Editorial

Mast cell disorders – the hidden cause of idiopathic pain conditions?

Mieszko Więckiewicz[1,A–D,F], Victor Geller[2,A–D,F], Marzena Dominiak[2,A,C,E,F]

[1] Department of Experimental Dentistry, Wroclaw Medical University, Poland
[2] Department of Oral Surgery, Wroclaw Medical University, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2026;63(6):1367–1372

Address for correspondence
Mieszko Więckiewicz
E-mail: mieszko.wieckiewicz@umw.edu.pl

Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
None declared

Received on September 24, 2026
Reviewed on September 26, 2026
Accepted on September 29, 2026

Published online on November 26, 2026

Cite as
Więckiewicz M, Geller V, Dominiak M. Mast cell disorders – the hidden cause of idiopathic pain conditions? *Dent Med Probl*. 2026;63(6):1367–1372. doi:10.17219/dmp/240462

DOI
10.17219/dmp/240462

Copyright
Copyright by Author(s)
This is an article distributed under the terms of the Creative Commons Attribution 3.0 Unported (CC BY 3.0) (https://creativecommons.org/licenses/by/3.0/)

Keywords: mast cell, mastocytosis, pain, idiopathic, disorders

The mast cell–sensory neuron interface may define an underrecognized biological pain phenotype in selected patients, but it should not be equated with systemic mast-cell disease.

Rethinking idiopathic pain: The mast-cell perspective

Persistent pain for which structural, inflammatory, neurological, or dental diagnostic investigations fail to identify an adequate cause is often classified as idiopathic, primary, functional, or nociplastic. Persistent pain may remain inadequately explained after structural, inflammatory, neurological, or dental assessment. Idiopathic, primary, functional, and nociplastic describe distinct diagnostic or mechanistic constructs. Nociplastic pain denotes altered nociception and may coexist with nociceptive pain.[1] Diagnostic uncertainty does not imply an absence of biological mechanisms.

Accurate diagnosis is essential. In 2024, Valent et al. proposed an alignment of the World Health Organization (WHO), International Consensus Classification (ICC), and American Initiative in Mast Cell Diseases/European Competence Network on Mastocytosis (AIM/ECNM) frameworks for mastocytosis, a clonal myeloid disorder characterized by pathological mast-cell accumulation.[2] Contemporary consensus criteria define mast cell activation syndrome (MCAS) differently – by the presence of 3 essential features: recurrent, severe systemic symptoms consistent with mast-cell mediator release; objective, even-related biochemical evidence of mast-cell activation; and a clinical response to mediator-targeted therapy.[3] The most established biochemical criterion is a transient increase in serum tryptase exceeding the individual baseline by 20% plus 2 ng/mL.[4] Mastocytosis, clonal mast-cell disease, systemic MCAS, local mast-cell accumulation or activation, and mast cell–neuron crosstalk in the context of another disease are therefore distinct concepts.

Mast cells beyond allergy: A neuroimmune unit

Comparative evidence from the tunicate *Ciona intestinalis* identifies mast-cell-like cells that store histamine and heparin-associated proteases and undergo regulated degranulation, suggesting that mast-cell-like cells originated more than 500 million years ago, before the emergence of vertebrate adaptive immunity.[5]

In mammals, mast-cell populations exhibit extensive tissue specialization, as demonstrated by distinct transcriptional states distributed across human organs and tissues.[6]

They are tissue-adapted immune sentinels positioned near microvessels and sensory nerve endings, where bidirectional signaling can influence nociception.[7,8] Classical immunoglobulin E (IgE)-dependent activation through the high-affinity IgE receptor (FcεRI) is one pathway, but IgE-independent mechanisms are increasingly recognized. Of particular interest are Mas-related G protein-coupled receptor X2 (MRGPRX2) and its murine functional counterpart, Mas-related G protein-coupled receptor B2 (MrgprB2).[8] These receptors provide a plausible molecular interface for neuropeptide-induced mast-cell activation, although human MRGPRX2 and mouse MrgprB2 differ in expression patterns and ligand pharmacology, and should not be considered equivalent.

