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The signaling pathway and polymorphisms of Mrgprs

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Abstract

Mas-related G protein-coupled receptors (Mrgprs) are a family of receptors implicated in a diverse array of human diseases. Since their discovery in 2001, great progress has been made in determining their relation to human disease. Vital for Mrgprs therapeutic efforts across all disease disciplines is a thorough understanding of Mrgprs signal transduction pathways and polymorphisms, as these offer insights into new drug candidates, existing discrepancies in drug response, and differences in disease susceptibility. In this review, we discuss the current state of knowledge regarding Mrgprs signaling pathways and polymorphisms.

Keywords

Mrgprs; signaling pathways; polymorphism

Introduction

Mas-related G protein-coupled receptors (Mrgprs) are a family of receptors expressed primarily in small-diameter sensory neurons of the dorsal root ganglia (DRG) and trigeminal ganglia (TG) [18]. Due to this concentration in sensory neurons, Mrgprs have been widely studied for their role in somatosensation, with most research focused on itch and pain sensation [17, 26, 46–48, 72]. Later studies have shown that Mrgprs are expressed in a variety of other tissues and are implicated in a growing variety of disease pathologies and processes, such as bronchoconstriction, anaphylaxis, antibacterial immunity, and tumorigenesis [20, 44, 49, 53]. Understanding Mrgprs signal pathways and accompanying polymorphisms will greatly improve therapeutic efforts across disease disciplines by leading to the identification of new drug candidates and elucidating discrepancies in both existing drug response and disease susceptibility. Thus, herein we attempt to provide a brief but concise overview of the changing state of knowledge regarding Mrgprs signaling pathways and polymorphisms.

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Overview of Mrgprs Signaling Pathways

Canonically, when an agonist molecule binds inactive G protein-coupled receptors (GPCRs) it induces the exchange of GDP for GTP on the bound Gα subunit. This induces a conformation change in the GPCR as the transmembrane helices V and VI move to create an opening on the cytoplasmic side, freeing the Gβγ dimer from being bound to the Gα protein. Newly activated Gα and Gβγ subunits can then bind downstream effectors, amplifying the GPCR signal. There exist four known families of Gα subunits ($G\alpha_{stimulatory}$ or $G\alpha_s$, $G\alpha_{inhibitory}$ or $G\alpha_{i/o}$, $G\alpha_{q/11}$, and $G\alpha_{12/13}$), each with a different signaling pathway [8, 40, 51, 65]. To date, Mrgprs have been found to utilize $G\alpha_{q/11}$, $G\alpha_{i/o}$, $G\alpha_s$, and Gβγ but not $G\alpha_{12/13}$ pathways.

Most known Mrgprs are associated with $G\alpha_{q/11}$-dependent signaling. The typical downstream signaling pathway for $G\alpha_{q/11}$ involves the activation of β-phosphodipase C (PLC), which then cleave phosphatidylinositol 4,5-biphosphate (PIP_2) into diacyl glycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). IP_3 can then activate calcium channels in the endoplasmic reticulum (ER), which along with DAG can culminate in protein kinase C (PKC) signaling [41].

Only MrgprD has been shown to utilize $G\alpha_s$ signaling. Activated $G\alpha_s$ binds adenylyl cyclase (AC) to produce cAMP, which in turn activates Protein Kinase A (PKA). PKA then performs a variety of functions including the phosphorylation of CREB proteins and TRP channels [41]. Specifically, PKA has been shown to sensitize both TRPV1 and TRPA1 [7, 45]. Many Mrgprs have been found to utilize the $G\alpha_{i/o}$ pathway, which directly inhibits adenylyl cyclase (AC) from producing cAMP, thus inhibiting the $G\alpha_s$ pathway [41]. Finally, several Mrgprs including MrgprA3, MrgprC11, and hMrgprX1 have been shown to utilize Gβγ-signaling. Similar to many Gα signaling pathways, Gβγ can activate PLC-β, PKC, and PKA [41].

