世界华人消化杂志®
wcjd@wjgnet.com
世界华人消化杂志 2012年7月8日; 20(19): 1747-1751
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

肥大细胞在肠易激综合征发病机制中的研究进展

罗和生, 赵运志, 张法灿, 张 国

罗和生, 赵运志, 武汉大学人民医院消化内科 湖北省武汉市 430060
赵运志, 张法灿, 张国, 广西壮族自治区人民医院消化内科 广西壮族自治区南宁市 530021
罗和生, 主任医师, 博士生导师, 教授, 主要从事消化内科方面的研究.
国家自然科学基金资助项目, No. 81160053
作者贡献分布: 本文综述由罗和生指导; 赵运志完成; 罗和生与张国修改; 张法灿审校.
通讯作者: 张法灿, 教授, 主任医师, 530021, 广西壮族自治区南宁市, 广西壮族自治区人民医院消化内科. zhangfacan@126.com
电话: 0771-2186184
收稿日期: 2012-03-29 修回日期: 2012-05-20
接受日期: 2012-06-16 在线出版日期: 2012-07-08

Progress in understanding the role of mast cells in the pathogenesis of irritable bowel syndrome

He-Sheng Luo, Yun-Zhi Zhao, Fa-Can Zhang, Guo Zhang

He-Sheng Luo, Yun-Zhi Zhao, Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei Province, China
Yun-Zhi Zhao, Fa-Can Zhang, Guo Zhang, Department of Gastroenterology, the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning 530021, Guangxi Zhuang Autonomous Region, China
Supported by: National Natural Science Foundation of China, No. 81160053
Correspondence to: Fa-Can Zhang, Professor, Department of Gastroenterology, the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning 530021, Guangxi Zhuang Autonomous Region, China. zhangfacan@126.com
Received: 2012-03-29 Revised: 2012-05-20
Accepted: 2012-06-16 Published online: 2012-07-08

Abstract

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by abdominal pain/discomfort and changes in bowel habit. The global prevalence of IBS is 2%-15%. The etiology and pathogenesis of IBS are still unclear. It is currently believed that a variety of factors, such as abnormal gastrointestinal motility, visceral hypersensitivity, infection and inflammation, neuro-endocrine maladjustment, mental or psychological causes, and food allergy, may contribute to the development of IBS. The "neuro-immuno-endocrine network" hypothesis has been proposed in recent years to explain the pathogenesis of IBS. Mast cells in the digestive tract play an important role in the pathogenesis of IBS. In this article, we will review the recent advances in understanding the role of mast cells plays in the pathogenesis of IBS.

Key Words: Irritable bowel syndrome; Mast cells; Pathogenesis

Luo HS, Zhao YZ, Zhang FC, Zhang G. Progress in understanding the role of mast cells in the pathogenesis of irritable bowel syndrome. Shijie Huaren Xiaohua Zazhi 2012; 20(19): 1747-1751

摘要

肠易激综合征(irritable bowel syndrome, IBS)是以腹痛、腹部不适伴排便习惯改变和/或大便性状异常为特征的常见功能性胃肠病. IBS全球患病率为2%-15%. 本病病因及发病机制尚不十分明确, 目前认为多与胃肠动力异常、内脏高敏、感染与炎症、神经-内分泌失调、精神心理、食物过敏等多种因素有关. 近年来提出的"神经-免疫-内分泌网络"理论在IBS发病机制中占有重要地位. 研究发现, 胃肠道的肥大细胞(mast cells, MCs)在IBS的发病中发挥着重要作用. 本文拟以MCs在IBS中的发病机制的最新研究进展作一综述.

