DOI: 10.16781/j.CN31-2187/R.20230315

·专题报道·

肥大细胞参与子宫内膜异位症疼痛机制的研究进展

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［摘要］ 疼痛是子宫内膜异位症最常见和最严重的症状，目前尚无有效的治疗方法，且疼痛机制仍然不明。肥大细胞是一种可以与感觉神经相互作用、介导疼痛的免疫细胞，近年来研究发现肥大细胞在子宫内膜异位症疼痛发生中发挥重要作用。本文总结了肥大细胞通过炎症反应、血管生成、神经生长、外周和中枢神经敏化等途径参与子宫内膜异位症疼痛发生机制的最新进展，以期为子宫内膜异位症疼痛的机制研究和临床治疗开拓新思路。

［关键词］ 子宫内膜异位症；疼痛；肥大细胞；炎症；血管生成；神经生长；神经敏化
［引用本文］ 毛心齐，张信美. 肥大细胞参与子宫内膜异位症疼痛机制的研究进展[J]. 海军军医大学学报，2024，45(9)：1089-1096. DOI: 10.16781/j.CN31-2187/R.20230315.

Role of mast cells in development of endometriosis pain: research progress

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［Abstract］ Pain is the most common and severe symptom of endometriosis. However, there is no effective treatment nowadays, and the mechanism of endometriosis pain remains poorly defined. Mast cells are immune cells that can interact with sensory nerves to induce endometriosis pain. Recent studies have shown that mast cells play a vital role in the development of endometriosis pain. This article summarizes the latest research to highlight advances in mast cells involving in endometriosis pain through inflammatory response, angiogenesis, nerve growth, and peripheral and central sensitization, hoping to provide new ideas for the mechanism research and clinical treatment of endometriosis pain.

［Key words］ endometriosis; pain; mast cells; inflammation; angiogenesis; nerve growth; neurosensitization
［Citation］ MAO X, ZHANG X. Role of mast cells in development of endometriosis pain: research progress[J]. Acad J Naval Med Univ, 2024, 45(9): 1089-1096. DOI: 10.16781/j.CN31-2187/R.20230315.

子宫内膜异位症（endometriosis，EM）是发生在育龄期女性、以疼痛与不孕为主要临床症状的一种妇科常见病，属于雌激素依赖性的慢性免疫炎症性疾病。疼痛是EM的特征性临床症状，包括痛经、性交痛及慢性盆腔疼痛等。虽然研究发现高达90%的EM患者伴有不同程度与不同类型的疼痛症状，但EM疼痛的机制至今未明，严重影响妇女的身心健康及生活质量[1-3]。目前的研究表明EM疼痛是一种神经炎症性疼痛，其机制包括EM患者局部腹腔液与病灶中免疫细胞数量增加、活性增强并分泌大量炎症因子，以及病灶神经纤维异常生长导致外周与中枢神经敏化等[4-6]。

肥大细胞是一种几乎分布于全身各个器官的多功能免疫细胞。在人类，肥大细胞根据其分泌颗粒所含蛋白酶不同大体分为两个亚型：仅含有类胰蛋白酶的肥大细胞（trypase positive, chymase negative mast cell；MCT）和同时含有类胰蛋白酶及类糜蛋白酶的肥大细胞（tryptase positive, chymase positive mast cell；MCTC）。MCT常存在于胃肠道和呼吸道黏膜，又称为黏膜肥大细胞；而MCTC多存在于结缔组织中，又称为结缔组织肥大细胞[7]。肥大细胞可以通过免疫途径和非免疫途径活化脱颗粒，先释放储存的介质如组胺，然后进一步合成、释放其他炎症介质。它能针对各种不同的内外刺激进行信息加工，向下游传递各自的信号，导致不同的生物学效应。肥大细胞除了介导一

［收稿日期］ 2023-06-07　［接受日期］ 2023-11-09
［基金项目］ 国家自然科学基金面上项目（82171636）. Supported by General Program of National Natural Science Foundation of China (82171636).
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系列速发型超敏反应和变态反应性疾病的发生外，还能介导炎症性疾病的发生，在Ⅰ型超敏反应、先天性与获得性免疫、神经系统疾病、肿瘤、炎症与感染、损伤修复、生殖系统疾病等多个领域中发挥重要的生理与病理作用[8-13]。

近年来研究发现，肥大细胞能够被雌激素激活，并脱颗粒分泌炎症介质或细胞因子促进EM病灶血管生成与神经生长，在EM疼痛发生机制中发挥关键作用[3,14-17]。本文就近年来有关肥大细胞通过炎症反应、血管生成、神经生长及神经敏化等信号通路参与EM疼痛发生机制的最新进展作一综述。

1　EM疼痛的可能机制

1.1　*炎症*　目前最广为接受的EM病因是Sampson提出的“经血逆流”理论：月经期间，活跃的子宫内膜细胞和组织碎片随经血通过输卵管收缩进入盆腔，附着在盆腔结构表面，从而诱发局部免疫反应[18]，募集各种免疫细胞（如中性粒细胞、巨噬细胞、肥大细胞、自然杀伤细胞和T细胞）；免疫细胞分泌炎症介质，维持和进一步扩大炎症微环境[19]，同时释放IL-6、IL-8、TNF-α和前列腺素E2（prostaglandin E2，PGE2）等致痛因子，这些介质都能够直接激活感觉神经末梢，产生周期性疼痛[20-21]。

1.2　*神经和血管生成*　异位子宫内膜可以通过神经和血管生成的过程募集神经和血管供应。在EM病灶中发现，小的无髓鞘神经纤维（包括感觉传入神经、交感神经和副交感神经传出神经等）密度增加[22-24]。这些无髓鞘神经纤维多为C型纤维感觉传入神经，通常作为痛觉感受器，因此病灶神经密度增高与EM疼痛相关，提示病灶处神经生长在EM疼痛发生中发挥重要作用[25]。而血管生成保证了EM病灶的血液和氧气供应，支持病灶的生长和建立，是EM发展和持续所必需的。血管生成通常与神经发生伴行，有助于病灶中神经纤维的侵入和活化[26]。