MrgprA3

MrgprA3, which is expressed in about 6-7% of DRG neurons, mediates chloroquine-induced sensory neuron activation and itch sensation [37]. Controversial evidence has been presented arguing the key molecules required for MrgprA3 intracellular signaling. For instance, Wilson et al. demonstrated that both chloroquine-evoked calcium signals and action potentials in cultured mouse DRG sensory neurons are abolished with application of the Gβγ inhibitor gallein, suggesting that MrgprA3 couples to Gβγ in DRG sensory neurons [80]. They also found that chloroquine-induced neuronal responses were not affected by U73211, an inhibitor for the PLC family, suggesting that MrgprA3 does not couple to $G\alpha_{q/11}$. However, Than et al. have shown that chloroquine induced depletion of PIP_2 in HEK293 cells transfected with MrgprA3, suggesting the involvement of PLC in MrgprA3 downstream signaling in HEK293 cells [71]. It is possible that MrgprA3 couples to different signaling pathways in different cell types. Since *in vitro* heterologous systems are frequently used to investigate the GPCR signaling pathway, caution should be taken when interpreting the results and comparing them to the *in vivo* physiological condition.

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Chloroquine-induced calcium responses in sensory neurons were completely blocked in the absence of extracellular Ca^{2+}, suggesting that MrgprA3 activation by chloroquine leads to the opening of transduction channels. Several TRP channel family members including TRPC3, TRPVI, and TRPA1 have been tested for their role in MrgprA3 downstream signaling since they coexpress with MrgprA3 and are key transduction channels mediating the function of nociceptors [74, 81]. A possible role for TRPC3 has been suggested by Than et al., since both the general TRPC family blocker BTP2 and the TRPC3 specific inhibitor Pyr3 blocked chloroquine-induced sensory neuron excitation [71]. Sharif et al. found that while the TRPC3 blocker pyrazole 10, did not reduce chloroquine-induced itch-behavior suggesting that TRPC3 may not play a key role in MrgprA3 signaling [61].

The role of TRPV1 in MrgprA3 signaling is not clear. Studies have suggested that TRPV1 is not required for MrgprA3 signaling because both sensory neuron excitation and mouse scratching behavior induced by chloroquine were unaffected in TRPV1 knockout mice [58, 80]. However, Sharif et al. showed that TRPV1 inhibitor significantly reduced chloroquine-inducted itch behavior suggesting a potential role of TRPV1 in MrgprA3 downstream signaling pathway [61].

HC-030031, a TRPA1 inhibitor, successfully blocked Ca^{2+} responses in sensory neurons and scratching responses induced by chloroquine, suggesting the role of TRPA1 in MrgprA3 signaling [55, 61, 71, 80]. Liu et al. also found that application of ruthenium red, a broad TRP channel blocker, could reduce the calcium response elicited by chloroquine in primary sensory neurons [37]. However, recent evidence has shown that both ruthenium red and HC-030031 are not specific to TRP channels. They can induce inhibition of voltage-gated calcium channels (VGCC) in sensory neurons [13, 73], raising the possibility that the inhibitions of chloroquine signaling by ruthenium red and HC-030031 are independent of TRPA1.

Wilson et al. also demonstrated that chloroquine-induced intracellular Ca^{2+} signals in NG108 cells transfected with both TRPA1 and MrgprA3, but not in cells transfected with MrgprA3 alone. These data suggest that MrgprA3 couples to TRPA1 in NG108 cells to induce calcium influx. They also found that both sensory neuron activation and mouse scratching behaviors induced by chloroquine were abolished in TRPA1 knockout mice, leading to the conclusion that TRPA1 is the main downstream target for MrgprA3 [80].

However, recent evidence from Ru et al. argues against the requirement of TRPA1 for MrgprA3 signaling in sensory neurons [58]. Using *ex vivo* DRG nerve–skin preparation, Ru et al. performed extracellular recordings from cell bodies of sensory neurons while tested chemicals were applied to the skin. They found that chloroquine-induced action potential discharge in sensory neurons was not affected by HC-030031, ruthenium red, or the Gβγ inhibitor gallein. The behavioral analysis from Ru et al. is consistent with their cellular recording results, showing that chloroquine-induced scratching behavior was not affected in TRPA1 knockout mice. They also found that sensory neurons in TRPC3/TRPC6 double knockout mice exhibit similar action potential discharge induced by chloroquine in the WT neurons, suggesting that TRPC3 is not required for MrgprA3 signaling, which is consistent with Sharif et al.'s findings [61]. The discrepancy between these results and other studies

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may be due to differences in the subtleties of experimental design. It may also represent potential different mechanisms at the cell soma vs nerve terminals in the skin.

