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The Return of the Mast Cell: New Roles in Neuroimmune Itch Biology

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Abstract

The mast cell-nerve unit has classically represented a fundamental neuroimmune axis in the development of itch due to the traditional prominence of histamine as a pruritogen. However, it is increasingly appreciated that most chronic itch disorders are likely non-histaminergic in nature, provoking the hypothesis that other novel effector itch mechanisms derived from mast cells are important. In this review, we present an overview of classical mast cell biology and put these concepts into the context of recent advances in our understanding of the regulation and function of the mast cell-nerve unit in itch biology.

Introduction

Originally described by Paul Ehrlich over a century ago, mast cells (MCs) have been viewed as important effector cells in allergic inflammatory processes that underlie diseases such as anaphylaxis, asthma, food allergy, and urticaria. Arising from pluripotent progenitor cells of the bone marrow, MC precursors circulate in the blood and enter tissues where they receive specific signals to undergo maturation and are long-lived (Galli et al., 2005, Pasparakis et al., 2014). Mature MCs are activated by binding of allergens to IgE, which is attached to the

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cell surface via the high-affinity receptor FcεRI. Binding of antigen results in crosslinking of IgE on FcεRI which then rapidly induces MC degranulation and the release of various preformed effector molecules (Amin, 2012). Although this is the most well described mode of MC activation, there are new pathways emerging that confer unique effector mechanisms and physiology.

MCs have been shown to reside in close proximity with neurons in multiple tissues including the bladder (Letourneau et al., 1996), gut (Stead et al., 1987), lung (Undem et al., 1995), and skin (Egan et al., 1998), provoking the hypothesis that a primary function of the MC-nerve unit is to regulate a variety of neuroimmune interactions. Indeed, many mediators released from MCs are classified as pruritogens. Although histaminergic itch elicited by MCs has been recognized as one of the most well-known physiologic processes, surprisingly, antihistamines have notoriously demonstrated poor efficacy for most chronic itch conditions. Thus, the clear role of MCs in many clinical itch disorders has yet to be defined. Additionally, the release of various factors like neuropeptides (NPs) from innervating neurons such as substance P (SP) and vasoactive intestinal peptide (VIP) have been reported to modulate MC function (Kulka et al., 2008), suggesting that previously unrecognized mechanisms of regulation and effector function may shed new light on the relevance of MCs to chronic itch.

In this review, we will focus on recent advances in MC biology that may explain new mechanisms by which MCs are regulated to elicit itch via histamine-independent pathways and have previously unrecognized roles in clinical itch disorders. These developments will likely open new avenues to novel therapeutic approaches for chronic itch.

Classical and emerging MC-derived pruritogens

Biogenic amines

Histamine is a classical pruritogen released from MCs (Figure 1) and acts on four distinct G protein-coupled receptors (GPCRs [H1R, H2R, H3R, and H4R]). Although neurons can broadly express H1R, H3R, and H4R, only H1R has been clearly demonstrated to be expressed by pruriceptive dorsal root ganglion (DRG) neurons in humans and mice, whereas H4R expression has been reported on rat DRG (Dimitriadou et al., 1994, Shim et al., 2007, Strakhova et al., 2009). The binding of histamine to H1R triggers the opening of the nonspecific cation channel transient receptor potential V1 (TRPV1) on sensory neurons, resulting in membrane depolarization, a subsequent action potential, and itch sensation. However, given that current antihistamines currently target H1R or H2R, the role of H4R in itch remains an open question. *In vitro* experiments demonstrate that TRPV1 is also involved in the histamine-H4R itch axis and that H4R contributes to itch in preclinical murine models (Jian et al., 2016, Mack and Kim, 2018). Indeed, H4R antagonists are currently in development for conditions like atopic dermatitis (AD) and future studies will be required to fully determine the role of histamine in chronic itch.