The biology extends well beyond histamine. Mast cells can release tryptase, chymase, prostaglandins, cysteinyl leukotrienes, tumor necrosis factor (TNF), interleukin-1 beta (IL-1β), IL-6, nerve growth factor (NGF), and other neuroactive mediators. Histamine can act through histamine H1–H4 receptors (HRH1–HRH4), tryptase through protease-activated receptor 2 (PAR-2) and NGF through tropomyosin receptor kinase A (TrkA). These pathways can lower nociceptor thresholds and increase neuronal excitability, including through the activation or sensitization of transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1). Sensory neurons can reciprocally release substance P, pituitary adenylate cyclase-activating polypeptide (PACAP) and calcitonin gene-related peptide (CGRP). The effects of CGRP on mast cells appear to be tissue- and context-dependent.[8]

From transient activation to persistent pain

In mice, mast-cell granule particles transport TNF through lymphatics to draining lymph nodes, while mast-cell activation can engage neural circuits that suppress brown adipose tissue thermogenesis during anaphylaxis.[9,10] These observations illustrate that mast-cell effects may extend beyond the immediate site of activation and involve interactions with neural and lymphatic systems. More broadly, we propose, as conceptual scaffolding rather than an established biological model, that tissue-resident mast-cell populations may be viewed as components of a distributed neuroimmune network whose functional consequences depend on tissue context, cellular composition, spatial organization, previous activation states, and interactions with neural, vascular, epithelial, stromal, lymphatic, and immune compartments. This framework remains speculative and requires direct experimental validation. Within this framework, the mast cell–sensory neuron unit represents one local interface through which persistent nociceptive signaling could theoretically be amplified or maintained.

A candidate local mechanism involves a positive-feedback loop: mast-cell activation may increase the release of algogenic mediators and promote nociceptor sensitization. Activated neurons may then release neuropeptides that further stimulate mast cells, thereby promoting neurogenic inflammation and peripheral sensitization. Repeated signaling may also promote NGF-dependent axonal sprouting and hyperinnervation, sustaining afferent input even after overt inflammation has diminished. In some settings, persistent peripheral input could contribute to spinal neuroplasticity; however, current evidence does not support the claim that mast cells universally cause central sensitization.

Provoked vulvodynia provides one of the strongest experimental illustrations of this mechanism. Human vestibular tissue has shown mast-cell accumulation and neuronal sprouting, while repeated vulvar inflammation in rats has been associated with persistent hypersensitivity, hyperinnervation, increased TRPV1 and TRPA1 expression, and longer-lasting changes in the dorsal root ganglia and spinal cord.[11] Ketotifen attenuated NGF-associated changes, hyperinnervation and hypersensitivity in the experimental model.[11] The human findings remain associative, whereas the intervention data support a contribution of the mast cell–NGF–sensory neuron axis in that model. This sequence offers a plausible explanation for the persistence of pain when conventional inflammatory markers, imaging findings or structural examination results are normal or nonspecific.

Converging evidence, different levels of certainty

Biopsy supernatants from a small cohort of patients with post-infectious irritable bowel syndrome (IBS) sensitized murine sensory neurons through HRH1-dependent TRPV1 signaling, despite lower mucosal mast-cell counts.[12] In a placebo-controlled trial involving patients with nonconstipated IBS, ebastine improved a combined global symptom and abdominal pain response endpoint, although the improvement in the separate pain endpoint was not statistically significant.[13] These findings support the involvement of this pathway without establishing mast-cell-specific causality. Mechanistic evidence has strengthened the case for a mast cell–sensory neuron contribution in at least a subset of patients. Aguilera-Lizarraga et al. showed in experimental models that gastrointestinal infection can disrupt local oral tolerance, leading to dietary antigen-specific IgE production, mast-cell activation, histamine-dependent HRH1-mediated sensitization of visceral afferents, and visceral hypersensitivity.[14] In patients with IBS, intramucosal

food-antigen challenge induced local edema and mast-cell activation. Furthermore, IgE-positive mast cells were located closer to nerve fibers, and this spatial relationship correlated with abdominal pain severity.[14] A subsequent translational review emphasized that altered mast-cell function and mediator release, rather than the mast-cell number alone, may drive nociceptor hyperexcitability through histamine, proteases and TRP-channel sensitization.[15] It also stressed that IBS is biologically heterogeneous and that mast-cell mechanisms should not be generalized to every patient.[15] The most recent pathophysiological synthesis by Nasser et al. likewise frames IBS as a disorder of the gut–brain interaction arising from integrated peripheral and central mechanisms, including visceral hypersensitivity, increased intestinal permeability, low-grade mucosal inflammation, and altered immune function.[16] Irritable bowel syndrome is therefore informative to the present argument not because it should be reclassified as an idiopathic mast-cell disorder, but because it illustrates how abdominal pain that remains unexplained by routine structural investigations may, in a mechanistically defined subgroup of patients, reflect a measurable peripheral neuroimmune process involving mast cells.