Ru et al. suggest the role of PLCβ3 in MrgprA3 signaling [58]. PLCβ3 is the only one among the 13 PLC family members that are highly expressed in $MrgprA3^+$ neurons [74, 81]. Both chloroquine-induce scratching behavior and neuronal activities in the *ex vivo* nerve-skin preparation were abolished in PLCβ3 knockout mice [58], whereas Imamachi et al. showed that PLCβ3 knockout mice exhibited normal chloroquine-induced scratching responses [27].

Recent work from Sharif et al. has showed the multimodality of $MrgprA3^+$ neurons [61]. Their results suggest that metabotropic Gq-linked stimulation of $MrgprA3^+$ neurons (chloroquine or Dreadd) induces itch, whereas ionotropic stimulation (ChR2 or ATP gated P2X3 channels) induces pain sensation. They found that blockers for TRP channels attenuated itch behavior evoked by chloroquine, but did not affect pain behavior evoked by optical activation of $MrgprA3^+$ neurons. These interesting results suggest that MrgprA3 can engage distinct intracellular signaling to exert different somatosensory effects.

MrgprC11

MrgprC11 is expressed in a subset of nociceptors that constitute approximately 18% of DRG neurons and includes almost all $MrgprA3^+$ neurons [21, 22, 39]. It can be activated by multiple agonists including Bam8-22, SLIGRL, Cathepsin S, and RF-amide peptide family characterized by common C-terminal -RF(Y)G or -RF(Y) amide motif [22, 37, 38, 54]. Activation of $MrgprC11^+$ nerves at different locations exert different somatosensory effects. Excitation of peripheral $MrgprC11^+$ nerves in the skin by multiple pruritogens evokes itch sensation [17], whereas stimulation of central $MrgprC11^+$ nerves by intrathecally delivered agonists induces analgesic effects [19, 35].

Results from several groups suggest that MrgprC11 mediated itch signaling involve $G\alpha_{q/11}$. TRPA1, and Nav1.9. Han et al. utilized mouse embryotic fibroblast (MEF) cells derived from $G\alpha_{q/11}$ or $G\alpha_{12/13}$ KO mice to examine the required G proteins for downstream signaling of both MrgprC11 and MrgprA1 [22]. γ2-MSH and FLRFa were used to activate MrgprC11 and MrgprA1 transfected in MEFs respectively and induce calcium responses. They observed normal calcium responses in $G\alpha_{12/13}$ KO MEFs. However, calcium responses were completely abolished in $G\alpha_{q/11}$ KO MEFs, and the calcium responses were then rescued in $G\alpha_{q/11}$ KO MEFs co-transfected with wildtype $G\alpha_q$, suggesting that MrgprC11 and MrgprA1 utilize $G\alpha_{q/11}$-dependent signaling in MEFs. Additionally, Han et al. found that γ2-MSH and FLRFa activation of HEK293 cells expressing MrgprC11 or MrgprA1 was not affected by pretreatment with pertussis toxin (PTX), which inhibits the $G\alpha_{i/o}$ [22], suggesting that $G\alpha_{i/o}$ is not required for MrgprC11 signaling.

Consistent with Han et al.'s finding, Wilson et al. later showed that activation of DRG sensory neurons by Bam8-22 was blocked by the PLC-inhibitor U73122, but not by the Gβγ inhibitor gallein, suggesting that MrgprC11 couples to $G\alpha_{q/11}$ and activates PLC to induce neuronal excitation [80]. Their results also suggest the role of TRPA1 for MrgprC11-

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mediated neuronal activation, as TRPA1 knockout mice exhibited reduced sensory neuron responses and scratching behavior in response to Bam8-22. However, recent results from Tseng et al showed that TRPA1 knockout mice exhibited similar scratching bouts as WT mice in response to Bam8-22 [73]. Therefore, whether TRPA1 is required for MrgprC11 signaling is still unclear.

Recent results from Salvatinerra et al. demonstrate the role of Nav1.9 in itch sensation mediated by both MrgprA3 and MrgprC11 [59]. Nav1.9 is a voltage-gated Na^+ channel that is critical for the propagation of action potentials in nociceptors [15]. Salvatinerra et al. has shown the expression of Nav1.9 in both MrgprA3$^+$ and MrgprC11$^+$neurons. Nav1.9 knockout mice exhibited a significant reduction of scratching behaviors induced by chloroquine and Bam8-22, suggesting that Nav1.9 is required for MrgprA3 and MrgprC11-mediated neuronal excitation. Intriguingly, Nav1.9$^{L799P/WT}$ mice, which carry a Nav1.9 gain-of-function mutation, exhibited robust spontaneous scratching, demonstrating the critical role of Nav1.9 in itch signaling. It is unclear how Nav1.9 is activated by MrgprA3 and MrgprC11 signaling.