Although rodent MCs are described to be an important source of serotonin (5-hydroxytryptamine, 5-HT), release of serotonin from human MCs have been implicated in specific disease contexts such as mastocytosis (Herr et al., 2017, Kushnir-Sukhov et al.,

2007). Notwithstanding of this, serotonin is defined as a pruritogen because cutaneous injection with serotonin successfully elicits itch in healthy humans and mice (Akiyama et al., 2010, Weisshaar et al., 1997). Indeed, serotonin signaling is not only associated with itchy skin disorders such as AD (Huang et al., 2004), allergic contact dermatitis (ACD) (Liu et al., 2013, Lundeberg et al., 1999), and psoriasis (Nordlind et al., 2006), but has also been linked to itch caused by systemic conditions like cholestasis, uremia, and morphine-induced pruritus (Aly et al., 2018, Kerr et al., 1992, Schworer et al., 1995). However, the precise and robust manner in which serotonin can be effectively manipulated to treat chronic itch disorders in patients remains to be shown.

Lipid mediators

Lipids are the major components of cell membranes. Phospholipase A2s (PLA2s) are a group of enzymes required for release of arachidonic acid (AA) and lysophosphatidic acid. More than 30 PLA2s are encoded in the mammalian system (Murakami and Taketomi, 2015). A recent RNA-sequencing study has found that the group IV PLA2 family is significantly enriched in itchy skin lesions compared to non-pruritic and non-lesional skin in either AD patients or psoriasis patients (Nattkemper et al., 2018). These data indicate that MC-derived lipid mediators are highly connected to itch mechanisms underlying inflammatory skin conditions.

Prostaglandins (PGs) are AA metabolites, and are broadly involved in inflammatory processes. Among the subtypes of PGs, PGD2 and PGE2 are the most significantly implicated in itch (Figure 1). Intradermal injection of PGE2 in human subjects has been shown to elicit itch via enhancing histamine- and serotonin-induced itching (Fjellner and Hagermark, 1979, Hagermark and Strandberg, 1977). However, intradermal injection of PGE2 does not induce itch behavior in mice (Andoh and Kuraishi, 1998), and even surprisingly, a topical application of PGE2 significantly suppressed spontaneous scratching in NC/Nga mice with AD-like disease (Arai et al., 2004). Similar to PGE2, application of PGD2 or the potent PGD2 agonist (BW245C) to the ocular surface can elicit itching and mild burning sensations in human subjects when treating glaucoma (Nakajima et al., 1991). In contrast, topical applications of PGD2 or TS-022, a DP1 receptor agonist, have shown suppressive effects on spontaneous scratching in NC/Nga mice (Arai et al., 2004, Arai et al., 2007). Clinically, mast cell activation syndrome (MCAS) is a newly recognized collection of disorders that typically involves multiorgan inflammation due to the release of mast cell mediators. Patients with MCAS can present with chronic and relapsing itch (Petra et al., 2014). Indeed, nonsteroidal anti-inflammatory drugs which inhibit PG synthesis, have been reported to be effective in MCAS-associated itch (Kesterson et al., 2018). However, future studies will be required to fully define the role of PGs in various chronic itch disorders.

Generated from AA via the 5-lipoxygenase (5-LO) pathway, LTs are divided into two classes, namely, the chemoattractant LTB4 and the cysteinyl LTs (CysLTs: LTC4, LTD4, and LTE4) (Luster and Tager, 2004). In mice, intradermal injections of LTB4 have been shown to induce scratching behavior (Andoh and Kuraishi, 1998, Fernandes et al., 2013). Additionally, TRPV1 or transient receptor potential ankyrin 1 (TRPA1) antagonists have been shown to inhibit itch behavior in this context, suggesting that these may be pruritogens

(Fernandes et al., 2013). In the eye, subconjunctival injections of LTB4 have been shown to provoke site-directed scratching and application of the LTB4 receptor antagonist ONO-4057 inhibits ragweed pollen-associated ocular scratching in mice (Andoh et al., 2012). However, the role of CysLTs as pruritogens remains controversial. Studies have shown that applications of different CysLTs (LTC4, LTD4 or LTE4) to the eye do not induce itch behavior in guinea pigs (Woodward et al., 1995) and scratching does not increase in mice receiving intradermal injections of LTD4 (Andoh et al., 2001). Notwithstanding this, a recently published study has shown that intradermal injection of LTC4, causes robust itch behavior in mice (Solinski et al., 2019). Collectively, these studies indicate that the role of various LTs in mediating itch remains a complex area requiring further investigation.