关键词: 肠易激综合征; 肥大细胞; 发病机制

罗和生, 赵运志, 张法灿, 张国. 肥大细胞在肠易激综合征发病机制中的研究进展. 世界华人消化杂志 2012; 20(19): 1747-1751
http://www.wjgnet.com/1009-3079/20/1747.asp

0 引言

肥大细胞(mast cells, MCs)来源于骨髓造血干细胞, 主要分布于与外界相通的皮肤、气道和消化系[1-5]. 在慢性、持续性炎症时, MCs的数量增加, 表型活化[6]. MCs是消化系内重要的免疫活性细胞, 也是肠道主要的抗原感受器, 参与肠黏膜的免疫应答与调节. 其胞质中含有大量的内分泌颗粒, 对刺激应答时可以合成、释放颗粒内多种生物活性介质和因子, 如组胺、5-羟

■背景资料
近年来, 人们对肠易激综合征(IBS)的病因和发病机制进行了大量的研究, 发现肥大细胞(MCs)在其中扮演着极其重要的角色. 目前, MCs与肠易激综合征之间的确切分子机制仍不清楚、因果关系尚不明确.

■同行评议者
潘秀珍, 教授, 主任医师, 福建省立医院消化科

■相关报道
大量研究发现, IBS患者结肠MCs数目及活化水平显著升高, 且与相关症状严重程度呈正相关, 此外类胰蛋白酶在其中的作用也已被证实, 类胰蛋白酶抑制剂的研究显示出积极的意义.

色胺、类胰蛋白酶(tryptase)、前列腺素、白三烯、血小板活化因子和细胞因子等[7], 通过这些活性介质的广泛作用, MCs在神经和免疫机制之间起到重要的沟通作用: 包括炎症和黏膜的免疫生理、产生大量多功能生物化学介质、与神经免疫的联系和脑-肠轴的关系、肠道高敏感性、胃肠动力紊乱等[8]. 研究表明, IBS患者结肠MCs增多, 细胞脱颗粒明显增加, 并与IBS患者的腹痛、腹胀等症状相关[9]. 因此, 对MCs在IBS中的深入了解显得尤为重要.

1 相应部位肥大细胞数量的增加与活化

MCs在胃肠道分布广泛, 而早在50年前, Spiller等[10]在经外科手术获取的IBS患者结肠标本中检测到增多的肥大细胞. Weston等[11]在1993年报道过IBS患者回肠末端黏膜固有层MCs数目增多, 使得人们开始意识到MCs的改变可能在IBS中起到重要作用. 2005年姜敏等[12]在对IBS患者及正常组回盲部和直肠乙状结肠交界部MCs的分布特点和数量观察中发现, IBS组回盲部MCs计数明显增多, 其中以腹泻型IBS患者增加更加明显. 两处均可见明显MCs脱颗粒现象. Barbara等[13,14]的两项研究均表明MCs在结肠的高浓度及活化程度与腹痛的严重程度有关, Piche等[15]2008年对IBS患者、正常对照组和疲劳抑郁症患者的结肠活检显示IBS患者MCs数量的明显增加, 是盲肠低度炎症浸润的关键指征, 并且与焦虑抑郁程度显著相关. Wang等[16]对IBS患者小肠MCs进行了相关探讨, 结果显示除末端回肠MCs明显增加外, 与正常组无明显差异, 而正是这种改变导致IBS相关症状. 以上研究我们可以发现MCs的异常表达在IBS进展上起着关键作用.