Endometriosis-associated pain provides further convergent translational evidence. Human lesions show mast-cell infiltration or degranulation, with mast cells frequently located in close proximity to nerve fibers. Mao et al. reported increased numbers of MRGPRX2-positive mast cells and experimental findings consistent with the MRGPRX2–histamine–HRH1–TRPV1 signaling axis.[17] In mice, mast-cell deficiency and MrgprB2 disruption reduced hyperalgesia.[17] These interventions support a causal role for mast cells and MrgprB2 within the experimental model, but do not establish causality in humans. A complementary review links neuroinflammation and neurogenesis to mast-cell activity and the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway, although the potential analgesic effects of JAK inhibition remain hypothetical.[18]

Migraine is anatomically plausible as a mast cell–sensory neuron interaction, since meningeal mast cells lie in close proximity to trigeminal afferents.[19] Experimental studies indicate that PACAP can activate mast cells through MRGPRX2/MrgprB2 signaling and that the disruption of these receptors attenuates migraine-like hypersensitivity in mice.[20] Son et al. showed that repetitive stress increased the levels of pituitary adenylate cyclase-activating polypeptide-38 (PACAP38), while MrgprB2 deficiency attenuated stress- and PACAP38-associated mast-cell degranulation, trigeminal sensitization, and headache-like behavior.[21] These findings provide strong mechanistic evidence from preclinical models. However, direct evidence that mast cells are necessary for human migraine remains limited.

Gout, although not idiopathic, provides instructive mechanistic evidence. Yang et al. showed that the genetic deletion of MrgprB2 reduced synovial mast-cell activation, inflammatory mediator production, joint swelling, and mechanical and thermal hyperalgesia in mice.[22] Complementary experiments implicated substance P as a potential endogenous ligand for this receptor.[22] Thus, mast cells can causally modulate inflammatory pain in this experimental context.

Evidence is less definitive in other conditions. In bladder pain syndrome/interstitial cystitis, suburothelial mast-cell activation and leukotriene signaling remain candidate mechanisms. In a small randomized pediatric trial, the addition of montelukast increased the proportion of pain-free participants from 56.3% to 84.4% after 14 days, but did not significantly improve urgency, frequency, incontinence, or nocturnal enuresis.[23] The short follow-up, limited sample size, subjective pain assessment, and the pediatric population preclude causal attribution. In discogenic low back pain, more painful nucleus pulposus samples contained higher numbers of tryptase-positive mast cells, while hemokinin-1 (HK-1), IL-12p70, and pain severity were also associated.[24] In osteoarthritis, human synovial tissue shows mast-cell activation and active tryptase, whereas animal experiments implicate the IgE/FcεRI/spleen tyrosine kinase (Syk) and tryptase/PAR-2 pathways in inflammation and cartilage degeneration.[25] These findings do not establish mast cells as the cause of pain in human osteoarthritis.

The orofacial question

The hypothesis is particularly relevant to dentistry, as mast cells and trigeminal sensory fibers coexist in densely innervated orofacial tissues. In a rat formalin model, sodium cromoglicate and magnesium sulfate modified mast-cell degranulation and inflammatory orofacial nociception.[26] To date, there is insufficient evidence to establish mast-cell activation as a causative mechanism in burning mouth syndrome, persistent idiopathic facial pain, persistent idiopathic dentoalveolar pain, or other conditions classified under the International Classification of Orofacial Pain (ICOP).

The evidentiary gap is therefore particularly large in idiopathic orofacial pain. At present, anatomical plausibility and experimental modulation of orofacial nociception cannot be extrapolated to establish mast-cell involvement in burning mouth syndrome, persistent idiopathic facial pain or persistent idiopathic dentoalveolar pain. A minimally informative human study would require prospectively phenotyped patients meeting the contemporary ICOP criteria, carefully matched pain-free controls, the exclusion of odontogenic and structural causes, and the predefined assessment of both mast-cell and sensory-neural variables. Depending on the tissue accessible for investigation and the clinical phenotype, these could include mast-cell density and activation status, the tryptase/chymase phenotype,

MRGPRX2 expression, spatial proximity between mast cells and nerve fibers, sensory-nerve density, NGF and TRPV1/TRPA1 expression, together with quantitative sensory testing and standardized pain phenotyping. Demonstrating coupled mast-cell and neural abnormalities associated with pain severity or longitudinal pain persistence would provide substantially stronger evidence than mast-cell counts alone.