MC-associated cytokines: IL-4, IL-13, and IL-31

Beyond classical pruritogens, specific cytokines are increasingly recognized for their ability to function as pruritogens. Indeed, a recent study demonstrated that the MC-associated type 2 cytokines IL-4 and IL-13 can directly stimulate peripheral sensory neurons *in vitro*. Further, conditional deletion of the gene for IL-4Rα, which mediates both IL-4 and IL-13 signaling, on sensory neurons resulted in attenuation of AD-like itch in mice (Oetjen et al., 2017). However, whether type 2 cytokines derived specifically from MCs mediate itch *in vivo* and in what contexts remains to be fully defined.

IL-31, first discovered in 2004 (Dillon et al., 2004), belongs to gp130/IL-6 cytokine family. It is the first cytokine to be defined as a pruritogen because of its ability to directly stimulate sensory neurons to evoke itch (Cevikbas et al., 2014). Although originally identified to be derived mainly from T helper type 2 cells, increasing evidence suggests that MCs might be a source of IL-31. Indeed, IL-31 mRNA was detected in a human MC line activated by the epithelial cell-derived antimicrobial peptides human β-defensin and LL-37 (Niyonsaba et al., 2010). More recently, IL-33 has been shown to activate human MCs to evoke the release of IL-31 (Petra et al., 2018). Additionally, in a number of chronic itch disorders closely associated with MC dysfunction including chronic spontaneous urticaria, mastocytosis, and myeloproliferative neoplasms, serum/plasma levels of IL-31 have been found to be elevated (Hartmann et al., 2013, Lin et al., 2017, Raap et al., 2010). Thus, studying the exact role of MCs in modulating IL-31 expression and the therapeutic potential of disruption of IL-31-IL31RA interactions for MC-related itch disorders remains and exciting area of investigation.

Regulation of MCs by Mrgprb2/MRGPRX2

Although classically activated by IgE-mediated FcεRI aggregation, MCs have been shown to respond to a variety of other stimuli including complement, chemokines, adenosine, nerve growth factor (NGF), SP, host defense peptides and basic peptides (Figure 1) (Metz et al., 2008, Serhan et al., 2019, Subramanian et al., 2016, Tatemoto et al., 2006). These diverse pathways of MC activation result in the release of a wide range inflammatory mediators (Tal and Liberman, 1997, Thangam et al., 2018). However, the precise contribution of these different pathways has remained poorly understood.

It has been well recognized since the 1950s that the compound 48/80 (48/80) is a rapid and potent activator of MCs (Paton, 1951). Indeed, intradermal injection of 48/80 has been used as a tool in both mice and humans to probe the mechanisms underlying MC-elicited itch (Fjellner et al., 1989, Goldberg et al., 1991). However, for decades the mechanism by which MCs responded to 48/80 was elusive. In 2015, McNeil et al. discovered that the Mas-related GPCR Mrgprb2 is a highly specific receptor for MCs and mediates 48/80-induced MC responses *in vitro* and pseudoanaphylactic responses *in vivo* in mice (McNeil et al., 2015). The human ortholog, MRGPRX2 is also present on human MCs. Beyond 48/80, many synthetic compounds, peptidomimetic drugs, and endogenous peptides and amines have demonstrated activity in stimulating Mrgprb2/MRGPRX2. More recently, Staphylococcus δ-toxin as well as antimicrobial peptides have been shown to directly stimulate this pathway to evoke MC activation (Azimi et al., 2017, Zhang and McNeil, 2019). We speculate that this highly conserved mechanism may underlie conditions such as contact urticaria, in which patients develop rapid urticarial reactions to classical haptens, but often independently of IgE, and much too rapid to be driven by a delayed hypersensitivity reaction. In addition, MRGPRX2 also has high fold changes on RNA level in itchy skin lesions biopsied from AD or psoriasis patients (Nattkemper et al., 2018), which indicates its broad involvement in itch-related dermatoses.

Furthermore, Gaudenzio et al. showed that different stimuli influence the dynamics and features of MC degranulation in distinct ways. Stimulation of MRGPRX2 and other GCPRs (e.g., C3aR, C5aR, and endothelin-1R) resulted in the rapid release of smaller and uniformly sized granules from human MCs, while IgE-induced degranulation led to slower and sustained activation associated with the release of larger granules (Gaudenzio et al., 2016). Collectively, these findings provoked the hypothesis that Mrgprb2/MRGPRX2-mediated activation of MCs may elicit distinct processes from the classical IgE-histamine axis so closely attributed to the physiology of the MC-nerve functional unit.