The analgesic effect that results from activation of MrgprC11$^+$central nerves has been demonstrated by several groups independently and shown in a variety of rodent pain behavioral models including inflammatory pain, neuropathic pain, and cancer pain [19, 23, 29, 60, 69, 76–79]. This inhibitory effect was abolished in Mrgpr-cluster knockout mice, suggesting the role of MrgprC11 in pain inhibition [19]. Several reports from Guan's group have investigated the molecular mechanisms underlying these MrgprC11-mediated analgesic effects. They found that activation of MrgprC11 by Bam8-22 or JHU58, a dipeptide and MrgprC11 selective agonist, inhibits N-type high-voltage-activated (HVA) calcium channels [34, 35], a critical molecule for neurotransmitter release in sensory neurons [42], and eventually leads to reduced evoked excitatory postsynaptic currents in the spinal neurons [19]. The inhibition of HVA current can be blocked by the PLC inhibitor U73122 and the $G\beta\gamma$ blocker gallein, but not by the $G\alpha i$ pathway blocker pertussis toxin or the $G\alpha s$ pathway inhibitor cholera toxin, suggesting that MrgprC11 couples to PLC to attenuate HVA current [34].

They later found that MrgprC11 can also positively regulate the analgesic effect of the μ-opioid receptor (MOR) by forming a heteromeric complex with MOR and promote MOR recycling. Intrathecal administration of Bam8-22 potentiated acute morphine analgesia and inhibit chronic morphine tolerance in WT mice. This effect was not observed in Mrgpr-cluster knockout mice. These results suggest the possibility to achieve efficient pain relief with a low dose of morphine without tolerance by targeting MrgprC11.

MrgprD

MrgprD was initially thought to be a sensory neuron-specific GPCR mediating somatosensation [18, 84]. Later extensive studies identified multiple potent agonists including β-alanine, almandine, and angiotensin-(1-7), as well as its expression in a variety of tissues such as testes, artery, uterus, and adipose [5]. MrgprD has been shown to couple to different signaling pathways in different cell types.

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Several cellular studies have provided evidence demonstrating that MrgprD is coupled to both $G\alpha_{i/o}$ and $G\alpha_{q/11}$ subunits. Specifically, Shinohara et al. found β-alanine activation of MrgprD induced elevated intracellular calcium signaling in Chinse Hamster Ovary (CHO) cells [63], while Ajit et al. demonstrated that direct activation of MrgprD by β-alanine was completely abolished in CHO cells pre-treated with the PLC inhibitor U73122 [1]. Consistently, almandine activation of MrgprD was inhibited by the PLC inhibitor U73122 in adipose cells collected from rats [16]. These results are indirect indicators $G\alpha_{q/11}$ signaling because PLC and elevated intracellular calcium signaling are also downstream of $G\beta\gamma$. Providing more direct evidence of $G\alpha_{q/11}$ signaling, Uchiyama et al. demonstrated that leptin mRNA expression induced by almandine activation of MrgprD was reversed in the presence of the $G\alpha_{q/11}$ specific-inhibitor YM25490 within adipose cells [16].

Although almandine-induced MrgprD signaling was unchanged by PTX in adipose cells [16], both Ajit et al. and Shinohara et al. found evidence of PTX-sensitivity of MrgprD signaling in CHO cells, implicating $G\alpha_{i/o}$. Ajit et al. found that β-alanine induced calcium mobilization in CHO cells expressing MrgprD was inhibited by PTX [1], while Shinohara et al. found that PTX reversed β-alanine suppression of forskolin-induced cAMP production [63]. This difference in PTX-sensitivity may be due to different signaling pathways employed by different ligands (β-alanine vs alamandine) or different cell types (CHO vs adipose cells).

Moreover, Crozier et al. found that β-alanine-induced activation of MrgD leads to inhibition of KCNQ2/3 subunits, an M-type potassium channel, in both CHO cells and DRG sensory neurons [14]. This effect can be effectively blocked by both PLC inhibitor U73122 and PTX, suggesting the involvement of $G\alpha_{i/o}$ and $G\alpha_{q/11}$ signaling.