1.3　*外周神经敏化*　外周神经敏化是指外周的伤害性神经元对伤害性刺激的反应增加和阈值降低[27]，研究已证实EM小鼠支配盆腔的感觉传入神经发生敏化[28]。EM中免疫细胞（如肥大细胞）和外周神经纤维相互作用构成“神经源性炎症”环境，正反馈回路的存在导致神经纤维的持续兴奋，引起痛觉感受器长期过敏[29]。同时，EM病灶中TNF-α[30]、P物质（substance P，SP）[31]、瞬态电位感受器阳离子通道v1（transient receptor potential cation channel, subfamily V, member 1；Trpv1）[32-33]等致痛介质或伤害性离子通道表达上调，进一步驱动外周痛觉感受器的敏化，这可能是导致EM疼痛持续存在的原因。

1.4　*中枢神经敏化*　致敏神经末梢产生的动作电位传入脊髓背角，并刺激二级投射神经元；而脊髓背根神经节（dorsal root ganglia，DRG）细胞的持续兴奋会导致感觉传入的长期中枢敏化。中枢神经敏化使中枢神经系统在没有伤害性刺激的情况下仍然长期处于过度兴奋状态，这解释了在手术病灶切除后患者仍出现持续疼痛以及诊断的病变评分与疼痛强度无关的原因[2,34-35]。同时，中枢神经敏化不仅可以使损伤区域产生长期的“疼痛记忆”，还可引起看似不相关区域的“异位疼痛”。研究发现EM模型动物出现了对阴道和结直肠膨胀、膀胱功能改变、热刺激、机械性伤害等不同有害刺激的异位痛和痛觉过敏[5]，同时脊髓背角内的神经胶质细胞激活，伤害性感觉神经元发生敏化[28]。丘脑及脑岛等区域是与疼痛处理密切相关的大脑区域，在急性和慢性疼痛状态下会被持续激活。通过磁共振功能成像和地西泮刺激试验发现，与健康女性相比，EM患者的前脑岛区域谷氨酸等兴奋性神经递质水平增加[36]，功能连通性改变[37]，γ-氨基丁酸A型受体的抑制功能受损[38]。这些证据都表明EM患者会出现中枢神经敏化，但潜在机制仍不清楚。

2　肥大细胞在EM疼痛中的作用

EM患者病灶中肥大细胞总数与脱颗粒数量显著上调，而这些被激活脱颗粒的肥大细胞几乎全部沿着EM病灶间质中的神经纤维分布，且非常靠近神经纤维[22]。同时，病灶中脱颗粒的肥大细胞数量与患者疼痛的严重程度呈正相关[14]。在EM大鼠模型中，除了证实模型病灶中肥大细胞总数与脱颗粒数量较假手术组明显上调外，还发现模型大鼠DRG组织中肥大细胞总数与脱颗粒数量较假手术组也呈现显著上调。模型大鼠病灶及DRG组织中的脱颗粒肥大细胞数量与模型大鼠热痛觉和机械痛觉的阈值呈负相关。给予模型大鼠肥大细胞稳定剂色甘酸二钠或酮替芬后，模型大鼠病灶及DRG组织中肥大细胞总数与脱颗粒数量均显著减少，模型大鼠热痛觉和机械痛觉的阈值均显著增高[39]。以上这些结果提示肥大细胞直接参与EM疼痛的发生。

EM病灶中被激活的肥大细胞可分泌多种炎症介质，包括TNF-α[40]、血管内皮生长因子（vascular endothelial growth factor，VEGF）[41]、神经生长因子（nerve growth factor，NGF）[42]、IL-1[43]、IL-6[44-45]等。这些介质不仅能够引起外周感觉神经的募集、增生和敏化，还可引起新生血管形成，对病灶中神经纤维起支持作用。同时，被活化的外周感觉神经可释放炎症介质进一步激活肥大细胞，放大EM病灶局部炎症微环境，使外周神经纤维长期受刺激，形成外周神经敏化，并通过神经传递最终引起中枢神经敏化[46]，维持EM慢性疼痛。

3　肥大细胞介导EM疼痛的具体机制

3.1　*肥大细胞介导EM炎症反应放大*　Zhu等[39]在EM大鼠模型研究中发现，模型大鼠TNF-α、VEGF、NGF、IL-6及细胞黏附分子的表达水平显著增高，当给予肥大细胞稳定剂色甘酸二钠或酮替芬后，随着大鼠模型EM病灶中肥大细胞总数和脱颗粒肥大细胞数量的显著减少，EM病灶中的TNF-α、VEGF、NGF、IL-6及细胞黏附分子的表达水平也显著下降，而模型大鼠热痛觉和机械痛觉的阈值却显著增高。这提示EM病灶局部微环境可促使肥大细胞活化，活化的肥大细胞分泌各种炎症介质，通过炎症疼痛信号通路参与EM疼痛发生过程。

研究发现，EM的高雌激素环境可以上调异位子宫内膜细胞上干细胞因子（stem cell factor，SCF）、TGF-β和单核细胞趋化因子1（monocyte chemoattractant protein-1，MCP1）的表达[14]，促进肥大细胞的迁移、成熟、增殖和激活[47-50]。同时，雌激素还可以触发肥大细胞释放NGF，引发神经性疼痛[14]。

在另一项研究中，雌激素通过雌激素反应元件（estrogen responsive element，ERE）活化肥大细胞，激活核受体雌激素受体α（estrogen receptor-α，ER-α），并使NOD样受体热蛋白结构域相关蛋白3（NOD-like receptor family pyrin domain containing 3，NLRP3）表达上调。NLRP3的升高诱导钾离子外流，激活NLRP3炎症小体信号通路，促使IL-1β成熟和分泌[51]。IL-1β是与神经性疼痛相关的一个“疼痛基因”，可以介导痛风性关节炎疼痛和偏头痛的发生[52-53]，目前研究证实EM疼痛组患者腹腔液中IL-1β较非疼痛组显著升高[20]，且IL-1β可以增加EM病灶的神经支配[54]，提示EM病灶中的肥大细胞可以通过核启动的雌激素信号通路促进EM疼痛的发生。