The MC-itch nerve unit: beyond IgE and histamine

Due to the early history of histamine being defined as a pruritogen (Dale and Laidlaw, 1910), the MC-nerve unit has classically been viewed as the key neuroimmune interaction that mediates itch. Indeed, the discovery of numerous itch-specific pathways on neurons including gastrin-releasing peptide receptor (Sun and Chen, 2007), MrgprA3 (Liu et al., 2009), natriuretic polypep-tide b (Nppb) (Mishra and Hoon, 2013), IL-31 (Cevikbas et al., 2014), and thymic stromal lymphopoietin (Wilson et al., 2013) employed various methods to prove that these pathways were non-histaminergic and/or MC-independent. However, despite the prominence of MCs in the neuroimmune paradigm of itch, their precise contribution to various chronic itch disorders and the effector mechanisms employed by these cells to evoke itch have remained poorly understood.

To directly and simply address the role MCs in itch, Solinski et al. recently undertook an elegant approach whereby mice expressing Cre-recombinase expressed under MC-specific mast cell protease 5 were crossed to r26-LSL-hMRDq mice. This approach allowed for targeted insertion of the artificial Hm3Dq receptor into MCs, allowing for pharmacogenetic activation of MCs in a specific manner in response to clozapine-N-oxide (CNO). As

hypothesized, CNO-induced activation of MCs was sufficient to induce itch, and *in vitro* activation of MCs led to the release of a variety of mediators including LTC4, serotonin, and sphingosine-1-phsophate. Strikingly, these mediators stimulated $Nppb^{+}$ neurons which in turn depended on the canonical gastrin-releasing peptide-spinal cord circuit to ultimately evoke itch (Solinski et al., 2019).

In terms of regulation of MCs in itch, Meixiong et al. demonstrated that activation of Mrgprb2 by the endogenous pro-adrenomedullin peptide (PAMP) 9–20 resulted in itch that commenced independently of the IgE-histamine axis (Meixiong et al., 2019). Although PAMP is classically a vasoregulatory peptide released from the adrenal medulla, the authors found that it was highly expressed in keratinocytes from lesional skin of patients with ACD in conjunction with MC enrichment in the dermis. These findings provoked the hypothesis that epithelial cell-derived PAMP-dermal MC interactions may elicit ACD-associated itch. Indeed, ACD itch across three different murine models demonstrated dependence on Mrgprb2. Strikingly, PAMP-mediated Mrgprb2 stimulation resulted in preferential release of tryptase and lower release of histamine and serontonin from MCs, which is a distinct pattern of sensory neuronal activation from IgE-elicited itch (Figure 2), indicating that differential pathways to MC activation result in distinct neuronal responses. However, in contrast to PAMP, 48/80 was found to induce release of similar amounts of histamine as IgE-mediated stimulation (McNeil et al., 2015, Yao et al., 2014). Thus, it is possible that different ligands induce different effector functions on MCs even upon stimulation of the same Mrgprb2 receptor. Further, in humans, skin injection of PAMP was shown to be mitigated by co-injection with an antihistamine (Hasbak et al., 2006), demonstrating the complexity of how MC stimulation may result in itch responses.

In addition to pruritogens, MCs are also a source of other mediators that may contribute to neurite elongation or outgrowth of sensory neurons. Nerve growth factor (NGF) is one such molecule. Sensory nerve density has been shown to be increased in itchy skin lesions in AD and psoriasis and accompanied by increased numbers of degranulated MCs (Chang et al., 2007, Tominaga and Takamori, 2014). Thus, NGF released by MCs may be an underlying mechanism of this phenomenon.

Neurons promoting MC activation and neuroinflammation

The primary afferent neurons responding to MC-derived mediators consequently release NPs like calcitonin gene-related peptide (CGRP), SP, and VIP through calcium influx. Indeed, multiple prior studies have demonstrated that some NPs can directly stimulate MCs to evoke the release of various proinflammatory factors (Figure 1) (Lee et al., 2008, Manning et al., 2016, Roosterman et al., 2006, Serhan et al., 2019, Steinhoff et al., 2000). A recent study demonstrated that SP activates MCs via Mrgprb2 to evoke neurogenic inflammation and pain behavior (Green et al., 2019). It is increasingly appreciated that MCs can be activated by NPs to promote neurogenic inflammation in a variety of contexts. However, how itch-sensory neurons are directly involved in this process is an exciting field of future investigation.