A more defensible hypothesis is that a biologically defined subgroup of patients currently classified as having idiopathic or nociplastic pain may exhibit a peripheral mast cell–trigeminal phenotype that standard dental diagnostics do not detect. This distinction matters, since unexplained (idiopathic) orofacial pain may lead to repeated investigations and, in some cases, irreversible dental procedures despite the absence of an adequate odontogenic cause.

The prevalence of such a phenotype is currently unknown. No validated diagnostic definition or biomarker panel is available to estimate its frequency among patients with persistent idiopathic or nociplastic pain, including orofacial pain. It may represent a small, mechanistically distinct subgroup rather than a common explanation for otherwise unexplained pain. Epidemiological characterization should therefore follow, rather than precede, the development and validation of reproducible phenotypic and biomarker criteria. Until such data become available, mast-cell involvement should be considered selectively, on the basis of clinical context, rather than assumed to be widespread across populations with idiopathic pain.

Mast-cell disorders are not synonymous with local mast-cell activation

Increased tissue mast-cell density does not necessarily indicate mast-cell activation, and activation can occur without an increased mast-cell burden. Local mast-cell activation does not establish systemic MCAS, pain alone is insufficient to diagnose MCAS, and improvement with antihistamines, ketotifen, sodium cromoglicate, or montelukast cannot serve as a diagnostic test.[2–4]

Phenotypic clustering also requires caution. A 2026 systematic review and meta-analysis of postural orthostatic tachycardia syndrome (POTS) reported migraine in 35.6% of patients, fibromyalgia in 21.6%, and MCAS in 36.3%, together with a high burden of gastrointestinal symptoms.[27] However, substantial heterogeneity, differences in diagnostic definitions, frequent reliance on self-reported MCAS, and selection bias limit the interpretation of these findings. These observations are hypothesis-generating and cannot establish a shared neuroimmune mechanism.

Clinical implications: Phenotype before therapy

The clinical implication is not the routine use of mast-cell-directed treatment for unexplained pain. Mast-cell involvement may be considered as one component of mechanistic assessment when unexplained pain coexists with episodic or multisystem symptoms suggestive of mediator release. However, the established criteria for systemic mast-cell disorders must still be fulfilled.

Histamine H1 and H2 receptor antagonists, ketotifen, sodium cromoglicate, leukotriene receptor antagonists, and KIT receptor tyrosine kinase-directed therapies have established indications for selected allergic and mast-cell disorders, depending on the agent and jurisdiction. However, they are not established treatment options for idiopathic pain. MRGPRX2 antagonism, tryptase/PAR-2 inhibition, NGF/TrkA-targeted strategies, TRPV1/TRPA1 modulation, and interventions targeting selected cytokine or JAK pathways remain experimental or repurposing concepts in this setting. Therapeutic response should not be interpreted as the confirmation of the underlying pathophysiology. Ultimately, targeting a specific mast cell–neuron signaling node may prove more informative than nonspecific mast-cell suppression.

From mast-cell counts to a neuroimmune pain phenotype

The key research question is whether a reproducible mast cell–neuroimmune pain phenotype exists within disorders currently classified as idiopathic. Prospective studies should integrate validated pain phenotyping, contemporary diagnostic criteria for mast-cell disorders, event-related and baseline mediator measurements where appropriate, mast-cell density and activation status, the tryptase/chymase phenotype, MRGPRX2 expression, spatial proximity between mast cells and nerve fibers, sensory-nerve density, NGF and TRPV1/TRPA1 expression, cytokine and lipid-mediator profiling, quantitative sensory testing, small-fiber assessment where relevant, autonomic phenotyping, and longitudinal evaluation before and after mechanism-specific interventions. Spatial and functional biomarkers should be interpreted in the context of the evolving tissue states. A key issue is whether coupled changes in mast-cell states and neural, vascular or immune activity predict pain persistence and treatment response beyond what can be explained by cell counts and isolated mediator measurements. Mast-cell-directed interventions introduced during pain induction and after pain has become established could help distinguish the initiating effects from the mechanisms involved in ongoing pain maintenance and persistent downstream remodeling.