3.2　*肥大细胞促进EM病灶血管生成*　肥大细胞具有合成和释放强效血管生成细胞因子的能力，如VEGF[41]、成纤维细胞生长因子2（fibroblast growth factor 2，FGF-2）[55]、TGF-β[56]、TNF-α[40]和IL-8[57]等。其中，VEGF是最有效的促血管生成因子，能够通过其在内皮细胞上的血管内皮生长因子受体（vascular endothelial growth factor receptor，VEGFR）2与神经纤毛蛋白1（neuropilin-1，NRP-1）调节内皮细胞的生存、增生及凋亡，促进新生血管生成[58]，以维持EM的发生、发展；还能够通过其在神经轴突上的VEGFR1调节神经生长，诱发神经性痛觉过敏和异常性疼痛[59]。与安慰剂治疗组相比，对EM大鼠模型给予靶向肥大细胞的超微粒化棕榈酰乙醇酰胺（palmitoylethanolamide，PEA）后，病灶中肥大细胞数量减少，血管数量减少，VEGF及其受体VEGFR2也明显减少，EM的血管生成和疼痛行为均得到有效缓解[60]。这提示EM病灶局部微环境中的肥大细胞可以通过调控VEGF/VEGFR2轴促进EM病灶血管生成和神经生长，参与疼痛发生过程。

另外，将肥大细胞与子宫内膜细胞进行共培养发现，肥大细胞上C-C基序趋化因子配体8（C-C motif chemokine ligand 8，CCL8）表达上调。CCL8增加了内皮细胞的增殖、迁移和管状形成能力，有效促进血管生成。给予其受体C-C基序趋化因子受体1（C-C motif chemokine receptor 1，CCR1）拮抗剂BX471后，病灶数量和血管密度均显著减少，EM的发生和血管生成被抑制[15]。由此可见，肥大细胞可以通过CCL8/CCR1轴促进EM病灶的新生血管生成，但通过该途径介导EM疼痛的具体机制还需进一步研究。

3.3　*肥大细胞促进EM病灶神经生长*　EM病灶中的肥大细胞位于初级传入神经末梢附近，受雌激素刺激活化的肥大细胞释放NGF[14]等活性介质，直接影响神经末梢，促进神经增生和疼痛发生[61]。NGF是交感神经元和感觉神经元发育和存活所必需的营养因子[62]，可通过其在神经轴突上的酪氨酸激酶受体A（tyrosine kinase A，TrkA）调控神经元的发育、分化、生长和再生[63]。在EM病灶中，神经生长和血管形成密不可分，研究发现NGF还能够通过TrkA和下游信号通路如PI3K和ERK的控制，调节内皮细胞新生血管形成[64]。对EM模

型大鼠给予NGF siRNA治疗发现，EM病灶的交感和感觉神经纤维密度、血管密度均降低，全身痛觉过敏得到改善[65]，提示肥大细胞释放的NGF能够通过自身受体作用于周围神经和血管内皮，促进病变部位神经和血管生成，有潜力成为治疗EM疼痛的一个靶点。

Xu等[16]研究发现雌激素也可与巨噬细胞膜上的G蛋白偶联雌激素受体30（G-protein-coupled estrogen receptor 30，GPR30）结合，介导丝裂原活化蛋白激酶激酶（mitogen-activated protein kinase kinase，MEK）/ERK通路，使肥大细胞释放纤维细胞生长因子2（fibroblast growth factor 2，FGF2）。FGF2是一种神经营养因子，可以维持和促进神经元的存活、生长、成熟[66-67]。EM局部病灶处的肥大细胞分泌FGF2，与周围神经上的成纤维细胞生长因子受体1（fibroblast growth factor receptor 1，FGFR1）相互作用，促进神经轴突生长，引起EM疼痛[16]。

3.4　肥大细胞参与EM外周神经敏化　EM病变部位的炎症反应持续加重，分布于神经周围的肥大细胞持续大量释放组胺、NGF、VEGF、SP等活性介质，不断刺激外周感觉神经，促使外周神经敏化。同时，被激活的神经纤维末梢释放促炎调节剂，包括SP和降钙素基因相关肽（calcitonin gene-related peptide，CGRP）等神经肽[23,68]，引起肥大细胞的募集和活化。被激活的肥大细胞脱颗粒释放组胺、神经肽和其他致痛介质，进一步刺激感觉神经[69-70]，使外周感觉神经持续受到刺激，神经元激活阈值下降，从而维持外周痛觉感受器的长期过敏，使EM疼痛持续存在。

通过体外共培养肥大细胞和DRG细胞发现，雌激素刺激的肥大细胞分泌NGF，可以上调DRG细胞中电压门控钠离子通道（voltage-gated sodium channel，Nav）1.8和Trpv1的表达[14]，有可能促进EM神经敏化[71-73]。肥大细胞所释放的TNF-α可使痛觉感受器释放CGRP，促进外周神经中的Aβ和C型纤维敏化[74]。TNF-α还可通过NK-κB、p38-MAPK、信号转导及转录激活因子3（signal transduction and activator of transcription 3，STAT3）等信号通路上调Nav1.3、Nav1.6、Nav1.7在DRG中的表达[75]，通过调节疼痛信号转导引起外周神经致敏。此外，肥大细胞释放的组胺[76]、PGE2[73]、IL-1β[77]、IL-6[78]等炎症介质也参与了外周神经敏化的过程。

由此可见，在EM神经源性炎症的正反馈环路中，病变部位的肥大细胞与外周神经发生相互作用，肥大细胞活化并持续释放NGF、TNF-α、IL-1β、IL-6、PGE2等致痛介质，降低神经元激活阈值，增加痛觉感受器的反应性，进而加重EM的外周神经敏化，维持EM慢性疼痛。