In addition to utilizing $G\alpha_{i/o}$ and $G\alpha_{q/11}$ pathways, Tetzner et al. has also linked Angiotensin-(1-7)-induced MrgprD responses with $G\alpha_s$. Angiotensin-(1-7) activated MrgprD expressed in HEK293 cells and induced a dose-dependent increase in cAMP and PKA, downstream molecules of $G\alpha_s$, which was decreased by the adenylyl cyclase inhibitor SQ22536 [70].

Similar to MrgprA3 and MrgprC11, Wang et al. suggested that MrgprD also couples to TRPA1 in DRG sensory neurons [75]. Specifically, they demonstrate that the TRPA1 inhibitor HC-030031 suppresses β-alanine-induced responses in DRG neurons. β-alanine-induced neuronal responses are also decreased in TRPA1 knockout mice. Consistent with the results from Tetzner et al., they demonstrate that β-alanine-induced Ca^{2+} response in DRG sensory neurons can be inhibited by the PKA inhibitor H89 dihydrochloride, but not by PKC inhibitor chelerythrine chloride or the PLC inhibitor U73122 [70], suggesting that MrgprD couples to $G\alpha_s$ and PKA in DRG sensory neurons.

Finally, using Xenopus oocytes transfected with MrgprD Zhao et al. showed that calcium-activated chloride channels (CaCCs) are downstream effectors for MrgprD signaling [83]. They found that β-alanine-induced currents were blocked by EGTA, PLC inhibitor U73122, IP3 receptor antisense oligoneucleotide, and CaCCs inhibitor FFA. The PKC inhibitor, calphostin, did not induce any change in β-alanine-induced currents. Their data suggest that

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activation of MrgprD induces the opening of CaCC via the $G\alpha_{q/11}$-PLC-IP3-Ca^{2+} pathway [83].

hMrgprX1

hMrgprX1 is expressed in human DRG sensory neurons and mediates itch sensation [10, 64]. Based on the ligand binding affinity, hMrgprX1 is considered as a functional orthologue for both MrgprA3 and MrgprC11 [43]. Several heterologous systems including cell lines, rat primary neuron culture, and transgenic mice have been used to understand the intracellular signaling pathways that can be recruited by hMrgprX1, although it is not clear if the discovered results are true in human cells naturally expressing hMrgprX1. HEK293 cells expressing hMrgprX1 exhibit calcium signals upon Bam8-22 activation [33]. Tseng et al. examined hMrgprX1 expressed in DRG sensory neurons using a "humanized" transgenic mouse line in which endogenous mouse Mrgprs was replaced with hMrgprX1 [73]. They found that hMrgprX1 mediated excitation of sensory neurons are mediated by PLC pathways in a $G\beta\gamma$ dependent manner, and is also sensitive to $G\alpha_{i/o}$ inhibitor pertussis toxin.

Chen & Ikeda used rat primary neurons overexpressed with hMrgprX1 to examine hMrgprX1 signaling [11]. Similar to MrgprC11, they found that Bam8-22 activation of hMrgprX1 expressed in both rat superior cervical ganglion neurons and DRG neurons inhibited high-voltage-activated (HVA) calcium current. Bam8-22 also induced inhibition of evoked excitatory postsynaptic currents in hippocampal neurons expressing hMrgprX1. Consistent results were presented by Li et al. showing that Bam8-22 inhibits HVA calcium current and attenuates synaptic transmission in the "humanized" mouse sensory neurons expressing hMrgprX1 [36]. However, the inhibition of HVA current by MrgprC11 in native DRG sensory neurons and hMrgprX1 in tested heterologous neuron systems seems to utilize different signaling pathways. MrgprC11 couples to $G\beta\gamma$ and PLC signaling, and is insensitive to $G\alpha i$ pathway blocker pertussis toxin [34]. hMrgprX1 mediated inhibition of HVA calcium current is insensitive to the PLC inhibitor U73122, but is $G\alpha_{i/o}$ and $G_{\beta\gamma}$-dependent [36].

Solinski et al. have shown that TRPV1 is a downstream component of hMrgprX1 when overexpressed in F11 cells, a rat neuron cell line [66]. They found that Bam8-22 stimulation of hMrgprX1 in F11 cells both directly activate TRPV1 via DAG and PIP_2 and sensitize TRPV1 via PKC phosphorylation [66]. However, using the "humanized" mouse sensory neurons expressing hMrgprX1, Tseng et al. did not observe the involvement of TRPA1 or TRPV1 as the TRPA1 inhibitor HC030031 and TRP channels blocker ruthenium red had no inhibitory effect on Bam8-22 evoked action potentials or firing rates [73]. They suggested the involvement of Nav1.8 and Nav1.9 since TTX reduced the number of action potentials induced by Bam8-22.