A conceptual summary of these considerations is presented in Fig. 1.

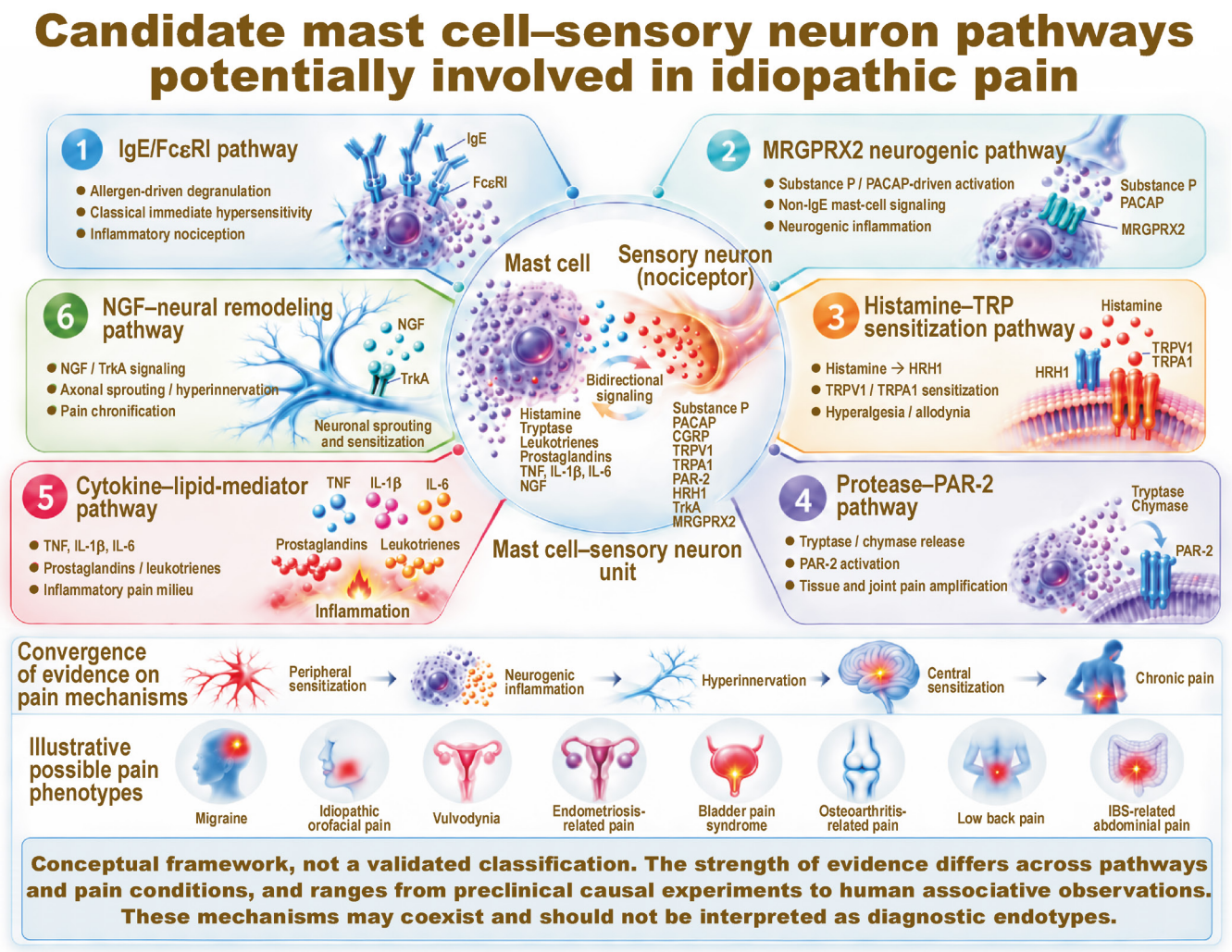

Fig. 1. The figure illustrates candidate mast cell–sensory neuron pathways through which bidirectional neuroimmune signaling may promote peripheral sensitization, neurogenic inflammation, neural remodeling, sustained afferent input, and ultimately central sensitization across selected idiopathic pain phenotypes

CGRP – calcitonin gene-related peptide; FcεRI – IgE receptor; HRH1 – histamine H1 receptor; IBS – irritable bowel syndrome; IgE – immunoglobulin E; IL – interleukin; MRGPRX2 – Mas-related G protein-coupled receptor X2; NGF – nerve growth factor; PACAP – pituitary adenylate cyclase-activating polypeptide; PAR-2 – protease-activated receptor 2; TNF – tumor necrosis factor; TrkA – tropomyosin receptor kinase A; TRP – transient receptor potential; TRPA1 – transient receptor potential ankyrin 1; TRPV1 – transient receptor potential vanilloid 1.