2 类胰蛋白酶

类胰蛋白酶贮存在MCs胞质的小颗粒内, 是MCs中重要的生物活性分子, 是其激活脱颗粒的特异性标志[17]. 类胰蛋白酶通过刺激外周血T细胞、单核细胞和气道上皮细胞释放IL-6、TNF-α、IL-1β、IL-8和GM-CSF等众多细胞因子, 直接或间接募集、激活嗜酸性粒细胞和中性粒细胞等炎症细胞, 增加血管通透性、诱导炎性细胞浸润、刺激上皮细胞增生[18]; 其次类胰蛋白酶本身也具有激活MCs的作用[19]. 在体内, 类胰蛋白酶激活蛋白酶活化受体-2(protease-activated receptor 2, PAR-2), 通过促细胞分裂活化蛋白激酶(MAPK)信号通路, 促进细胞异常增生及结构改变[20,21]. 实验证实结肠内广泛存在PAR-2阳性的神经元[22], 在IBS类胰蛋白酶通过肠黏膜细胞表面PAR-2的活化, 可增加细胞通透性[23]; PAR-2阳性的伤害感受神经元, 作为传入神经终止于脊髓背角, 在PAR-2激活后可释放传递伤害性信息神经递质P物质(substance P, SP)和降钙素基因相关肽(calcitonin gene related peptide, CGRP)[24-26], 导致内脏高敏感性的发生. 此外, PAR-2的活化可导致结肠低度炎症迁延存在, 肠道黏膜渗透性的增加, 炎症细胞包括MCs的浸润, 反过来使类胰蛋白酶表达增加, 使伤害感受神经元持续兴奋,导致IBS症状反复[27,28]. Vivinus-Nébot等[29]研究结果表明, IBS患者MCs的数量及胰蛋白酶的分泌明显增加, 并决定着患者病症的严重程度. MCs的活化及其脱颗粒、类胰蛋白酶的释放是引起IBS的重要原因.

■创新盘点
本文阐述了MCs在IBS发病中的作用, 将各方面理论观点联系起来, 更好的集中说明相关问题.

3 肥大细胞在脑肠轴中的作用

近年来许多研究证明中枢神经系统在多个水平参与信号通路调节而影响胃肠运动, 参与IBS的发病过程[30,31]. 有研究表明, IBS患者对外周刺激表现出中枢的高反应性, 同时对中枢的应激事件表现出内脏的高敏感性[32]. Newson等[33]、Stead等[34]、Bauer等[35] 3项研究均发现MCs与胃肠黏膜的神经纤维联系紧密, 提示MCs在IBS的病理生理过程中可能发挥着重要的作用, 在肠道和神经系统之间可能是他们相互联系和相互影响的一种中间媒介. 杨云生等[36]应用组织化学染色法检测了19名正常人及20例IBS患者回盲部MCs的计数, 同时应用免疫组织化学和电镜观察研究MCs与神经纤维的关系. 结果显示IBS患者回盲部MCs计数明显增多; 神经纤维与MCs密切毗邻, 相邻的神经纤维多是无髓神经纤维. 无髓神经纤维是内脏的传入纤维, 主要传导内脏的慢痛. Park等[37]通过电镜对14名腹泻型IBS-D患者和14名正常人结肠与直肠活检标本MCs观察发现, 除了MCs数量明显增加外, 在肠神经附近活化MCs明显多于其他部位. 来自MCs的组胺、5-HT、血小板活化因子、前列腺素、细胞因子和白三烯等活性物质有激活内脏传入神经的潜能[38], 可能通过作用于肠神经系统, 产生胃肠道不适症状和高敏感性[39]. 有证据表明肠MCs同时受到中枢神经系统的支配[40-42], 当一些精神心理因素如焦虑、抑郁等便会造成肠道动力及分泌异常、内脏高敏感性等外周情况. 脑干兴奋神经元通过释放促甲状腺激素释放激素(thyrotropin-releasing hormone, TRH)激发小鼠黏

膜MCs脱颗粒进一步证明中枢系统与MCs之间的紧密联系[43]. Levy等[44]的实验也证实, 通过诱导MCs脱颗粒可直接作用于背侧角神经元, 造成疼痛及感觉高敏感. 并且与神经节部位相一致. Barbara等[13]也发现肠神经纤维毗邻部位的MCs数目与IBS患者腹痛频率和程度呈正相关, 认为MCs的浸润和介质释放与IBS患者腹痛感觉高敏有关.