MrgprB2/hMrgprX2

MrgprB2 and its human homolog MrgprX2 are mainly expressed in mast cells. They can be activated by basic secretagogues, a group of positively charged molecules, to induce

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IgE-independent mast cell degranulation, a reaction to release numerous bioactive molecules involved in various processes including immune responses, vascular tone, and nociception [44, 52].

Subramanian et al. demonstrate that MrgprX2 serves as the receptor to mediate mast cell activation by both antimicrobial peptide LL-37 and β-defensins [67, 68]. Mast cells exhibit calcium response and degranulation often via a pertussis toxin-sensitive $G\alpha_{i/o}$ pathway upon stimulation by an agonist. However, they found that pertussis toxin inhibited degranulation, but not calcium mobilization in human mast cells in response to both LL-37 and β-defensins. These data suggest that MrgprX2 couples to a $G\alpha_{i/o}$-independent pathway for calcium response and $G\alpha_{i/o}$-dependent pathway for degranulation in human mast cells. In support of these findings, Substance P induced degranulation and calcium mobilization in rat basil leukemia (RBL-2H3) cells expressing MrgprX2 were found to be abolished when exposed to both PTX and the $G\alpha_{q/11}$ inhibitor YM-254890 [12].

GPCRs are known to activate a G proteins-independent pathway which involves the adaptor proteins β-arrestins [28]. β-arrestins not only serve as inhibitors of GPCRs by promoting GPCR desensitization, but also play an important role in G protein-independent signaling to regulate a variety of cellular events. Assays examining β-arrestins recruitment and translocation have been widely used to identify agonists for GPCRs [33]. Although extensive studies have not been performed to examine the role of β-arrestins in Mrgprs signaling, several agonists for MrgprX2 and MrgprX4 have been identified using β-arrestins recruitment assays [4, 33], suggesting that β-arrestins are activated by Mrgprs. Roy et al. have demonstrated that MrgprX2 in mast cells, when stimulated by different agonists, recruits different downstream signaling pathways [56]. For example, while MrgprX2 recruits both G protein signaling and β-arrestin signaling when stimulated by compound 48/80, it only recruits G protein signaling when activated by AG-30/5C, an angiogenic host defense peptide. They later showed that MrgprB2-mediated degranulation of peritoneal mast cells induced by both ciprofloxacin and compound 48/80 were significantly enhanced in β-arrestin-2 knockout mice, demonstrating the involvement of β-arrestin-2 in MrgprB2 signaling [57]. Finally, Babina et al. recently showed that silencing of β-arrestin-1, but not β-arrestin-2, by siRNA attenuated MrgprX2 internalization in skin mast cells induced by Codeine [4].

Mast cell degranulation follows the intracellular calcium mobilization. Ample evidence has demonstrated that IgE-dependent mast cell activation is mediated by the store-operated Ca^{2+} entry (SOCE) via stromal interaction molecule 1 (STIM1) [3, 6, 62]. STIM1 is the central proponent of SOCE and contains Ca^{2+}-binding domains oriented towards the lumen of the endoplasmic reticulum (ER). When cellular activation results in the depletion of Ca^{2+} in the ER, ER-lumen oriented Ca^{2+} binding domains of STIM1 become unbound, resulting in the formation of a complex with calcium release-activated calcium (CRAC) channels and TRPC channels to allow for Ca^{2+} influx into the cytoplasm. Occhiuto et al. showed that hMrgprX2 utilizes a similar mechanism for IgE-independent mast cell activation [50]. They demonstrate that MrgprX2 agonist CST-14 induced calcium signal and degranulation in LAD2 human mast cells and these effects were decreased by the CRAC channel antagonist YM 58483 and the SOCE inhibitor SKF 96365 HC1. In contrast, the TRP channel inhibitors

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Nifedipine and A425619 had no effect on either degranulation or calcium signal. These conclusions are supported by evidence from an *in vivo* mouse model of pseudo-allergy. SOCE inhibitor treated mice were injected with MrgprB2 agonist compound 48/40 to induce mast cell degranulation. Compared to control, the SOCE inhibitor treated mice were found to exhibit decreased paw swelling and decreased histamine levels in serum, indicating a reduction in mast cell degranulation.