Conclusions

Mast cells should neither be dismissed as cells relevant only to allergy nor regarded as a universal explanation for chronic pain. Human associations, animal studies demonstrating causality, and translational research identify the mast cell–sensory neuron interface as a credible and testable mechanism capable of amplifying nociception and, in selected experimental contexts, contributing to its maintenance. Some pain may remain "idiopathic" not because it lacks a biological basis, but because the relevant biology lies at a neuroimmune interface that routine diagnostic methods do not yet capture.

Ethics approval and consent to participate

Not applicable.

Data availability

Not applicable.

Consent for publication

Not applicable.

Use of AI and AI-assisted technologies

During the preparation of this work, the authors used ChatGPT (OpenAI) for language editing and for generating Fig. 1. The authors reviewed and edited the content, and take full responsibility for the final version of the manuscript.

ORCID iD

Mieszko Więckiewicz https://orcid.org/0000-0003-4953-7143
Victor Geller https://orcid.org/0009-0003-0446-6721
Marzena Dominiak https://orcid.org/0000-0001-8943-0549

References

1. Kosek E, Clauw D, Nijs J, et al. Chronic nociplastic pain affecting the musculoskeletal system: Clinical criteria and grading system. *Pain*. 2021;162(11):2629–2634. doi:10.1097/j.pain.0000000000002324
2. Valent P, Hartmann K, Hoermann G, et al. Harmonization of diagnostic criteria in mastocytosis for use in clinical practice: WHO vs ICC vs AIM/ECNM. *J Allergy Clin Immunol Pract*. 2024;12(12):3250–3260.e5. doi:10.1016/j.jaip.2024.08.044
3. Akin C, Gülen T, Castells MC, Oude Elberink H, Valent P. Diagnosis and management of patients with mast cell activation syndromes: Status 2026. *J Allergy Clin Immunol Pract*. 2026;14(1):19–28. doi:10.1016/j.jaip.2025.10.046
4. Valent P, Bonadonna P, Hartmann K, et al. Why the 20% + 2 tryptase formula is a diagnostic gold standard for severe systemic mast cell activation and mast cell activation syndrome. *Int Arch Allergy Immunol*. 2019;180(1):44–51. doi:10.1159/000501079
5. Wong GW, Zhuo L, Kimata K, Lam BK, Satoh N, Stevens RL. Ancient origin of mast cells. *Biochem Biophys Res Commun*. 2014;451(2):314–318. doi:10.1016/j.bbrc.2014.07.124
6. Tauber M, Basso L, Martin J, et al. Landscape of mast cell populations across organs in mice and humans. *J Exp Med*. 2023;220(10):e20230570. doi:10.1084/jem.20230570
7. Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. *N Engl J Med*. 2015;373(2):163–172. doi:10.1056/NEJMra1409760
8. Kagan T, Yosipovitch G. Beyond histamine: Mast cell–neuron communication in chronic pruritic and pain disorders. *Exp Dermatol*. 2026;35(8):e70320. doi:10.1111/exd.70320
9. Kunder CA, St John AL, Li G, et al. Mast cell-derived particles deliver peripheral signals to remote lymph nodes. *J Exp Med*. 2009;206(11):2455–2467. doi:10.1084/jem.20090805
10. Bao C, Chen O, Sheng H, et al. A mast cell–thermoregulatory neuron circuit axis regulates hypothermia in anaphylaxis. *Sci Immunol*. 2023;8(81):eadc9417. doi:10.1126/sciimmunol.adc9417
11. Awad-Igbaria Y, Edelman D, Ianshin E, et al. Inflammation-induced mast cell-derived nerve growth factor: A key player in chronic vulvar pain? *Brain*. 2025;148(1):331–346. doi:10.1093/brain/awae228