4 肥大细胞与感染免疫

有研究表明, 在感染性胃肠炎患者中, 有相当一部分会发展为IBS[45-47], 即感染后IBS(post-infective IBS, PI-IBS), 说明肠道感染在IBS的发病机理中起重要作用. 1997年Neal等[48]对544例急性胃肠炎患者进行随访发现, 在急性肠道感染6 mo后肠功能紊乱发生率是25%, 即使在清除病原体及肠黏膜炎症消退之后, 仍有患者存在IBS样症状. 胃肠道黏膜是人体内接触外界抗原面积最大的屏障体系, 他和存在于肠道黏膜层及黏膜固有层的大量免疫细胞共同抵御微生物、大分子抗原物质及其他有害物质的入侵. 而在肠道通透性改变和黏膜免疫上, MCs及其产物发挥了重要作用[49]. 一项对PI-IBS患者的研究发现[50], 患者末端回肠和直肠乙状结肠MCs数目与正常组比较明显增多、活化, 5-HT阳性迷走神经纤维密度亦明显增加, 且与MCs联系紧密. MCs活化分数与IBS患者的症状指数呈正相关, 即MCs活化分数越高, 症状指数也越高. MCs可被细菌、寄生虫或食物抗原等诱导合成和释放具有生物活性的组胺、5-HT、胰蛋白酶、前列腺素、白三烯等介质, 这些物质大多具致痛作用, 可能与IBS患者对消化**系痛觉的高敏感性有**关[14], 而组胺、5-HT分别作用于肠黏膜及肠平滑肌上的相应受体, 可影响到胃肠道的分泌和运动, 增加肠黏膜通透性和高敏感[51-53]. 近年来提出, 肠道感染后, 肠道黏膜炎症影响局部免疫-神经-内分泌网络, 并引起IBS症状, 但是具体机制仍不明确. 针对MCs、5-HT、SP与CGRP等这些参与免疫-神经-内分泌网络机制的关键性因子, 研究他们之间的联系有着重大的意义.

5 相应干预方法的研究

近年来, 随着对MCs在IBS发病机制重要性的认识逐渐深入, 针对MCs干预方法的探讨研究也逐渐受到关注. 早在1980年, Bolin等[54]在其研究中发现与对照组相比, 40%的IBS患者在使用色甘酸钠后症状有明显改善. Lunardi等[55]、Stefanini等[56]的研究也证实色甘酸钠可缓解IBS腹痛和腹部不适症状. 但上述研究由于样本量较少, 试验设计不够严谨(如无对照组、未遵循盲法、**治**疗时间过短、**缺乏后期随访**). **Klooker等**[57]通过对60例IBS患者随机分组, 分别给予酮替芬和安慰剂治疗, 结果显示酮替芬可明显改善内脏敏感性IBS患者的IBS症状, 提高生活质量. 在一项随机、双盲、安慰剂对照实验中, 与安慰剂相比, 美沙拉嗪能显著降低免疫细胞特别是抑制肥大细胞, 同时观察到患者整体状况的改善及腹痛的减轻, 尽管尚未达到统计学意义[58]. 而对肥大细胞分泌活性介质的拮抗剂(类胰蛋白酶抑制剂[20]、抗组胺剂[59]、抗白三烯药物[60]、布地奈德等[61])的研究也显示有着极大前景. 在中药方面, 胡瑞等[62]的研究表明与IBS-D型模型组大鼠相比, 模型组血清5-HT、**NO水平下降, SP含**量增加、MCs数目增多; 高、中剂量胃肠安丸可上调血清5-HT、**NO水平; 下调SP表达、减少**MCs数目. 据此推测, 胃肠安丸止泻的机制可能与其调节5-HT、NO水平, 进而参与调整胃肠动力有关; 亦可能通过抑制SP表达、减少MCs数目, 从而降低内脏高敏感性. 对中药在IBS的疗效进一步研究可能开辟新的治疗途径.