MrgprA1/hMrgprX4

MrgprA1 and hMrgprX4 mediate bilirubin-induced itch and have been implicated in cholestatic pruritus [47]. Consistent with Han et al.'s finding that MrgprA1 utilizes $G\alpha_{q/11}$-dependent pathways in MEFs that we discussed above [22], Meixiong et al. have shown that bilirubin-induced calcium responses in HEK293 cells expressing mMrgprA1 can be abolished by the $G\alpha_q$ specific-inhibitor YM-254890 or the PLC inhibitor U73122 [47].

Similar to MrgprA1, hMrgprX4 couples to $G\alpha_q$ in HEK293 cells. Yu et al. has demonstrated that bile acid can activate hMrgprX4 expressed in a $G\alpha_{q/11}$-dependent reporter assay, but not in a $G\alpha_s$-dependent reporter assay [82]. Both deoxycholic acid and bilirubin induced activation of hMrgprX4 were inhibited by the PLC inhibitor U73122 or the $G\alpha_q$ inhibitor YM254890 [47, 48]. Additionally, Kroeze et al. found that nateglinide induced calcium mobilization and phosphatidylinositol hydrolysis in HEK293 cells expressing hMrgprX4 [33].

Polymorphisms in Mrgprs

Single nucleotide polymorphisms (SNPs) are among the most common types of genetic variation, with missense SNPs often cited as the main explanatory cause for disease variation due to their effects on the structure of the protein, and thus its ability to transduce signals [9]. Many SNPs have been identified in human Mrgpr family members and can be found in publicly available human exome sequencing databases such as NCBI dbSNP, NHLBI GO Exome Sequencing Project, and 1000 Genomes. However, research investigating how Mrgprs polymorphisms contribute to human diseases is in its infancy. There are only a few reports showing the possible functional implications for naturally occurring missense variants of Mrgprs.

Heller et al. identifies two MrgprX1 mutations with allele frequency exceeding 0.1%, R131S and H133R, that result in loss and gain of function respectively with regard to their ability to bind Bam8-22, based on the results of luciferase reporter assays utilizing transfected HEK cells [24]. Whether these mutations have a human clinical relevance is not clear.

Alkanfari et al. tested several missense variants of MrgprX2 overexpressed in RBL-2H3 cells, a rat basophilic leukemia cell line, to examine if any of them display abnormal function [2]. The results showed that four of them including G165E, D184H, W243R, and H259Y disrupted RBL-2H3 cell degranulation in response to MrgprX2 ligands including substance P, hemokinin-1, β-defensin-3, and icatibant. Another study reported four loss of function naturally occurring MrgprX2 variants including V123F, R138C, R141C, and V282M [12]. These variants exhibit disrupted calcium mobilization and degranulation

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in RBL-2H3 cells in response to substance P. These results suggest that these missense mutations might protect the carrying individuals from MrgprX2-mediated pseudoallergy and chronic inflammatory diseases. Two gain of function MrgprX2 variants, S325L and L329Q, have also been identified since they showed enhanced mast cell activation upon substance P stimulation [12].

Using an exome-wide association study [32], Kozlitifna et al. identified two MrgprX4 variants, N245S and T43T, that are expressed exclusively within African American participants and associated with a 5-8 fold increase in the preference of menthol cigarette among smokers. They found that these MrgprX4 variants exhibit reduced signaling in HEK293 cells based on both β-arrestin-based and $G\alpha_q$-based reporter assays. They also identified menthol as a negative modulator for MrgprX4 since it reduced the MrgprX4 signaling in HEK293 cells in response to Nateglinide. However, it remains unknown how these MrgprX4 variants contribute to the preference for menthol cigarette use.

Conclusions

Mrgprs utilize multiple endogenous ligands through distinct signaling pathways to encode for and modulate different biological processes. Although many key signaling components have been identified, further research is needed to build upon the findings presented here as our understanding has evolved greatly in the last few decades. In particular, there are emerging caveats to the use of particular inhibitors as well as cell and tissue types that need to be taken into account. For example, the PLC inhibitor U73122 has been shown to have many non-specific effects [30, 31, 73]. Pertussis toxin is utilized almost exclusively for identifying $G\alpha_{i/o}$ signaling, despite one of the subfamilies, $G\alpha_z$, being unaffected by PTX [25]. While Tseng et al. found that the HC030031 is not a TRPA1 specific inhibitor since it also induces the inhibition of voltage-gated calcium channels in sensory neurons [73]. As such, evaluating the results from pharmacological inhibitors should be handled with care.

