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1 **Title**

2 Mas-related G protein-coupled receptors (Mrgprs) - Key regulators of neuroimmune
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4

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23 **Abstract**

24 Interplay between physiological systems in the body plays a prominent role in health and
25 disease. At the cellular level, such interplay is orchestrated through the binding of specific
26 ligands to their receptors expressed on cell surface. G protein-coupled receptors (GPCR) are
27 seven-transmembrane domain receptors that initiate various cellular responses and regulate
28 homeostasis. In this review, we focus on particular GPCRs named Mas-related G protein-
29 coupled receptors (Mrgprs) mainly expressed by sensory neurons and specialized immune
30 cells. We describe the different subfamilies of Mrgprs and their specific ligands, as well as
31 recent advances in the field that illustrate the role played by these receptors in neuro-immune
32 biological processes, including itch, pain and inflammation in diverse organs.

33 **Introduction**

34 Recent advances in the field of neuro-immunology successfully uncovered various
35 circuits responsible for itch sensation, pain transmission and inflammatory reactions. Mas-
36 related G protein-coupled receptors (Mrgprs) are key receptors involved in the regulation of
37 such biological processes. First described more than 25 years ago, the Mrgpr family now
38 comprises more than 50 members in humans and rodents. Many Mrgprs are still considered as
39 orphan receptors, with no identified endogenous or synthetic ligands. However, important
40 advances in molecular biology helped to deorphanize many of them expressed by primary
41 sensory neurons. Most Mrgprs are associated with nociception and itch transmission, through
42 their binding to various itch-inducing or pain-associated substances: such as β -alanine,
43 chloroquine (CQ), BAM(8-22) or substance P (SP) (Z. Li et al., 2017; Q. Liu et al., 2009,
44 2012; Meixiong, Vasavda, et al., 2019; Qu et al., 2014; Sanjel et al., 2019, 2019; Van
45 Remoortel et al., 2019; C. Wang et al., 2019). Recently, a member of the Mrgpr family was
46 found to be expressed on mast cells, a specialized innate immune cell involved in conveying
47 non-histaminergic and histaminergic itch, nociception, inflammation and host protection
48 (McNeil et al., 2014). Importantly, Mrgprs were found to be substantial actors in the
49 communication established between the nervous and immune systems, regulating mechanisms
50 involved in chronic inflammation (D. P. Green et al., 2019; Perner et al., 2020; Pundir et al.,
51 2019; Serhan et al., 2019). In this review, we describe the diversity of Mrgprs and identified
52 ligands, as well as the upshots of Mrgpr-mediated activation of sensory neurons and immune
53 cells, in the contexts of itch, pain and tissue inflammatory processes.

54

55 **Mrgprs: evolution, subfamilies, expression pattern and main functions**

56 Mrgprs are GPCRs encoded by the *Mrgpr* gene family. This family was characterized
57 more than 30 years ago with the description of the *Mas* gene encoding for oncogene-like
58 MAS receptors (Young et al., 1986). Rapid advances in molecular biology, cloning strategies
59 and bioinformatics helped decipher the *Mrgpr* gene family that now gathers more than 50
60 members in rodents and humans (Dong et al., 2001a; Lembo et al., 2002; Takeda et al., 2002;
61 Wittenberger et al., 2001; Lin Zhang et al., 2005). All the receptors have been relabeled
62 according to their functions and structures and were reassigned to several subfamilies: human
63 receptors include eight subfamilies, MRGPRX 1 to 4, and MRGPR D to G, whereas rodent
64 receptors include 7 subfamilies, Mrgpr A to G. *Mrgpr* gene clusters are all regrouped on
65 chromosome (CR)11 in human (with the exception of *Mas11* and *Mas* genes that are located
66 on CR6) and CR7 in mouse (with the exception of *Mas H* gene located on CR17). After the
67 identification of all coding sequences of these genes, the murine Mrgpr family now comprises
68 the MrgprA subfamily gathering 14 members, the MrgprB and MrgprC families regrouping
69 together 27 members, and the other families with unique members, the single-gene families,
70 Mrgpr D, E, F and G. As for human receptors, MRGPRX 1-4 can be paired to the mouse
71 MrgprA and B family members, while the other receptors (D to G) have clear defined
72 identical murine orthologs (Bader et al., 2014).