6 结论

IBS患者肠黏膜MCs的数目和脱颗粒功能的改变, 并由此影响局部肠黏膜类胰蛋白酶、5-HT浓度和其他可能与内脏感觉调控相关的介质水平, 并可能在PI-IBS内脏高敏感, 免疫应答的发生中发挥一定作用. 对肠黏膜MCs及其分泌的活性介质功能的研究, 特别是其参与将有助于揭示IBS发病机制的核心环节, 并由此推动治疗IBS的相关药物的研究进展. 而MCs与神经-免疫-内分泌系统间的联系将是以后研究的热点.

■应用要点

IBS发病机制尚不十分明确, 临床多采用对症治疗. 随着人们对MCs在IBS发病中发挥作用更为深入的认识, 各种针对MCs作用新型药物的研制开发可能会给IBS患者带来福音.

7 参考文献

1 Barbara G, Cremon C, Carini G, Bellacosa L, Zecchi L, De Giorgio R, Corinaldesi R, Stanghellini V. The immune system in irritable bowel syndrome. *J Neurogastroenterol Motil* 2011; 17: 349-359

2 Choung RS, Locke GR. Epidemiology of IBS. *Gastroenterol Clin North Am* 2011; 40: 1-10

3 Barbara G, De Giorgio R, Stanghellini V, Cremon C, Salvioli B, Corinaldesi R. New pathophysiological mechanisms in irritable bowel syndrome. *Aliment Pharmacol Ther* 2004; 20 Suppl 2: 1-9

4 Galli SJ, Grimbaldeston M, Tsai M. Immunomodulatory mast cells: negative, as well as positive, regulators of immunity. *Nat Rev Immunol* 2008; 8: 478-486

5 Metz M, Siebenhaar F, Maurer M. Mast cell functions in the innate skin immune system. *Immunobi-*

■同行评价
本文立题有依据, 内容集中, 观点明确, 阐明了MCs在IBS发病中的作用, 对临床IBS发病机制的研究和临床治疗有一定的参考意义.