3.5　肥大细胞参与EM中枢神经敏化　肥大细胞可以从所在的神经纤维区域迁移到脊髓[79]，调节神经活动和痛觉。EM大鼠模型的脊髓中肥大细胞数量显著增加，浸润程度与中枢神经敏化导致的内脏敏感程度相关。脊髓部位的肥大细胞脱颗粒释放NGF，上调*c-Fos*基因表达，引起神经活化和神经增敏[80]。这提示在EM中，肥大细胞可以迁移至脊髓处，释放致痛介质，促进神经细胞的活化和致敏，从而诱发中枢神经敏化。

肥大细胞也存在于脑膜和包括丘脑在内的大脑不同区域[81-84]，并且会促进疼痛敏化。Kissel等[82]通过构建小鼠脊髓神经结扎模型发现，小鼠丘脑区域肥大细胞脱颗粒数量的增加与小鼠热痛、机械痛阈值的降低密切相关。该研究还证实了NGF、甲醛和强啡肽诱导的痛觉过敏也与小鼠丘脑区域肥大细胞脱颗粒有关，提示位于中枢的肥大细胞可能在痛觉过敏的发展中起作用。

研究表明，在中枢神经系统中的肥大细胞与神经胶质细胞（如星形胶质细胞[85]、小胶质细胞[86]）存在相互作用。肥大细胞在大脑局部的空间上靠近神经胶质细胞与神经元，有利于它们之间的相互作用。肥大细胞释放组胺、IL-6、IL-1β、TNF-α等活性介质，刺激胶质细胞和神经元活化[81]；被激活的胶质细胞随后释放炎症因子（如TNF-α、IL-1β、IL-6、IL-10等）、活性氧和一氧化氮[12,87-88]，极大地放大了炎症反应，引发和维持神经性疼痛。同时，活化的胶质细胞和神经元还可以释放CCL2来招募和激活肥大细胞[89]。这表明中枢神经系统中的肥大细胞脱颗粒释放神经介质，与神经胶质细胞相互作用，放大神经炎症反应，加剧痛觉过敏，在介导中枢神经敏化中起着关键作用。Bashir等[90]研究发现EM小鼠模型的大脑中胶质细胞广泛激活，表明胶质细胞可能参与EM中枢神经敏化过程，但是在大脑区域的肥大细胞与胶质细胞互相作用介导EM疼痛的具体机制还需要进一步研究。

4 小　结

肥大细胞在EM疼痛的发生中扮演着重要角色。EM病灶局部微环境可激活肥大细胞，肥大细胞活化、脱颗粒并释放各种炎症介质，通过炎症疼痛信号通路机制参与EM疼痛发生。肥大细胞合成和分泌VEGF等细胞因子，并与病灶中的子宫内膜细胞串扰，促进和维持病灶的血管生成；肥大细胞还可释放NGF和FGF2等关键蛋白，直接作用于神经末梢，调节外周神经的生长和敏化。另外，肥大细胞可以与外周神经元、中枢神经系统的胶质细胞发生相互作用，放大神经源性炎症，促进外周神经和中枢神经敏化，形成EM的“疼痛记忆”，从而维持EM慢性疼痛过程。

肥大细胞在介导EM神经源性炎症和痛觉过敏中的作用正越来越受到关注。研究肥大细胞在EM病灶中活化、脱颗粒、释放炎症介质从而激活和敏化周围神经这一过程的关键基因和蛋白，是目前研究肥大细胞在EM疼痛发生机制中作用的重要任务。进一步研究肥大细胞与神经元、胶质细胞互相作用，促进和维持神经源性炎症，引起EM外周神经敏化和中枢神经敏化的具体分子机制，有可能为EM疼痛的治疗提供新思路。

[参 考 文 献]

[1] LINDGREN S, RICHARDSON L. Endometriosis pain and epistemic community: mapping discourses in online discussions among sufferers[J]. Soc Sci Med, 2023, 326: 115889. DOI: 10.1016/j.socscimed.2023.115889.

[2] ASHKENAZI M S, HUSEBY O L, KROKEN G, et al. The clinical presentation of endometriosis and its association to current surgical staging[J]. J Clin Med, 2023, 12(7): 2688. DOI: 10.3390/jcm12072688.

[3] MCCALLION A, NASIRZADEH Y, LINGEGOWDA H, et al. Estrogen mediates inflammatory role of mast cells in endometriosis pathophysiology[J]. Front Immunol, 2022, 13: 961599. DOI: 10.3389/fimmu.2022.961599.

[4] NISHIMOTO-KAKIUCHI A, SATO I, NAKANO K, et al. A long-acting anti-IL-8 antibody improves inflammation and fibrosis in endometriosis[J]. Sci Transl Med, 2023, 15(684): eabq5858. DOI: 10.1126/scitranslmed.abq5858.

[5] CASTRO J, MADDERN J, GRUNDY L, et al. A mouse model of endometriosis that displays vaginal, colon, cutaneous, and bladder sensory comorbidities[J]. FASEB J, 2021, 35(4): e21430. DOI: 10.1096/fj.202002441R.

[6] ZONG C, SUN L, XU X, et al. *Huayu Sanjie* enema liquid relieves pain in endometriosis model rats by inhibiting inflammation, peripheral sensitization, and pelvic adhesion[J]. Evid Based Complement Alternat Med, 2022, 2022: 5256578. DOI: 10.1155/2022/5256578.

[7] GRI G, FROSSI B, D' INCA F, et al. Mast cell: an emerging partner in immune interaction[J]. Front Immunol, 2012, 3: 120. DOI: 10.3389/fimmu.2012.00120.

[8] MAURER M, THEOHARIDES T, GRANSTEIN R D, et al. What is the physiological function of mast cells?[J]. Exp Dermatol, 2003, 12(6): 886-910. DOI: 10.1111/j.0906-6705.2003.0109a.x.

[9] ZHANG S, EDWARDS T N, CHAUDHRI V K, et al. Nonpeptidergic neurons suppress mast cells via glutamate to maintain skin homeostasis[J]. Cell, 2021, 184(8): 2151-2166.e16. DOI: 10.1016/j.cell.2021.03.002.