73 Originally, Mrgprs expression pattern was described in dorsal root ganglia (DRG) and
74 trigeminal ganglia (TG) by transcriptomic studies that revealed their expression in nociceptive
75 and pruriceptive neurons of the above-cited ganglia, and more specifically in isolectin B4-
76 positive small-diameter somatosensory afferents neurons (Dong et al., 2001a; Y. Liu et al.,
77 2008; Zylka et al., 2003). Some Mrgprs are since considered as the prevailing markers of
78 specific sensory neuron subsets in mice. Indeed, large-scale single-cell RNA sequencing
79 identified subsets of sensory neurons characterized by the expression of specific Mrgprs: the
80 non-peptidergic (NP) population 1 mostly expressed MrgprD, while the NP2 expressed

81 MrgprA3 & MrgprC11 (Usoskin et al., 2015). However, other works have shown that Mrgpr
82 expression is not limited to sensory neurons and could also be found in other tissues, like the
83 heart (MrgprH) (Wittenberger et al., 2001), genitals (MrgprB3, MrgprB8 and MrgprD) (Y.-H.
84 Huang et al., 2013; Shinohara et al., 2004), cerebellum (MrgprE and MrgprF) (Ross et al.,
85 1990), cerebral cortex and hippocampus (MrgprE), smooth muscle-containing tissues
86 (MrgprF, drastically upregulated during monocyte-to-macrophage differentiation)
87 (Hohenhaus et al., 2013; Ross et al., 1990) and in the enteric nervous system (MrgprD)
88 (Avula et al., 2011; Zhou et al., 2019), the latter still being controversial (Van Remoortel &
89 Timmermans, 2019).

90 Beside highly-innervated tissues, immune cells are also listed as Mrgpr-expressing
91 cells (Dwyer et al., 2016). In particular, MRGPRX2 was found to be expressed at the surface
92 of human cutaneous mast cells, and the ortholog MrgprB2 by murine skin, peritoneal,
93 esophagus and tracheal mast cells (Fujisawa et al., 2014; McNeil et al., 2014; Subramanian et
94 al., 2016; Subramanian, Gupta, et al., 2011a; Subramanian, Kashem, et al., 2011).

95 Diversified expression patterns imply a wide selection of ligands and consequently different
96 functions for these receptors and for the resulting signaling. Divergent ligand specificities
97 have been delineated for some Mrgprs, nevertheless many of them are left orphaned until
98 today. Known ligands (listed in **Table 1**) include proteins and peptides, as well as non-
99 peptidic ligands, such as lipids and some metabolites (e.g. alamandine, angiotensin(1-7),
100 opioid precursor proenkephalin-derived peptides such as Bovine Adrenal Medulla [BAM]22,
101 proopiomelanocortin [melanocyte-stimulating hormone] and many others) (S.-K. Han et al.,
102 2002; Karnik et al., 2017; Kashem et al., 2011; Lautner et al., 2013; Lembo et al., 2002;
103 Santos et al., 2003). The following sections describe the role of Mrgprs in sensory neurons
104 and immune cells biological functions.

105 **Role of Mrgprs in itch and pain**106 ***Implication of Mrgprs in the itch pathway.***

107 Mrgprs were first identified on specialized sensory neurons that encode itch
108 (pruriceptors) and pain (nociceptors) (Dong et al., 2001a; Usoskin et al., 2015). Both of these
109 neuronal subtypes have their cell bodies residing in the DRG and the TG (Dubin &
110 Patapoutian, 2010; Hunt & Mantyh, 2001). Importantly, activation of Mrgprs expressed at the
111 surface of sensory neurons has been shown to induce both itch and pain sensations.