ology 2008; 213: 251-260
6 Taylor ML, Metcalfe DD. Mast cells in allergy and host defense. *Allergy Asthma Proc* 2001; 22: 115-119
7 陈丽珠, 王承党. 肥大细胞相关介质在肠易激综合征发病机制中的作用. 国际消化病杂志 2010; 30: 325-328
8 Gui XY. Mast cells: a possible link between psychological stress, enteric infection, food allergy and gut hypersensitivity in the irritable bowel syndrome. *J Gastroenterol Hepatol* 1998; 13: 980-989
9 Park JH, Rhee PL, Kim HS, Lee JH, Kim YH, Kim JJ, Rhee JC. Mucosal mast cell counts correlate with visceral hypersensitivity in patients with diarrhea predominant irritable bowel syndrome. *J Gastroenterol Hepatol* 2006; 21: 71-78
10 Spiller R, Garsed K. Infection, inflammation, and the irritable bowel syndrome. *Dig Liver Dis* 2009; 41: 844-849
11 Weston AP, Biddle WL, Bhatia PS, Miner PB. Terminal ileal mucosal mast cells in irritable bowel syndrome. *Dig Dis Sci* 1993; 38: 1590-1595
12 姜敏, 李红菊, 汤浩, 张义侠, 傅宝玉. 肥大细胞在肠易激综合征患者结肠的分布特点及其作用. 中国医科大学学报 2005; 34: 335-336
13 Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, Pasquinelli G, Morselli-Labate AM, Grady EF, Bunnett NW, Collins SM, Corinaldesi R. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* 2004; 126: 693-702
14 Barbara G, Wang B, Stanghellini V, de Giorgio R, Cremon C, Di Nardo G, Trevisani M, Campi B, Geppetti P, Tonini M, Bunnett NW, Grundy D, Corinaldesi R. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. *Gastroenterology* 2007; 132: 26-37
15 Piche T, Saint-Paul MC, Dainese R, Marine-Barjoan E, Iannelli A, Montoya ML, Peyron JF, Czerucka D, Cherikh F, Filippi J, Tran A, Hébuterne X. Mast cells and cellularity of the colonic mucosa correlated with fatigue and depression in irritable bowel syndrome. *Gut* 2008; 57: 468-473
16 Wang SH, Dong L, Luo JY, Gong J, Li L, Lu XL, Han SP. Decreased expression of serotonin in the jejunum and increased numbers of mast cells in the terminal ileum in patients with irritable bowel syndrome. *World J Gastroenterol* 2007; 13: 6041-6047
17 Abraham WM. Tryptase: potential role in airway inflammation and remodeling. *Am J Physiol Lung Cell Mol Physiol* 2002; 282: L193-L196
18 Mullan CS, Riley M, Clarke D, Tatler A, Sutcliffe A, Knox AJ, Pang L. Beta-tryptase regulates IL-8 expression in airway smooth muscle cells by a PAR-2-independent mechanism. *Am J Respir Cell Mol Biol* 2008; 38: 600-608
19 He SH. Key role of mast cells and their major secretory products in inflammatory bowel disease. *World J Gastroenterol* 2004; 10: 309-318
20 Cenac N, Andrews CN, Holzhausen M, Chapman K, Cottrell G, Andrade-Gordon P, Steinhoff M, Barbara G, Beck P, Bunnett NW, Sharkey KA, Ferraz JG, Shaffer E, Vergnolle N. Role for protease activity in visceral pain in irritable bowel syndrome. *J Clin Invest* 2007; 117: 636-647
21 Yoshii M, Jikuhara A, Mori S, Iwagaki H, Takahashi HK, Nishibori M, Tanaka N. Mast cell tryptase stimulates DLD-1 carcinoma through prostaglandin- and MAP kinase-dependent manners. *J Pharmacol Sci* 2005; 98: 450-458