A large proportion of primary afferent neurons express protease-activated receptor (PAR)-2, one of the known receptors for tryptase, whose activation promotes the release of CGRP and SP leading to neurogenic tissue inflammation and edema (Roosterman et al., 2006, Steinhoff et al., 2000). Other MC-derived itch mediators such as histamine, also interact with their specific receptors on neurons to cause the release of NPs as well (Gupta and Harvima, 2018, Subramanian et al., 2016). Both SP and VIP have been shown to activate murine and human MCs via Mrgprb2 and MRGPRX2, respectively (Subramanian et al., 2016). Thus, in addition to the new insights into the MC-nerve unit as a key mediator of itch sensation, understanding how sensory neurons directly regulate MC function and tissue inflammation is also a major outstanding area of inquiry.

It is well-known that stress aggravates itch symptoms, however, the mechanisms remain poorly understood. Intriguingly, animal experiments have shown that both brain and skin MCs are activated in the setting of stress (Esposito et al., 2002, Singh et al., 1999). Additionally, in AD patients, stress increases allergen-induced skin wheal reactions and serum levels of SP, VIP and NGF (Kimata, 2003). Thus, MCs could be key mediators of the stress-itch axis and remains a major gap in understanding itch behavior.

Summary and future directions

Although the MC-nerve unit has classically represented a fundamental link in the neuroimmune itch circuit, their precise contribution to various chronic itch disorders have remained poorly defined. Based on new understanding, several major questions remain: 1) What is the precise role of MCs in other chronic itch disorders like AD, chronic pruritus of unknown origin (Xu et al., 2016), and prurigo nodularis (Zeidler et al., 2018)? 2) Can antagonists for various GPCRs like Mrgprb2 be employed to treat such chronic itch disorders and which effector molecules are the most important therapeutic targets? Lastly, given that MC stabilizers have poor efficacy in chronic itch disorders such as AD (Benton et al., 1990) and the striking similarity between MCs and basophils, do homologous mechanisms exist within their rare, circulating counterparts? Ever since their original discovery, MCs continue to unveil their complex and important role in neurosensory biology and beyond.

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Abbreviations

48/80	compound 48/80
5-HT	5-hydroxytryptamine

AA	arachidonic acid
AD	atopic dermatitis
ACD	allergic contact dermatitis
CGRP	calcitonin gene-related peptide
CNO	clozapine-N-oxide
CysLTs	cysteinyl LTs
DRG	dorsal root ganglion
ET-1R	endothelin-1 receptor
GCPR	G-protein-coupled receptor
HDP	host defense peptide
LPS	lipopolysaccharide
LT	leukotriene
MCAS	mast cell activation syndrome
MCDPs	mast cell degranulating peptides
MC	mast cell
Mrgpr	MAS-related G protein-coupled receptor
NGF	nerve growth factor
NP	neuropeptide
Nppb	natriuretic peptide b
PAMP	pro-adrenomedullin peptide
PAR	protease-activated receptor
PGN	peptidoglycan
PG	prostaglandin
SCF	stem cell factor
SP	substance P
TLR	Toll-like receptor
TRPA1	transient receptor potential A1
TRPV1	transient receptor potential V1
VIP	vasoactive intestinal peptide