[10] BAO C, CHEN O, SHENG H, et al. A mast cell-thermoregulatory neuron circuit axis regulates hypothermia in anaphylaxis[J]. Sci Immunol, 2023, 8(81): eadc9417. DOI: 10.1126/sciimmunol.adc9417.

[11] WANG Q, YANG H, LIU Y, et al. Awakening allies for breaking microenvironment barriers: NIR-Ⅱ guided orthogonal activation of tumor-infiltrating mast cells for efficient nano-drug delivery[J]. Adv Healthc Mater, 2023, 12(23): e2300420. DOI: 10.1002/adhm.202300420.

[12] VANGANSEWINKEL T, LEMMENS S, TIANE A, et al. Therapeutic administration of mouse mast cell protease 6 improves functional recovery after traumatic spinal cord injury in mice by promoting remyelination and reducing glial scar formation[J]. FASEB J, 2023, 37(6): e22939. DOI: 10.1096/fj.202201942RR.

[13] VALERO-PACHECO N, TANG E K, MASSRI N, et al. Maternal IL-33 critically regulates tissue remodeling and type 2 immune responses in the uterus during early pregnancy in mice[J]. Proc Natl Acad Sci U S A, 2022, 119(35): e2123267119. DOI: 10.1073/pnas.2123267119.

[14] ZHU T H, DING S J, LI T T, et al. Estrogen is an important mediator of mast cell activation in ovarian endometriomas[J]. Reproduction, 2018, 155(1): 73-83. DOI: 10.1530/rep-17-0457.

[15] LI T, WANG J, GUO X, et al. Possible involvement of crosstalk between endometrial cells and mast cells in the development of endometriosis via CCL8/CCR1[J]. Biomed Pharmacother, 2020, 129: 110476. DOI: 10.1016/j.biopha.2020.110476.

[16] XU X, WANG J, GUO X, et al. GPR30-mediated non-classic estrogen pathway in mast cells participates in endometriosis pain via the production of FGF2[J]. Front Immunol, 2023, 14: 1106771. DOI: 10.3389/fimmu.2023.1106771.

[17] LEMBRECHTS J J, VAN DEN HOOGEN J, AALTO J, et al. Global maps of soil temperature[J]. Glob Chang Biol, 2022, 28(9): 3110-3144. DOI: 10.1111/gcb.16060.

[18] ZONDERVAN K T, BECKER C M, MISSMER S A. Endometriosis[J]. N Engl J Med, 2020, 382(13): 1244-1256. DOI: 10.1056/nejmra1810764.

[19] FAN D, WANG X, SHI Z, et al. Understanding

endometriosis from an immunomicroenvironmental perspective[J]. Chin Med J, 2023, 136(16): 1897-1909. DOI: 10.1097/CM9.0000000000002649.

[20] RAHMAWATI N Y, AHSAN F, SANTOSO B, et al. IL-8 and IL-12p70 are associated with pelvic pain among infertile women with endometriosis[J]. Pain Med, 2023, 24(11): 1262-1269. DOI: 10.1093/pm/pnad080.

[21] CARDOSO J V, MACHADO D E, DA SILVA M C, et al. Influence of interleukin-8 polymorphism on endometriosis-related pelvic pain[J]. Hum Immunol, 2023, 84(10): 561-566. DOI: 10.1016/j.humimm.2023.07.004.

[22] ANAF V, CHAPRON C, EL NAKADI I, et al. Pain, mast cells, and nerves in peritoneal, ovarian, and deep infiltrating endometriosis[J]. Fertil Steril, 2006, 86(5): 1336-1343. DOI: 10.1016/j.fertnstert.2006.03.057.

[23] BOKOR A, KYAMA C M, VERCRUYSSE L, et al. Density of small diameter sensory nerve fibres in endometrium: a semi-invasive diagnostic test for minimal to mild endometriosis[J]. Hum Reprod, 2009, 24(12): 3025-3032. DOI: 10.1093/humrep/dep283.

[24] GUAN Q, VELHO R V, JORDAN A, et al. Nociceptin/orphanin FQ opioid peptide-receptor expression in the endometriosis-associated nerve fibers-possible treatment option?[J]. Cells, 2023, 12(10): 1395. DOI: 10.3390/cells12101395.

[25] WANG G, TOKUSHIGE N, MARKHAM R, et al. Rich innervation of deep infiltrating endometriosis[J]. Hum Reprod, 2009, 24(4): 827-834. DOI: 10.1093/humrep/den464.

[26] LASCHKE M W, MENGER M D. Basic mechanisms of vascularization in endometriosis and their clinical implications[J]. Hum Reprod Update, 2018, 24(2): 207-224. DOI: 10.1093/humupd/dmy001.

[27] FITZCHARLES M A, COHEN S P, CLAUW D J, et al. Nociplastic pain: towards an understanding of prevalent pain conditions[J]. Lancet, 2021, 397(10289): 2098-2110. DOI: 10.1016/S0140-6736(21)00392-5.

[28] CASTRO J, MADDERN J, ERICKSON A, et al. Peripheral and central neuroplasticity in a mouse model of endometriosis[J]. J Neurochem, 2023. DOI: 10.1111/jnc.15843.

[29] VELHO R V, SEHOULI J, MECHSNER S. Mechanisms of peripheral sensitization in endometriosis patients with peritoneal lesions and acyclical pain[J]. Arch Gynecol Obstet, 2023, 308(4): 1327-1340. DOI: 10.1007/s00404-023-07110-9.

[30] TAPMEIER T T, RAHMIOGLU N, LIN J, et al. Neuropeptide S receptor 1 is a nonhormonal treatment target in endometriosis[J]. Sci Transl Med, 2021, 13(608): eabd6469. DOI: 10.1126/scitranslmed.abd6469.

[31] YAN D, LIU X, GUO S W. Neuropeptides substance P and calcitonin gene related peptide accelerate the development and fibrogenesis of endometriosis[J]. Sci Rep, 2019, 9: 2698. DOI: 10.1038/s41598-019-39170-w.