22 Kayssi A, Amadesi S, Bautista F, Bunnett NW, Vanner S. Mechanisms of protease-activated receptor 2-evoked hyperexcitability of nociceptive neurons innervating the mouse colon. *J Physiol* 2007; 580: 977-991
23 Jacob C, Yang PC, Darmoul D, Amadesi S, Saito T, Cottrell GS, Coelho AM, Singh P, Grady EF, Perdue M, Bunnett NW. Mast cell tryptase controls paracellular permeability of the intestine. Role of protease-activated receptor 2 and beta-arrestins. *J Biol Chem* 2005; 280: 31936-31948
24 李兆申, 董文珠, 邹多武, 满晓华, 邹晓平, 尹宁, 朱爱勇. 肠易激综合征肠黏膜SP、VIP、CGRP变化的研究. 第二军医大学学报 2003; 24: 147-151
25 La JH, Kim TW, Sung TS, Kim HJ, Kim JY, Yang IS. Role of mucosal mast cells in visceral hypersensitivity in a rat model of irritable bowel syndrome. *J Vet Sci* 2004; 5: 319-324
26 Guilarte M, Santos J, de Torres I, Alonso C, Vicario M, Ramos L, Martínez C, Casellas F, Saperas E, Malagelada JR. Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. *Gut* 2007; 56: 203-209
27 Cenac N, Garcia-Villar R, Ferrier L, Larauche M, Vergnolle N, Bunnett NW, Coelho AM, Fioramonti J, Bueno L. Proteinase-activated receptor-2-induced colonic inflammation in mice: possible involvement of afferent neurons, nitric oxide, and paracellular permeability. *J Immunol* 2003; 170: 4296-4300
28 王承党, 郭朝书. 肥大细胞和类胰蛋白酶在腹泻型肠易激综合征升结肠黏膜中的表达及意义. 世界华人消化杂志 2010; 18: 1682-1686
29 Vivinus-Nébot M, Dainese R, Anty R, Saint-Paul MC, Nano JL, Gonthier N, Marjoux S, Frin-Mathy G, Bernard G, Hébuterne X, Tran A, Theodorou V, Piche T. Combination of allergic factors can worsen diarrheic irritable bowel syndrome: role of barrier defects and mast cells. *Am J Gastroenterol* 2012; 107: 75-81
30 Kraneveld AD, Rijnierse A, Nijkamp FP, Garssen J. Neuro-immune interactions in inflammatory bowel disease and irritable bowel syndrome: future therapeutic targets. *Eur J Pharmacol* 2008; 585: 361-374
31 Ohman L, Simrén M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. *Nat Rev Gastroenterol Hepatol* 2010; 7: 163-173
32 Fukudo S, Nomura T, Muranaka M, Taguchi F. Brain-gut response to stress and cholinergic stimulation in irritable bowel syndrome. A preliminary study. *J Clin Gastroenterol* 1993; 17: 133-141
33 Newson B, Dahlström A, Enerbäck L, Ahlman H. Suggestive evidence for a direct innervation of mucosal mast cells. *Neuroscience* 1983; 10: 565-570
34 Stead RH, Dixon MF, Bramwell NH, Riddell RH, Bienenstock J. Mast cells are closely apposed to nerves in the human gastrointestinal mucosa. *Gastroenterology* 1989; 97: 575-585
35 Bauer O, Razin E. Mast Cell-Nerve Interactions. *News Physiol Sci* 2000; 15: 213-218
36 杨云生, 周殿元, 张万岱, 张振书, 宋于刚. 肠易激综合征回盲部肥大细胞的研究. 中华内科杂志 1997; 36: 231-233
37 Park CH, Joo YE, Choi SK, Rew JS, Kim SJ, Lee MC. Activated mast cells infiltrate in close proximity to enteric nerves in diarrhea-predominant irritable bowel syndrome. *J Korean Med Sci* 2003; 18: 204-210
38 Vergnolle N, Bunnett NW, Sharkey KA, Brussee