112 Itch or pruritus is clinically defined as the subjective and unpleasant sensation of a
113 desire to scratch (Ikoma et al., 2006; LaMotte et al., 2014). The pathophysiological causes of
114 pruritus are still largely unknown, but it is thought to be mainly mediated by molecules
115 known as “pruritogens” particularly efficient at activating pruriceptors. Two distinct chemical
116 itch pathways have been described: the histaminergic (involving mainly Histamine Receptor
117 H1 activation by mast cell-derived histamine) and non-histaminergic (involving other
118 pruritogens and other receptors) (LaMotte et al., 2014). In the periphery, itch is mainly
119 encoded by two specialized populations of sensory neurons, the NP2 population expressing
120 MrgprA3 and the NP3 population expressing Natriuretic Peptide B Precursor (NPPB)
121 (Meixiong et al., 2020; Usoskin et al., 2015). Altogether, these two populations form the so-
122 called pruriceptors. Furthermore, some pruritogens can also activate mixed
123 nociceptive/pruriceptive populations, such as the β -alanin that can trigger the activation of the
124 NP1 MrgprD⁺ population of sensory neurons (Shinohara et al., 2004), or the highly specific
125 mu-opioid receptor agonist [D-Ala², N-MePhe⁴, Gly-ol]-enkephalin (DAMGO) that can
126 activate the TRPV1⁺ population of sensory neurons to induce itch (Melo et al., 2018).

127 Numerous studies have characterized known pruritogens as “Mrgpr agonists”, such as
128 the Chloroquine (CQ), BAM(8-22) or the β -alanine (Davidson et al., 2012; Sator et al.,

129 2003). Importantly, all these pruritogens stimulate the non-histaminergic itch pathway. CQ is
130 an antimalarial drug that has been known for long to induce itch in human and animal models
131 (Ezeamuzie *et al.*, 1991; A. D. Green *et al.*, 2006; Inan & Cowan, 2004; Onigbogi *et al.*,
132 2000). In mice, loss and gain of function mutations showed that CQ can activate *MrgprA3*.
133 Accordingly, CQ also activates MRGPRX1 which is the human ortholog of *MrgprA3*
134 resulting in non-histaminergic itch (Q. Liu *et al.*, 2009). Nociceptor ablation based on Cre
135 recombinase expression under the control of the *Mrgpra3* promoter resulted in a less severe
136 and inducible itch by most tested pruritogens (L. Han *et al.*, 2013). Other pruritogens that
137 activate *Mrgprs* also include endogenous peptides like BAM(8-22), a peptide derived from the
138 proopiomelanocortin protein. Indeed, Lembo *et al.* described that BAM(8-22) can activate
139 *MrgprC11* (Lembo *et al.*, 2002). *Mrgprc11* mutant mice were shown to have significantly less
140 susceptibility to BAM(8-22)-induced itch. To further validate the crucial role of *Mrgpr* in
141 mediating the itch response to both CQ and BAM(8-22), it was shown that mice in which the
142 *Mrgpr* gene cluster was deleted (altering up to 12 coding frames, including those coding for
143 *MrgprA3* and *MrgprC11*) did not scratch in response to either molecule (Lembo *et al.*, 2002;
144 Q. Liu *et al.*, 2009). In humans, injections of BAM(8-22) resulted in stinging and burning
145 sensations accompanied by a strong itch, that could eventually be driven by sustained
146 activation of MRGPRX1 (Sikand *et al.*, 2011). The absence of a neurogenic flare and the lack
147 of efficacy of pre-treatment with anti-histaminic provided further complementary evidence of
148 a potential non-histaminergic type of itch. Interestingly, a very recent study showed that
149 *MrgprC11* and human MRGPRX1 are the main receptors for two tick salivary peptides,
150 IPDef1 and IRDef2. Accordingly, IPDef1 and IRDef2-mediated activation of *MrgprC11/X1*-
151 on DRG neuron resulted in non-histaminergic itch via the Transient Receptor Potential
152 Vanilloid (TRPV1), independently of the TRP Ankyrin 1 (TRPA1) (X. Li *et al.*, 2020). These
153 findings round off the clinical observation of the inefficiency of anti-histaminic drugs to treat