[32] HAYASHI N, KAWAMORITA N, ISHIZUKA Y, et al. Ectopic endometriosis in the pelvic cavity evokes bladder hypersensitivity via transient receptor potential ankyrin 1 hyperexpression in rats[J]. Int Urogynecol J, 2023, 34(6): 1211-1218. DOI: 10.1007/s00192-022-05335-x.

[33] CHEN D, REN Y, JIN J, et al. *Pingchong Jiangni* recipe through nerve growth factor/transient receptor potential vanilloid 1 signaling pathway to relieve pain in endometriosis model rats[J]. J Ethnopharmacol, 2024, 318(Pt A): 116940. DOI: 10.1016/j.jep.2023.116940.

[34] TUCKER D R, NOGA H L, LEE C, et al. Pelvic pain comorbidities associated with quality of life after endometriosis surgery[J]. Am J Obstet Gynecol, 2023, 229(2): 147.e1-147. DOI: 10.1016/j.ajog.2023.04.040.

[35] CASARIN J, GHEZZI F, MUELLER M, et al. Surgical outcomes and complications of laparoscopic hysterectomy for endometriosis: a multicentric cohort study[J]. J Minim Invasive Gynecol, 2023, 30(7): 587-592. DOI: 10.1016/j.jmig.2023.03.018.

[36] AS-SANIE S, KIM J, SCHMIDT-WILCKE T, et al. Functional connectivity is associated with altered brain chemistry in women with endometriosis-associated chronic pelvic pain[J]. J Pain, 2016, 17(1): 1-13. DOI: 10.1016/j.jpain.2015.09.008.

[37] DE BLASIO F M, LOVE S, BARRY R J, et al. Frontocentral delta-beta amplitude coupling in endometriosis-related chronic pelvic pain[J]. Clin Neurophysiol, 2023, 149: 146-156. DOI: 10.1016/j.clinph.2023.02.173.

[38] SANDSTRÖM A, BIXO M, BÄCKSTRÖM T, et al. Altered $GABA_A$ receptor function in women with endometriosis: a possible pain-related mechanism[J]. Acta Obstet Gynecol Scand, 2023, 102(10): 1316-1322. DOI: 10.1111/aogs.14559.

[39] ZHU T H, ZOU G, DING S J, et al. Mast cell stabilizer ketotifen reduces hyperalgesia in a rodent model of surgically induced endometriosis[J]. J Pain Res, 2019, 12: 1359-1369. DOI: 10.2147/jpr.S195909.

[40] CHEN X, LIN L, WU Q, et al. Tumor necrosis factor-α promotes the tumorigenesis, lymphangiogenesis, and lymphatic metastasis in cervical cancer via activating VEGFC-mediated AKT and ERK pathways[J]. Mediators Inflamm, 2023, 2023: 5679966. DOI: 10.1155/2023/5679966.

[41] MARTÍNEZ-AGUILAR L M, IBARRA-SÁNCHEZ A, GUERRERO-MORÁN D J, et al. Lysophosphatidylinositol promotes chemotaxis and cytokine synthesis in mast cells with differential participation of GPR55 and CB2 receptors[J]. Int J Mol Sci, 2023, 24(7): 6316. DOI: 10.3390/ijms24076316.

[42] JIN X, GHARIBANI P, YIN J, et al. Neuro-immune modulation effects of sacral nerve stimulation for visceral hypersensitivity in rats[J]. Front Neurosci, 2021, 15: 645393. DOI: 10.3389/fnins.2021.645393.

[43] OLIVEIRA R G, DAMAZO A S, ANTONIELLI L F, et al. Dilodendron bipinnatum Radlk. extract alleviates ulcerative colitis induced by TNBS in rats by reducing inflammatory cell infiltration, TNF-α and IL-1β concentrations, IL-17 and COX-2 expressions, supporting mucus production and promotes an