Due to the critical role of Mrgpr family members in a variety of physiological processes, polymorphisms in Mrgprs can have a profound impact on human disease. However, despite the existence of many naturally occurring Mrgprs polymorphisms, few have been extensively studied to date. Future research focusing on Mrgprs polymorphisms will help to explain differences in disease incidence and drug effect across different populations.

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Highlights

- Mrgprs utilize canonical G protein signaling pathways
- Mrgprs couple to ion channels to excite neurons
- Functional implications of Mrgprs polymorphisms

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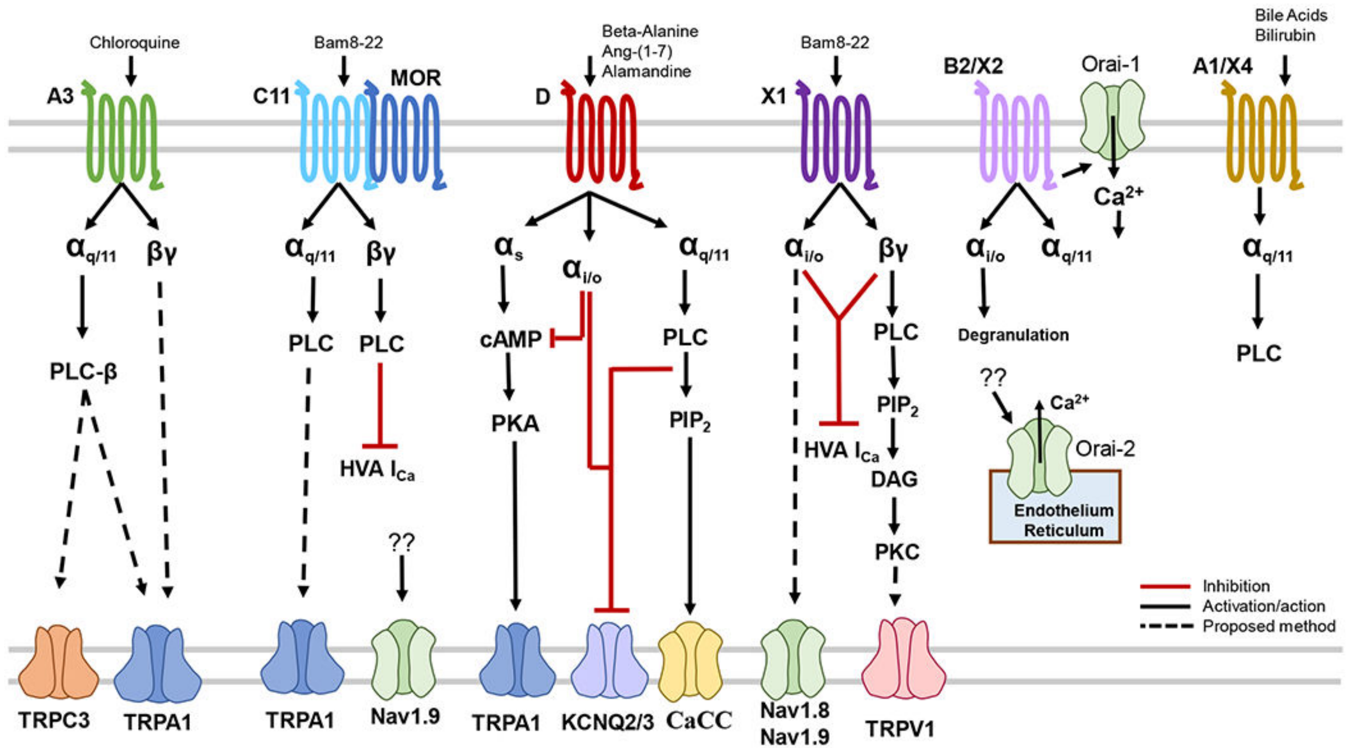

Fig. 1.

Overview of Mrgprs Signaling Pathways. Mrgprs have been found to utilize Gαq/11, Gαi/o, Gαs, and Gβγ pathways. Activation of G proteins stimulates the intracellular signaling pathways and leads to the opening of transduction channels.