154 tick bites-induced itch. Another well-known pruritogen is β -alanine, that binds and activates
155 MrgprD. β -alanine is a small amino acid present at high concentrations in muscles and skin
156 (Rau et al., 2009), and considered as a potent pruritogen, in human and rodents (Qu et al.,
157 2014; Shinohara et al., 2004). It has been shown that oral or intradermal administration of
158 β -alanine induced itch and scratching behavior in wild type mice, but not in *Mrgprd*^{-/-} mice
159 (Q. Liu et al., 2012). In a model of chemically-induced psoriatic itch, gene expression levels
160 of *Mrgprd* were found to be significantly decreased (Sakai et al., 2016), which might
161 eventually underline a protective mechanism against the development of excessive itch
162 sensation. In a model of contact hypersensitivity induced by haptens, MrgprD was found to
163 become “hypersensitive”, since MrgprD⁺ neurons innervating the hapten-challenged skin
164 exhibited spontaneous activity and/or abnormal after-discharges in response to mechanical
165 and heat stimuli, with a greater number of action potentials (Qu et al., 2014). Likewise,
166 spontaneous itch-like (biting or scratching) behaviors were reported in these mice.
167 Interestingly, intradermal injections of β -alanine in human subjects elicited itch, but without
168 wheal and flare, that are two clinical manifestations classically associated with histaminergic
169 itch. These data suggested a possible activation of the non-histaminergic itch pathway by
170 β -alanine (Q. Liu et al., 2012). Very recently, the bilirubin (an endogenous degradation
171 metabolite of hemoglobin) was described as a novel ligand for mouse MrgprA1 and human
172 MRGPRX4 in the pathological context of cholestatic pruritus. A study by Meixiong *et al.*
173 suggested that bilirubin activated sensory neurons through MrgprA1 in a TRP channel-
174 dependent mechanism (Meixiong, Vasavda, et al., 2019). In a mouse model of cholestasis,
175 removing either MrgprA1 or biliverdin reductase (the enzyme that facilitates the conversion
176 of biliverdin to bilirubin) both strongly attenuated cholestatic itch.

177 ***Implication of Mrgprs in the pain pathway.***

178 Mrgpr activation has also been shown to mediate pain signaling. Pain is defined as an
179 unpleasant sensory and emotional experience associated with actual or potential tissue
180 damage. It is characterized by hypersensitivities to multiple stimuli that lead to painful
181 sensation once integrated in the brain (M. J. Caterina et al., 2000; Michael J. Caterina et al.,
182 1999; Costigan & Woolf, 2000). The role for Mrgprs in the pain phenotype has not been
183 completely elucidated yet. Majority of the studies conducted focused on the role of MrgprD-
184 expressing nociceptors in mechanical hypersensitivity and neuropathic pain behavior in
185 mouse models rather than on the role of the receptor itself (Qu et al., 2014; C. Wang et al.,
186 2019). A recent study by *Huang et al.* used *Mrgprd^{DTR}* mice, in which the human diphtheria
187 toxin receptor (DTR) is driven from the *Mrgprd* locus, to specifically ablate MrgprD⁺ neurons
188 in adult mice. Basal mechanical thresholds were significantly increased in mice that lack
189 MrgprD⁺ nociceptor (T. Huang et al., 2019). Mrgprs could be involved in the modulation of
190 somatic pain phenotype. Intrathecal injection of the MrgprC agonist [Tyr⁶] γ 2-MSH(6-12) in
191 wild type mice induced acute-like pain behavior (Chang et al., 2009). Interestingly, in a
192 humanized mouse model expressing MRGPRX1, Zhe Li *et al.* showed that intrathecal
193 injection of BAM(8–22) reduced pain behavior in a model of chronic constriction injury.
194 These data strongly suggest that MRGPRX1 could be a potential target for the treatment of
195 chronic pain (Z. Li et al., 2017). Further studies would be pertinent to uncover and thoroughly
196 characterize the role of neuronal Mrgprs in somatic pain.