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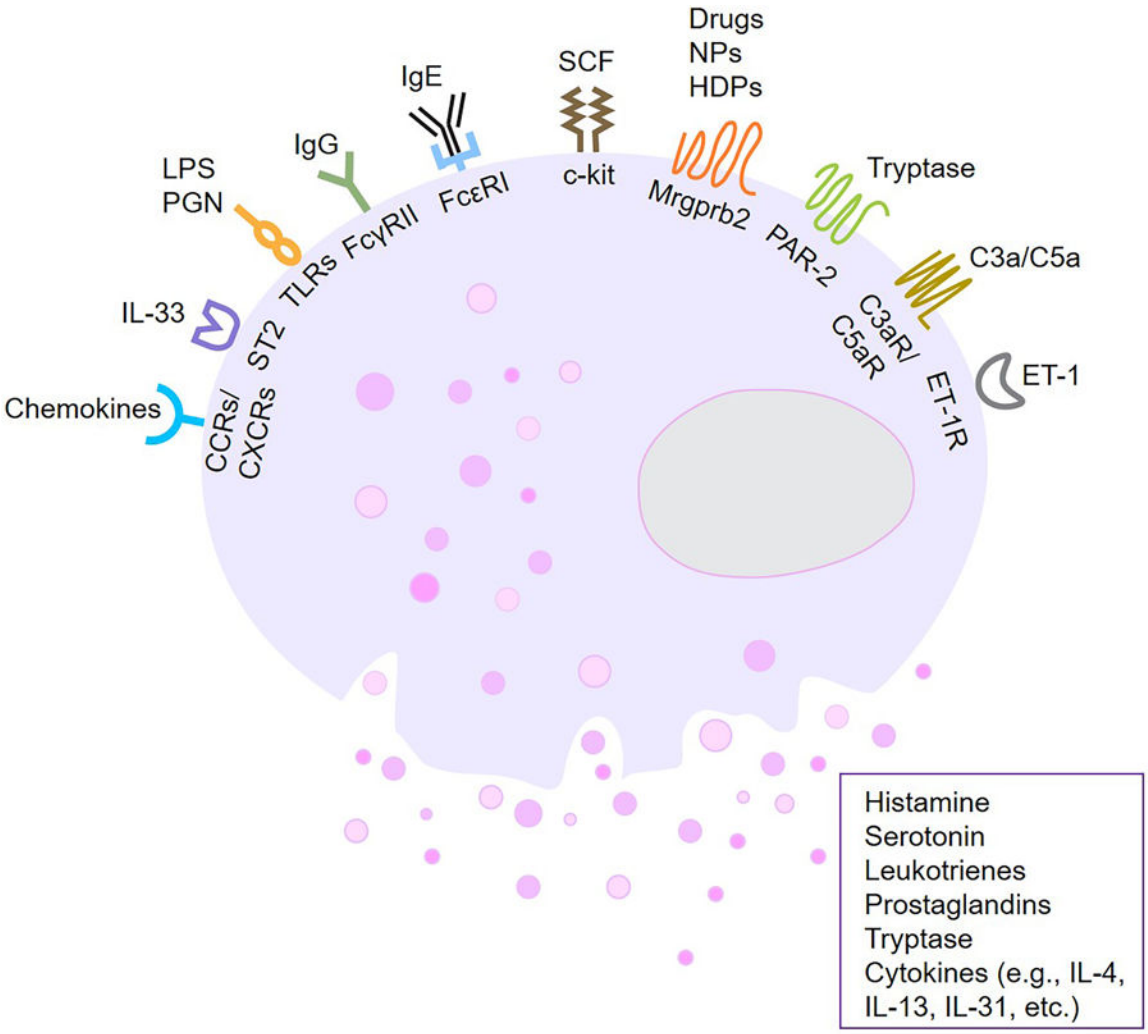

Figure 1. Various ligands and receptors known to stimulate the growth, migration, and/or activation of mast cells.

c-Kit (mast/stem cell growth factor receptor, CD117), which mediates responses to stem cell factor (SCF), is a key growth factor for the development of mast cells. IgE crosslinking of the high-affinity receptor FcεRI is the classical pathway leading to mast cell activation and degranulation. A recently identified receptor is Mrgprb2 (murine)/MRGPRX2 (human) which responds to cationic compounds, numerous drugs, and various neuropeptides (NPs) and host defense peptides (HDPs). Other receptors include protease-activated receptor (PAR)-2, chemokine receptors (CCRs/CXCRs) complement receptors, endothelin-1 receptor (ET-1R), FcγRII for IgG, Toll-like receptors (TLRs) for lipopolysaccharide (LPS) or peptidoglycan (PGN), ST2 for IL-33. Mast cell activation leads to the release of multiple mediators such as histamine, serotonin (5-hydroxytryptamine, 5-HT), leukotrienes (LTs), prostaglandins (PGs), tryptase and cytokines. Figure created with Biorender.