V, Compton SJ, Grady EF, Cirino G, Gerard N, Basbaum AI, Andrade-Gordon P, Hollenberg MD, Wallace JL. Proteinase-activated receptor-2 and hyperalgesia: A novel pain pathway. *Nat Med* 2001; 7: 821-826
39 Grundy D, Al-Chaer ED, Aziz Q, Collins SM, Ke M, Taché Y, Wood JD. Fundamentals of neurogastroenterology: basic science. *Gastroenterology* 2006; 130: 1391-1411
40 Stead RH, Tomioka M, Quinonez G, Simon GT, Felten SY, Bienenstock J. Intestinal mucosal mast cells in normal and nematode-infected rat intestines are in intimate contact with peptidergic nerves. *Proc Natl Acad Sci U S A* 1987; 84: 2975-2979
41 Williams RM, Berthoud HR, Stead RH. Vagal afferent nerve fibres contact mast cells in rat small intestinal mucosa. *Neuroimmunomodulation* 1997; 4: 266-270
42 Gottwald T, Lhoták S, Stead RH. Effect of truncal vagotomy and capsaicin on mast cells and IgA-positive plasma cells in rat jejunal mucosa. *Neurogastroenterol Motil* 1997; 9: 25-32
43 Santos J, Saperas E, Mourelle M, Antolín M, Malagelada JR. Regulation of intestinal mast cells and luminal protein release by cerebral thyrotropin-releasing hormone in rats. *Gastroenterology* 1996; 111: 1465-1473
44 Levy D, Kainz V, Burstein R, Strassman AM. Mast cell degranulation distinctly activates trigeminocervical and lumbosacral pain pathways and elicits widespread tactile pain hypersensitivity. *Brain Behav Immun* 2012; 26: 311-317
45 Ji S, Park H, Lee D, Song YK, Choi JP, Lee SI. Post-infectious irritable bowel syndrome in patients with Shigella infection. *J Gastroenterol Hepatol* 2005; 20: 381-386
46 Spiller R, Garsed K. Postinfectious irritable bowel syndrome. *Gastroenterology* 2009; 136: 1979-1988
47 Marshall JK, Thabane M, Garg AX, Clark WF, Moayyedi P, Collins SM. Eight year prognosis of postinfectious irritable bowel syndrome following waterborne bacterial dysentery. *Gut* 2010; 59: 605-611
48 Neal KR, Hebden J, Spiller R. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients. *BMJ* 1997; 314: 779-782
49 Ramsay DB, Stephen S, Borum M, Voltaggio L, Doman DB. Mast cells in gastrointestinal disease. *Gastroenterol Hepatol* (N Y) 2010; 6: 772-777
50 Wang LH, Fang XC, Pan GZ. Bacillary dysentery as a causative factor of irritable bowel syndrome and its pathogenesis. *Gut* 2004; 53: 1096-1101
51 Atkinson W, Lockhart S, Whorwell PJ, Keevil B, Houghton LA. Altered 5-hydroxytryptamine signaling in patients with constipation- and diarrhea-predominant irritable bowel syndrome. *Gastroenterology* 2006; 130: 34-43
52 Francis H, Glaser S, Demorrow S, Gaudio E, Ueno Y, Venter J, Dostal D, Onori P, Franchitto A, Marzioni M, Vaculin S, Vaculin B, Katki K, Stutes M, Savage J, Alpini G. Small mouse cholangiocytes proliferate in response to H1 histamine receptor stimulation by activation of the IP3/CaMK I/CREB pathway. *Am J Physiol Cell Physiol* 2008; 295: C499-C513
53 Schneider E, Rolli-Derkinderen M, Arock M, Dy M. Trends in histamine research: new functions during immune responses and hematopoiesis. *Trends Immunol* 2002; 23: 255-263
54 Bolin TD. Use of oral sodium cromoglycate in persistent diarrhoea. *Gut* 1980; 21: 848-850
55 Lunardi C, Bambara LM, Biasi D, Cortina P, Peroli P, Nicolis F, Favari F, Pacor ML. Double-blind cross-over trial of oral sodium cromoglycate in patients with irritable bowel syndrome due to food intolerance. *Clin Exp Allergy* 1991; 21: 569-572
56 Stefanini GF, Saggioro A, Alvisi V, Angelini G, Capurso L, di Lorenzo G, Dobrilla G, Dodero M, Galimberti M, Gasbarrini G. Oral cromolyn sodium in comparison with elimination diet in the irritable bowel syndrome, diarrheic type. Multicenter study of 428 patients. *Scand J Gastroenterol* 1995; 30: 535-541
57 Klooker TK, Braak B, Koopman KE, Welting O, Wouters MM, van der Heide S, Schemann M, Bischoff SC, van den Wijngaard RM, Boeckxstaens GE. The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. *Gut* 2010; 59: 1213-1221
58 Corinaldesi R, Stanghellini V, Cremon C, Gargano L, Cogliandro RF, De Giorgio R, Bartesaghi G, Canovi B, Barbara G. Effect of mesalazine on mucosal immune biomarkers in irritable bowel syndrome: a randomized controlled proof-of-concept study. *Aliment Pharmacol Ther* 2009; 30: 245-252
59 Jakate S, Demeo M, John R, Tobin M, Keshavarzian A. Mastocytic enterocolitis: increased mucosal mast cells in chronic intractable diarrhea. *Arch Pathol Lab Med* 2006; 130: 362-367
60 Fee WH. Irritable bowel syndrome helped by montelukast. *Chest* 2002; 122: 1497
61 Sokol H, Georgin-Lavialle S, Grandpeix-Guyodo C, Canioni D, Barete S, Dubreuil P, Lortholary O, Beaugerie L, Hermine O. Gastrointestinal involvement and manifestations in systemic mastocytosis. *Inflamm Bowel Dis* 2010; 16: 1247-1253
62 胡瑞, 唐方. 胃肠安丸对IBS-D大鼠血清NO, 5-HT及结肠组织SP, MC的影响. 中国中药杂志 2009; 34: 3073-3077

编辑 曹丽鸥 电编 鲁亚静