197 Mrgprs have also been reported to be important regulators of visceral pain phenotype.
198 Since its discovery in 2002, the expression of MrgprD was thought to be restricted to skin-
199 projecting neurons and its biological function limited to cutaneous somatosensation.
200 However, *Hockley et al.* reported the expression of *Mrgprd*, and of other Mrgprs including
201 *Mrgpra9*, *Mrgpra2b*, *Mrgprc11* (referenced as *Mrgprx1* in the study), *Mrgprb5* and *Mrgpra3*
202 in the soma of sensory neurons that project to the colon (Hockley et al., 2019). Additional

203 studies using single-cell quantitative PCR (qPCR) (Bautzova et al., 2018; Castro et al., 2019),
204 *Mrgprd*^{EGFP} reporter mice and retrogradely-traced mouse colonic sensory neurons (Bautzova
205 et al., 2018) also confirmed the expression of *Mrgprd* in sensory neurons innervating the
206 colon. In human, mRNA expression of *Mrgprd*, *Mrgpra3* and *Mrgpc11* have been detected
207 and quantified by reverse transcription (RT)-qPCR in spinal DRG well known to innervate the
208 colon (T9-L1). Of note, *Mrgpra3*, *Mrgpc11* and *Mrgprd* were found co-expressed together
209 with *Trpv1* and/or *Trpa1* (Bautzova et al., 2018; Castro et al., 2019). When global sensory
210 neuron populations were assessed, MrgprD and TRPV1 were detected in discrete and almost
211 mutually-exclusive neurons (Cavanaugh et al., 2009; Usoskin et al., 2015; Zylka et al., 2005).
212 In contrast, in colon-projecting sensory neurons, 41% of TRPV1-positive neurons were also
213 reported to express *Mrgprd* (Bautzova et al., 2018). To our knowledge, such co-expression
214 has only been reported in colonic sensory neurons.

215 Of most relevance to clinical practice, activation of MrgprD signaling in the colon has
216 been shown to participate in the development of pain sensation in the context of irritable
217 bowel syndrome (IBS). IBS is a functional bowel disorder in which recurrent abdominal pain
218 is associated with changes in bowel habit (Enck et al., 2016). The pathophysiology of IBS is
219 still elusive and the underlying mechanisms contributing to afferent sensitization remain
220 incompletely understood (Spiegel et al., 2008). In a recent study, Bautzova *et al.* quantified an
221 increase of the arachidonic acid metabolite 5-oxoETE in biopsies from patients with
222 clinically-established IBS compared to healthy subjects (Bautzova et al., 2018). Low-grade
223 inflammation associated with peripheral sensory nerves hyperactivity has been widely
224 described in IBS, with several fundamental studies implicating pro-inflammatory molecules in
225 the pathophysiology of IBS symptoms (Brierley & Linden, 2014; Enck et al., 2016). The 5-
226 oxoETE has been shown to induce calcium signaling in sensory neurons. In the absence of
227 MrgprD, activation of sensory neurons by 5-oxoETE was significantly decreased, suggesting

228 that 5-oxoETE might signal in neurons via MrgprD (Bautzova et al., 2018). However, because
229 of its lipid-based nature, 5-oxoETE could not be officially classified as a new MrgprD ligand
230 due to the lack of suitable binding assays.