antioxidant effect[J]. J Ethnopharmacol, 2021, 269: 113735. DOI: 10.1016/j.jep.2020.113735.
[44] TARUSELLI M T, KOLAWOLE E M, QAYUM A A, et al. Fluvastatin enhances IL-33-mediated mast cell IL-6 and TNF production[J]. Cell Immunol, 2022, 371: 104457. DOI: 10.1016/j.cellimm.2021.104457.
[45] SORIA-CASTRO R, ALFARO-DOBLADO Á R, RODRÍGUEZ-LÓPEZ G, et al. TLR2 regulates mast cell IL-6 and IL-13 production during Listeria monocytogenes infection[J]. Front Immunol, 2021, 12: 650779. DOI: 10.3389/fimmu.2021.650779.
[46] BISCETTI L, CRESTA E, CUPINI L M, et al. The putative role of neuroinflammation in the complex pathophysiology of migraine: from bench to bedside[J]. Neurobiol Dis, 2023, 180: 106072. DOI: 10.1016/j.nbd.2023.106072.
[47] ŁUGOWSKA-UMER H, ZABŁOTNA M, LANGE M, et al. -2518A/G polymorphism of monocyte chemotactic protein 1 (MCP-1/CCL2) is associated with cutaneous mastocytosis[J]. Postepy Dermatol Alergol, 2021, 38(6): 1039-1043. DOI: 10.5114/ada.2021.112277.
[48] NAKANO N, SAIDA K, HARA M, et al. Mucosal mast cell-specific gene expression is promoted by interdependent action of Notch and TGF-β signaling[J]. J Immunol, 2021, 207(12): 3098-3106. DOI: 10.4049/jimmunol.2100112.
[49] WERSHIL B K, TSAI M, GEISSLER E N, et al. The rat c-kit ligand, stem cell factor, induces c-kit receptor-dependent mouse mast cell activation *in vivo*. Evidence that signaling through the c-kit receptor can induce expression of cellular function[J]. J Exp Med, 1992, 175(1): 245-255. DOI: 10.1084/jem.175.1.245.
[50] LUO Y, ZHANG H, YU J, et al. Stem cell factor/mast cell/CCL2/monocyte/macrophage axis promotes Coxsackievirus B3 myocarditis and cardiac fibrosis by increasing Ly6C^{high} monocyte influx and fibrogenic mediators production[J]. Immunology, 2022, 167(4): 590-605. DOI: 10.1111/imm.13556.
[51] GUO X, XU X, LI T, et al. NLRP3 inflammasome activation of mast cells by estrogen via the nuclear-initiated signaling pathway contributes to the development of endometriosis[J]. Front Immunol, 2021, 12: 749979. DOI: 10.3389/fimmu.2021.749979.
[52] RAY P R, SHIERS S, CARUSO J P, et al. RNA profiling of human dorsal root ganglia reveals sex differences in mechanisms promoting neuropathic pain[J]. Brain, 2023, 146(2): 749-766. DOI: 10.1093/brain/awac266.
[53] HE W, LONG T, PAN Q, et al. Microglial NLRP3 inflammasome activation mediates IL-1β release and contributes to central sensitization in a recurrent nitroglycerin-induced migraine model[J]. J Neuroinflammation, 2019, 16(1): 78. DOI: 10.1186/s12974-019-1459-7.
[54] YU J, BERGA S L, ZOU E, et al. Neurotrophins and their receptors, novel therapeutic targets for pelvic pain in endometriosis, are coordinately regulated by IL-1β via the JNK signaling pathway[J]. Am J Pathol, 2023, 193(8): 1046-1058. DOI: 10.1016/j.ajpath.2023.04.007.
[55] WROBLEWSKI M, BAUER R, CUBAS CÓRDOVA M, et al. Mast cells decrease efficacy of anti-angiogenic therapy by secreting matrix-degrading granzyme B[J]. Nat Commun, 2017, 8(1): 269. DOI: 10.1038/s41467-017-00327-8.
[56] ARANGIA A, MARINO Y, FUSCO R, et al. Fisetin, a natural polyphenol, ameliorates endometriosis modulating mast cells derived NLRP-3 inflammasome pathway and oxidative stress[J]. Int J Mol Sci, 2023, 24(6): 5076. DOI: 10.3390/ijms24065076.
[57] CHAKI S, ALKANFARI I, ROY S, et al. Inhibition of orai channel function regulates mas-related G protein-coupled receptor-mediated responses in mast cells[J]. Front Immunol, 2021, 12: 803335. DOI: 10.3389/fimmu.2021.803335.
[58] SHU L, LI X, LIU Z, et al. Bile exosomal miR-182/183-5p increases cholangiocarcinoma stemness and progression by targeting HPGD and increasing PGE2 generation[J]. Hepatology, 2024, 79(2): 307-322. DOI: 10.1097/hep.0000000000000437.
[59] MICHELI L, PARISIO C, LUCARINI E, et al. VEGF-A/VEGFR-1 signalling and chemotherapy-induced neuropathic pain: therapeutic potential of a novel anti-VEGFR-1 monoclonal antibody[J]. J Exp Clin Cancer Res, 2021, 40(1): 320. DOI: 10.1186/s13046-021-02127-x.
[60] IUVONE T, AFFAITATI G, DE FILIPPIS D, et al. Ultramicronized palmitoylethanolamide reduces viscerovisceral hyperalgesia in a rat model of endometriosis plus ureteral calculosis: role of mast cells[J]. Pain, 2016, 157(1): 80-91. DOI: 10.1097/j.pain.0000000000000220.
[61] MWAURA A N, MARSHALL N, ANGLESIO M S, et al. Neuroproliferative dyspareunia in endometriosis and vestibulodynia[J]. Sex Med Rev, 2023, 11(4): 323-332. DOI: 10.1093/sxmrev/qead033.
[62] LINDSAY R M, HARMAR A J. Nerve growth factor regulates expression of neuropeptide genes in adult sensory neurons[J]. Nature, 1989, 337(6205): 362-364. DOI: 10.1038/337362a0.
[63] O-SULLIVAN I, KC R, SINGH G, et al. Sensory neuron-specific deletion of tropomyosin receptor kinase A (TrkA) in mice abolishes osteoarthritis (OA) pain via NGF/TrkA intervention of peripheral sensitization[J]. Int J Mol Sci, 2022, 23(20): 12076. DOI: 10.3390/ijms232012076.
[64] ROMON R, ADRIAENSSENS E, LAGADEC C, et al. Nerve growth factor promotes breast cancer angiogenesis by activating multiple pathways[J]. Mol Cancer, 2010, 9: 157. DOI: 10.1186/1476-4598-9-157.
[65] CHEN Y, LI D, ZHANG Z, et al. Effect of siRNA against β-NGF on nerve fibers of a rat model with endometriosis[J]. Reprod Sci, 2014, 21(3): 329-339. DOI: 10.1177/1933719113497279.
[66] SCHURIG K, ZIERIS A, HERMANN A, et al. Neurotropic growth factors and glycosaminoglycan based matrices to induce dopaminergic tissue formation[J]. Biomaterials, 2015, 67: 205-213. DOI: 10.1016/j.biomaterials.2015.