12. Balemans D, Mondelaers SU, Cibert-Goton V, et al. Evidence for long-term sensitization of the bowel in patients with post-infectious-IBS. *Sci Rep*. 2017;7(1):13606. doi:10.1038/s41598-017-12618-7
13. Decraecker L, De Looze D, Hirsch DP, et al. Treatment of non-constipated irritable bowel syndrome with the histamine 1 receptor antagonist ebastine: A randomised, double-blind, placebo-controlled trial. *Gut*. 2024;73(3):459–469. doi:10.1136/gutjnl-2023-331634
14. Aguilera-Lizarraga J, Florens MV, Viola MF, et al. Local immune response to food antigens drives meal-induced abdominal pain. *Nature*. 2021;590(7844):151–156. doi:10.1038/s41586-020-03118-2
15. Van Remoortel S, Hussein H, Boeckxstaens G. Mast cell modulation: A novel therapeutic strategy for abdominal pain in irritable bowel syndrome. *Cell Rep Med*. 2024;5(10):101780. doi:10.1016/j.xcrm.2024.101780
16. Nasser Y, Shin A, Ford AC, Camilleri M, Black CJ. Pathophysiology of irritable bowel syndrome. *Lancet Gastroenterol Hepatol*. 2026;11(11):1009–1020. doi:10.1016/S2468-1253(26)00148-2
17. Mao X, Wang J, Ding S, et al. MRGPRX2 mediates mast cell-induced endometriosis pain through the sensitization of sensory neurons via histamine/HRH1/TRPV1 signaling pathway. *FASEB J*. 2025;39(13):e70778. doi:10.1096/fj.202501493R
18. Golinska M, Wołyniak M, Kulesza P, Fendler W. Neuroinflammation is responsible for pain in endometriosis – targeting the JAK-STAT pathway and mast cell activation. *Front Immunol*. 2025;16:1621178. doi:10.3389/fimmu.2025.1621178
19. Guan LC, Dong X, Green DP. Roles of mast cells and their interactions with the trigeminal nerve in migraine headache. *Mol Pain*. 2023;19:17448069231181358. doi:10.1177/17448069231181358
20. Sbei S, Moncrief T, Limjunyawong N, Zeng Y, Green DP. PACAP activates MRGPRX2 on meningeal mast cells to drive migraine-like pain. *Sci Rep*. 2023;13(1):12302. doi:10.1038/s41598-023-39571-y
21. Son H, Zhang Y, Shannonhouse J, Gomez R, Kim YS. PACAP38/mast-cell-specific receptor axis mediates repetitive stress-induced headache in mice. *J Headache Pain*. 2024;25(1):87. doi:10.1186/s10194-024-01786-3
22. Yang L, Liu C, Xiao J, et al. Mast cell-expressed Mrgprb2/MRGPRX2 mediates gout pain and inflammation via a neuroimmune axis. *JCI Insight*. 2026;11(2):e201781. doi:10.1172/jci.insight.201781
23. Shabestari AA, Akbarzadeh F, Dorreh F, Yousefichaijan P, Almasi-Hashiani A. The effect of montelukast on urinary symptoms in children with bladder pain syndrome: A randomized clinical trial. *Clin Pediatr (Phila)*. 2025;64(1):111–117. doi:10.1177/00099228241260119
24. He S, Liu X, Luo S, Li H, Min J, Shi Q. Mast cells and their related gene *HK-1* are closely associated with discogenic low back pain: A bioinformatics and clinical sample study. *J Pain Res*. 2024;17:1401–1412. doi:10.2147/JPR.S454785
25. Wang Q, Lepus CM, Raghu H, et al. IgE-mediated mast cell activation promotes inflammation and cartilage destruction in osteoarthritis. *eLife*. 2019;8:e39905. doi:10.7554/eLife.39905
26. Srebro D, Dožić B, Vučković S, et al. The interactions of magnesium sulfate and cromoglycate in a rat model of orofacial pain; the role of magnesium on mast cell degranulation in neuroinflammation. *Int J Mol Sci*. 2023;24(7):6241. doi:10.3390/ijms24076241
27. Kulin D, Shah A, Fairlie T, et al. Gastrointestinal symptoms and systemic comorbidities in patients with POTS: A systematic review and meta-analysis. *Neurogastroenterol Motil*. 2026;38(4):e70305. doi:10.1111/nmo.70305