231 In the gut, Castro *et al.* hypothesized that the mechanisms of histamine-independent
232 itch involving MrgprA3 and MrgprC11 represent important biological components of visceral
233 sensory neuron sensitization (Castro et al., 2019). They highlighted clear individual roles for
234 MrgprA3 and MrgprC11 in the activation of colonic afferent neurons and induction of
235 mechanical hypersensitivity. In primary cultures of mouse DRG, 10% of colonic sensory
236 neurons were efficiently activated by CQ, allyl isothiocyanate ([AITC], a TRPA1 agonist) and
237 capsaicin (a TRPV1 agonist); and another 10% responded to BAM(8-22), AITC and capsaicin
238 (Castro et al., 2019). Functional interactions between MrgprA3, MrgprC11, TRPA1 and/or
239 TRPV1 have also been proposed in colonic sensory neurons (X. Li et al., 2020; Wilson et al.,
240 2011). In wild type mice, activation of MrgprA3 by CQ and MrgprC11 by BAM(8-22)
241 induced visceral hypersensitivity (Castro et al., 2019; Van Remoortel et al., 2019). As
242 demonstrated in the skin in the context of itch (Q. Liu et al., 2009), the effects of CQ and
243 BAM(8-22) on visceral sensitivity were abrogated in mice that lack a cluster of *Mrgpr* genes.
244 In addition, an itch cocktail combining 3-(2-chlorophenyl)-N-(4-chlorophenyl)-N,5-dimethyl-
245 4-isoxazolecarboxamide (CCDC), BAM(8-22) and CQ, triggered mechanical visceral
246 hypersensitivity, and had no effect in *Trpa1*^{-/-} mice (Castro et al., 2019). After confirming the
247 co-expression of MRGPRX1, TRPV1 and/or TRPA1, human sensory neurons were incubated
248 with inflammatory mediators known to be increased in biopsies of IBS patients (histamine,
249 PGE₂, serotonin and bradykinin). Consequently, the levels of intracellular calcium in response
250 to treatment with CQ were increased in such neurons, however this activation was not
251 observed with BAM(8-22). CQ activates the human MRGPRX1 with 1000-fold less affinity
252 and 2.5-fold less efficiency than BAM(8-22) (Hughes et al., 2009). Taken together, the

253 described experiments proposed that inflammatory mediators were able to sensitize and
254 increase the expression of Mrgprs in colonic sensory neurons, suggesting an important
255 function of Mrgprs in visceral hypersensitivity.

256 **Role of Mrgprs expression by immune cells during inflammation, host defense, and**
257 **neuroimmune interactions**

258 The immune system is made up of coordinated sets of cellular elements that
259 participate to many physiological processes (maintenance of tissue homeostasis, tissue
260 remodeling, cell-host relationship, etc.) and responsible for the protection against
261 environmental cues. Being part of the innate or adaptive responses, immune cells orchestrate a
262 large panel of effector mechanisms with distinct biological functions via the release of a large
263 array of cytokines and the engagement of specific surface and intracellular receptors.
264 Exacerbated activation of immune responses can often lead to the development of chronic
265 inflammation, pain, itch, and global disruptions of organs metabolism (Altan-Bonnet &
266 Mukherjee, 2019, 2019; Eisenbarth, 2019; Klose & Artis, 2016; Masopust & Soerens, 2019;
267 Ng et al., 2019).