07.029.
[67] WANG Z, WANG Z, WANG A, et al. The neuroprotective mechanism of sevoflurane in rats with traumatic brain injury via FGF2[J]. J Neuroinflammation, 2022, 19(1): 51. DOI: 10.1186/s12974-021-02348-z.
[68] GREEN D P, LIMJUNYAWONG N, GOUR N, et al. A mast-cell-specific receptor mediates neurogenic inflammation and pain[J]. Neuron, 2019, 101(3): 412-420.e3. DOI: 10.1016/j.neuron.2019.01.012.
[69] VAN REMOORTEL S, TIMMERMANS J P. Mas-related G protein-coupled receptors (Mrgprs) as mediators of gut neuro-immune signaling[J]. Adv Exp Med Biol, 2022, 1383: 259-269. DOI: 10.1007/978-3-031-05843-1_25.
[70] TSENG P Y, HOON M A. GPR15L is an epithelial inflammation-derived pruritogen[J]. Sci Adv, 2022, 8(24): eabm7342. DOI: 10.1126/sciadv.abm7342.
[71] ZHANG D, LI X, JING B, et al. α-Asarone attenuates chronic sciatica by inhibiting peripheral sensitization and promoting neural repair[J]. Phytother Res, 2023, 37(1): 151-162. DOI: 10.1002/ptr.7603.
[72] DE LIMA F O, LAURIA P S S, DO ESPÍRITO-SANTO R F, et al. Unveiling targets for treating postoperative pain: the role of the TNF-α/p38 MAPK/NF-κB/Nav1.8 and Nav1.9 pathways in the mouse model of incisional pain[J]. Int J Mol Sci, 2022, 23(19): 11630. DOI: 10.3390/ijms231911630.
[73] RUIZ-CANTERO M C, CORTÉS-MONTERO E, JAIN A, et al. The sigma-1 receptor curtails endogenous opioid analgesia during sensitization of TRPV1 nociceptors [J]. Br J Pharmacol, 2023, 180(8): 1148-1167. DOI: 10.1111/bph.16003.
[74] CHEN W, SHENG J, GUO J, et al. Tumor necrosis factor-α enhances voltage-gated Na^+ currents in primary culture of mouse cortical neurons[J]. J Neuroinflammation, 2015, 12: 126. DOI: 10.1186/s12974-015-0349-x.
[75] CHOI N R, KWON M J, CHOI W G, et al. The traditional herbal medicines mixture, Banhasasim-Tang, relieves the symptoms of irritable bowel syndrome via modulation of TRPA1, NaV1.5 and NaV1.7 channels[J]. J Ethnopharmacol, 2023, 312: 116499. DOI: 10.1016/j.jep.2023.116499.
[76] AGUILERA-LIZARRAGA J, FLORENS M V, VIOLA M F, et al. Local immune response to food antigens drives meal-induced abdominal pain[J]. Nature, 2021, 590(7844): 151-156. DOI: 10.1038/s41586-020-03118-2.
[77] ZHANG Y Y, LIU F, FANG Z H, et al. Differential roles of NMDAR subunits 2A and 2B in mediating peripheral and central sensitization contributing to orofacial neuropathic pain[J]. Brain Behav Immun, 2022, 106: 129-146. DOI: 10.1016/j.bbi.2022.08.010.
[78] MARINO Y, ARANGIA A, CORDARO M, et al. Analysis of the influence of IL-6 and the activation of the JAK/STAT3 pathway in fibromyalgia[J]. Biomedicines, 2023, 11(3): 792. DOI: 10.3390/biomedicines11030792.
[79] AICH A, AFRIN L B, GUPTA K. Mast cell-mediated mechanisms of nociception[J]. Int J Mol Sci, 2015, 16(12): 29069-29092. DOI: 10.3390/ijms161226151.
[80] GENOVESE T, CORDARO M, SIRACUSA R, et al. Molecular and biochemical mechanism of cannabidiol in the management of the inflammatory and oxidative processes associated with endometriosis[J]. Int J Mol Sci, 2022, 23(10): 5427. DOI: 10.3390/ijms23105427.
[81] HENDRIKSEN E, VAN BERGEIJK D, OOSTING R S, et al. Mast cells in neuroinflammation and brain disorders[J]. Neurosci Biobehav Rev, 2017, 79: 119-133. DOI: 10.1016/j.neubiorev.2017.05.001.
[82] KISSEL C L, KOVÁCS K J, LARSON A A. Evidence for the modulation of nociception in mice by central mast cells[J]. Eur J Pain, 2017, 21(10): 1743-1755. DOI: 10.1002/ejp.1086.
[83] KILINC E, TORUN I E, BARANOGLU KILINC Y. Meningeal mast cell-mediated mechanisms of cholinergic system modulation in neurogenic inflammation underlying the pathophysiology of migraine[J]. Eur J Neurosci, 2024, 59(9): 2181-2192. DOI: 10.1111/ejn.15888.
[84] REINL E L, BLANCHARD A C, GRAHAM E L, et al. The immune cell profile of the developing rat brain[J]. Brain Behav Immun, 2022, 106: 198-226. DOI: 10.1016/j.bbi.2022.08.012.
[85] TOTI A, MICHELI L, LUCARINI E, et al. Ultramicronized N-palmitoylethanolamine regulates mast cell-astrocyte crosstalk: a new potential mechanism underlying the inhibition of morphine tolerance[J]. Biomolecules, 2023, 13(2): 233. DOI: 10.3390/biom13020233.
[86] RAMÍREZ-PONCE M P, FLORES J A, BARRELLA L, et al. Ketotifen is a microglial stabilizer by inhibiting secretory vesicle acidification[J]. Life Sci, 2023, 319: 121537. DOI: 10.1016/j.lfs.2023.121537.
[87] WEI W, LI H, DENG Y, et al. The combination of *Alisma* and *Atractylodes* ameliorates cerebral ischaemia/reperfusion injury by negatively regulating astrocyte-derived exosomal miR-200a-3p/141-3p by targeting SIRT1[J]. J Ethnopharmacol, 2023, 313: 116597. DOI: 10.1016/j.jep.2023.116597.
[88] XU N, BAI Y, HAN X, et al. Taurochenodeoxycholic acid reduces astrocytic neuroinflammation and alleviates experimental autoimmune encephalomyelitis in mice[J]. Immunobiology, 2023, 228(3): 152388. DOI: 10.1016/j.imbio.2023.152388.
[89] HONG G U, CHO J W, KIM S Y, et al. Inflammatory mediators resulting from transglutaminase 2 expressed in mast cells contribute to the development of Parkinson's disease in a mouse model[J]. Toxicol Appl Pharmacol, 2018, 358: 10-22. DOI: 10.1016/j.taap.2018.09.003.
[90] BASHIR S T, REDDEN C R, RAJ K, et al. Endometriosis leads to central nervous system-wide glial activation in a mouse model of endometriosis[J]. J Neuroinflammation, 2023, 20(1): 59. DOI: 10.1186/s12974-023-02713-0.

［本文编辑］　孙　岩