, 31(8): 1983-1990.

- [27] CHEN Z P, ZHANG X Y, PENG S Y, et al. Histamine H1 receptor contributes to vestibular compensation[J]. *J Neurosci*, 2019, 39(3): 420-433.
- [28] PAUPERT J, ESPINOSA E, CENAC N, et al. Rapid and efficient production of human functional mast cells through a three-dimensional culture of adipose tissue-derived stromal vascular cells[J]. *J Immunol*, 2018, 201(12): 3815-3821.
- [29] ANDERSSON C, TUFVESSON E, DIAMANT Z, et al. Revisiting the role of the mast cell in asthma[J]. *Curr Opin Pulm Med*, 2016, 22(1): 10-17.
- [30] BRIGHTLING C E, KAUR D, BERGER P, et al. Differential expression of CCR3 and CXCR3 by human lung and bone marrow-derived mast cells: implications for tissue mast cell migration[J]. *J Leukoc Biol*, 2005, 77(5): 759-766.
- [31] LIANG Y, QIAO L, PENG X, et al. The chemokine receptor CCR1 is identified in mast cell-derived exosomes[J]. *Am J Transl Res*, 2018, 10(2): 352-367.
- [32] CHEN H R, LAI Y C, YEH T M. Dengue virus non-structural protein 1: a pathogenic factor, therapeutic target, and vaccine candidate[J]. *J Biomed Sci*, 2018, 25(1): 58.
- [33] RASPER D M, VAILLANCOURT J P, HADANO S, et al. Cell death attenuation by 'Usurpin', a mammalian DED-caspase homologue that precludes caspase-8 recruitment and activation by the CD-95 (Fas, APO-1) receptor complex[J]. *Cell Death Differ*, 1998, 5(4): 271-288.
- [34] BERENT-MAOZ B, GUR C, VITA F, et al. Influence of FAS on murine mast cell maturation[J]. *Ann Allergy Asthma Immunol*, 2011, 106(3): 239-244.
- [35] FÖRSTER A, GROTHA S P, SEEGER J M, et al. Activation of KIT modulates the function of tumor necrosis factor-related apoptosis inducing ligand receptor (TRAIL-R) in mast cells[J]. *Allergy*, 2015, 70 (7): 764-774.
- [36] BERENT-MAOZ B, PILIPONSKY A M, DAIGLE I, et al. Human mast cells undergo TRAIL-induced apoptosis[J]. *J Immunol*, 2006, 176 (4): 2272-2278.
- [37] SAMAYAWARDHENA L A, PALLAN C J. PTPalpha activates Lyn and Fyn and suppresses Hck to negatively regulate FcepsilonRI-dependent mast cell activation and allergic responses[J]. *J Immunol*, 2010, 185(10): 5993-6002.
- [38] CASLIN H L, KIWANUKA K N, HAQUE T T, et al. Controlling mast cell activation and homeostasis: Work influenced by bill paul that continues today[J]. *Front Immunol*, 2018, 9: 868.
- [39] WEISHAAR K M, EHRHART E J, AVERY A C, et al. c-Kit mutation and localization status as response predictors in mast cell tumors in dogs treated with prednisone and toceranib or vinblastine[J]. *J Vet Intern Med*. 2018, 32(1): 394-405.
- [40] JOHNSON C, HUYNH V, HARGROVE L, et al. Inhibition of mast cell-derived histamine decreases human cholangiocarcinoma growth and differentiation via c-kit/stem cell factor dependent signaling[J]. *Am J Pathol*. 2016, 186 (1): 123-133.
- [41] LENNARTSSON J, RÖNNSTRAND L. Stem cell factor receptor/c-Kit: from basic science to clinical implications[J]. *Physiol Rev*, 2012, 92 (4): 1619-1649.
- [42] GURISH M F, AUSTEN K F. Developmental origin and functional specialization of mast cell subsets[J]. *Immunity*, 2012, 37(1): 25-33.