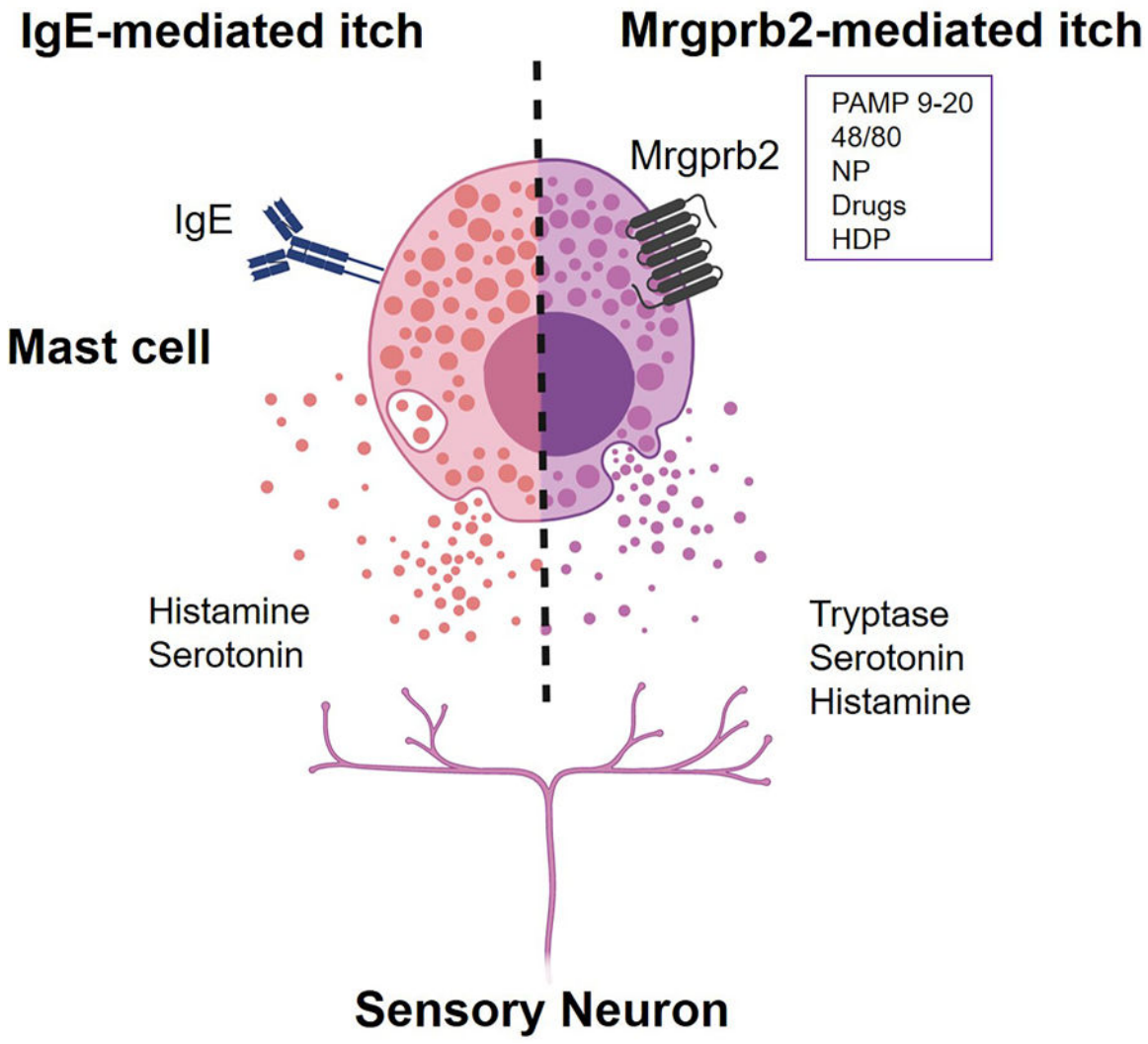

Figure 2. The IgE-mediated versus Mrgprb2-mediated itch axis.

Classical activation of mast cells by IgE results in the release of the monoamines such as histamine and serotonin. Mrgprb2 (murine)/MRGPRX2 (human) can be activated by various cationic substances, such as pro-adrenomedullin peptide 9–20 (PAMP 9–20), compound 48/80, drugs, neuropeptides (NPs), and host defense peptides (HDPs). Mrgbprb2-mediated activation of mast cells elicits distinct mechanisms of itch from classical IgE stimulation, in which tryptase is a major mediator while others such as histamine and serotonin are also included. Figure created with Biorender.