- [43] ISHIJIMA Y, OHMORI S, OHNEDA K. Mast cell deficiency results in the accumulation of preadipocytes in adipose tissue in both obese and non-obese mice[J]. *FEBS Open Bio*, 2014, 4: 18-24.
- [44] KASHYAP M, BAILEY D P, GOMEZ G, et al. TGF-beta1 inhibits late-stage mast cell maturation[J]. *Exp Hematol*, 2005, 33(11): 1281-1291.
- [45] HALOVA I, DRABEROVA L, DRABER P. Mast cell chemotaxis-chemoattractants and signaling pathways[J]. *Front Immunol*, 2012, 3: 119.
- [46] MALAVIYA R, ROSS E A, MACGREGOR J I, et al. Mast cell phagocytosis of FimH-expressing enterobacteria[J]. *J Immunol*, 1994, 152 (4): 1907-1914.
- [47] SHER A, HEIN A, MOSER G, et al. Complement receptors promote the phagocytosis of bacteria by rat peritoneal mast cells[J]. *Lab Invest*, 1979, 41 (6): 490-499.
- [48] LEAL-BERUMEN I, SNIDER D P, BARAJAS-LOPEZ C, et al. Cholera toxin increases IL-6 synthesis and decreases TNF- production by rat peritoneal mast cells[J]. *J Immunol*, 1996, 156 (1): 316-321.
- [49] MALAVIYA R, ROSS E, JAKSCHIK B A, et al. Mast cell degranulation induced by type 1 fimbriated *Escherichia coli* in mice[J]. *J Clin Invest*, 1994, 93(4): 1645-1653.
- [50] MATSUDA K, AOKI J, UCHIDA M K, et al. Datura stramonium agglutinin released histamine from rat peritoneal mast cells that was inhibited by pertussis toxin, haptenic sugar and N-acetylglucosamine-specific lectins: involvement of glycoproteins with N-acetylglucosamine residues[J]. *Jap J Pharm*, 1994, 66(2): 195-204.
- [51] KAUFMANN S H. How can immunology contribute to the control of tuberculosis?[J]. *Nat Rev Immunol*, 2001, 1(1): 20-30.
- [52] MUÑOZ S, HERNÁNDEZ-PANDO R, ABRAHAM S

- N, et al. Mast cell activation by Mycobacterium tuberculosis: mediator release and role of CD48[J]. J Immunol, 2003, 170(11): 5590-5596.
- [53] MUÑOZ S, RIVAS-SANTIAGO B, ENCISO J A. Mycobacterium tuberculosis entry into mast cells through cholesterol-rich membrane microdomains[J]. Scand J Immunol, 2009, 70(3): 256-263.
- [54] CARLOS D, DE SOUZA JÚNIOR D A, DE PAULA L, et al. Mast cells modulate pulmonary acute inflammation and host defense in a murine model of tuberculosis[J]. J Infect Dis, 2007, 196 (9): 1361-1368.
- [55] CARLOS D, FRANTZ F G, SOUZA-JÚNIOR D A, et al. TLR2-dependent mast cell activation contributes to the control of Mycobacterium tuberculosis infection[J]. Microbes Infect, 2009, 11 (8/9): 770-778.
- [56] SUTHERLAND R E, OLSEN J S, MCKINSTRY A, et al. Mast cell IL-6 improves survival from Klebsiella pneumonia and sepsis by enhancing neutrophil killing[J]. J Immunol, 2008, 181(8):5598-5605.
- [57] ANTONIELLI SILVEIRA A A, DOMINICAL V M, MORELLI VITAL D, et al. Attenuation of TNF-induced neutrophil adhesion by simvastatin is associated with the inhibition of Rho-GTPase activity, p50 activity and morphological changes[J]. Int Immunopharmacol, 2018, 58: 160-165.
- [58] SUTHERLAND R E, OLSEN J S, MCKINSTRY A, et al. Mast cell IL-6 improves survival from Klebsiella pneumonia and sepsis by enhancing neutrophil killing[J]. J Immunol. 2008, 181 (8): 5598-5605.
- [59] MICHELS N M, CHU H W, LAFASTO S C, et al. Mast cells protect against airway Mycoplasma pneumoniae under allergic conditions[J]. Clin Exp Allergy, 2010, 40 (9): 1406-1413.
- [60] XU X, ZHANG D J, ZHANG H, et al. Neutrophil histamine contributes to inflammation in mycoplasma pneumonia[J]. J Exp Med, 2006, 203(13): 2907-2917.
- [61] MARSHALL J S, PORTALES-CERVANTES L, LEONG E. Mast cell responses to viruses and pathogen products[J]. Int J Mol Sci, 2019, 20(17): 4241.
- [收稿日期] 2020-11-26

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- [10] MASAMUNE A, KOTANI H, SÖRGEL F L, et al. Variants that affect function of calcium channel TRPV6 are associated with early-onset chronic pancreatitis[J]. Gastroenterology, 2020, 158(6): 1626-1641.
- [11] ZOU W B, WANG Y C, REN X L, et al. TRPV6 variants confer susceptibility to chronic pancreatitis in the Chinese population[J]. Hum Mutat, 2020, 41(8): 1351-1357.
- [12] HUANG H, SWIDNICKA-SIERGIEJKO A K, DANILUK J, et al. Transgenic expression of PRSS1R122H sensitizes mice to pancreatitis[J]. Gastroenterology, 2020, 158(4): 1072-1082.
- [13] SUN C, LIU M, AN W, et al. Heterozygous spink1 c. 194+2T>C mutant mice spontaneously develop chronic pancreatitis[J]. Gut, 2020, 69(5): 967-968.
- [14] PATEL V, WILLINGHAM F. The management of chronic pancreatitis[J]. Med Clin North Am, 2019, 103(1): 153-162.
- [15] SHELTON C A, UMAPATHY C, STELLO K, et al. Hereditary pancreatitis in the United States: survival and rates of pancreatic cancer[J]. Am J Gastroenterol, 2018, 113(9): 1376-1384.
- [16] ZHU X, LIU D, WEI Q, et al. New-onset diabetes mellitus after chronic pancreatitis diagnosis: a systematic review and meta-analysis[J]. Pancreas, 2019, 48(7): 868-875.
- [17] PAN J, XIN L, WANG D, et al. Risk factors for diabetes mellitus in chronic pancreatitis: a cohort of 2011 patients[J]. Medicine (Baltimore), 2016, 95(14): e3251.
- [18] LI B R, PAN J, DU T T, et al. Risk factors for steatorrhea in chronic pancreatitis: a cohort of 2 153 Patients[J]. Sci Rep, 2016, 6(1): 21381.
- [19] 中国医师协会胰腺病专业委员会慢性胰腺炎专委会. 慢性胰腺炎诊治指南(2018 广州)[J]. 中华胰腺病杂志, 2018, 18(5): 289-296.
- [20] GARDNER T B, ADLER D G, FORSMARK C E, et al. ACG clinical guideline: chronic pancreatitis[J]. Am J Gastroenterol, 2020, 115(3): 322-339.
- [21] 中国医师协会胰腺病专业委员会慢性胰腺炎专委会. 胰腺外分泌功能不全诊治规范(2018年, 广州)[J]. 中华消化杂志, 2018, 38(12): 795.
- [22] ISSA Y, KEMPENEERS M A, BRUNO M J, et al. Effect of early surgery vs. endoscopy-first approach on pain in patients with chronic pancreatitis: the ESCAPE randomized clinical trial[J]. JAMA, 2020, 323(3): 237-247.
- [23] QIAN Y Y, HU L H, LIAO Z. Surgery vs. endoscopy for early treatment of chronic pancreatitis[J]. JAMA, 2020, 323(21): 2202.
- [收稿日期] 2020-11-12