268 The expression and the role of Mrgprs on immune cells remain a vast and exciting area of
269 exploration. Transcriptomic data suggested that mast cells are naturally-expressing some
270 Mrgprs at steady state (Dwyer et al., 2016). As active members of the innate immune system,
271 mast cells express a wide range of receptors activated upon binding of specific ligands such as
272 toxins, hormones, immunoglobulins and cytokines. Mast cell activation usually results in the
273 quasi-instantaneous release of granule-associated bioactive mediators (i.e., a phenomenon
274 named “degranulation”) and the sequential secretion of *de novo* molecules over time (lipid
275 mediators, cytokines and chemokines) (Wernersson & Pejler, 2014). Secreted substances
276 include histamine, proteases, lipid mediators and cytokines, all being efficient

277 immunomodulatory molecules. Among the pleiotropy of receptors expressed on mast cell
278 surface, MrgprB2 (and its human ortholog MRGPRX2) was the first Mrgpr found to be
279 detected outside of the sensory nervous system (Dwyer et al., 2016; Fujisawa et al., 2014;
280 McNeil et al., 2014; Subramanian, Gupta, et al., 2011a; Subramanian, Kashem, et al., 2011).
281 The spatio-temporal dynamics of MrgprB2/X2-mediated mast cell degranulation differs from
282 the canonical FcR-dependent activation and is characterized by a fast and local degranulation
283 with quasi-immediate effects on surrounding tissue and inflammation (Gaudenzio et al.,
284 2016). Activation of mast cell-MrgprB2 (or MRGPRX2) has been recently involved in
285 multiple pathophysiological processes.

286 MrgprB2 has been reported to be a mast cell receptor for quorum sensing molecules secreted
287 by bacterial populations, including the competence-stimulating peptide 1 (CSP-1). Upon
288 activation of MrgprB2, mast cells exteriorized their granular content which helped to control
289 bacterial infection by preventing bacterial growth and biofilm formation (Pundir et al., 2019).
290 In a recent study, small-molecule host-defense peptides have also been shown to signal
291 through MrgprB2/X2 and promote antifungal and antibacterial activity, presumably via a
292 similar mechanism (Alkanfari et al., 2019). Another report also showed that MrgprB2 could
293 also sense tick salivary defending peptides, IPDef1 and IRDef2, that were shown to efficiently
294 activate mast cells resulting in acute inflammation (X. Li et al., 2020).

295 Recently, complementary studies have shed new lights on the key role played by
296 MrgprB2 in regulating bidirectional interactions between mast cells and nociceptors, mainly
297 via the cationic neuropeptide SP. SP belongs to the tachykinin family and is considered as an
298 important element of pain perception (Donkin et al., 2007; Mantyh, 2002; Usoskin et al.,
299 2015). Recent findings by Green *et al.* involved SP binding to MrgprB2 and MRGPRX2 in
300 inflammatory mechanical and thermal hyperalgesia (D. P. Green et al., 2019). SP is enriched
301 in patients who suffer from post-operative pain. Compared to littermate controls, MrgprB2

302 knock-out mice were significantly less susceptible to develop inflammatory pain, such as in
303 models of postoperative incision or injection of complete Freund's adjuvant. These mice also
304 exhibited less nerve injury and a significant decrease in the recruitment of immune cells to the
305 site of injury (mainly CD11b⁺Ly6G⁻ myeloid cells). Ablation of MrgprB2⁺ mast cells *using*
306 *MrgprB2-cre; DTR* mice (in which the human DTR is under the control of *MrgprB2*
307 promotor) showed reductions in the perception of inflammatory pain (D. P. Green et al.,
308 2019). This study indicated that the SP-MrgprB2 axis could promote neurogenic
309 inflammation and be involved in pain mechanisms. Another study by Zhang *et al.* has also
310 documented a participation of MRGPRX2 in the development of morphine-induced
311 granulomas that could in turn cause persistent pain (T. Zhang et al., 2019).

312 Nociceptors and mast cells can also regulate the development of itch sensation. Mast
313 cells are known to be classically associated with histaminergic itch (Hall et al., 2012; Harvima
314 et al., 2008). However, recent findings have also highlighted the major role played by skin
315 mast cells in histamine-independent itch, through the activation of MrgprB2/X2. The authors
316 found that injection of the MrgprB2 agonist Pro-adrenomedullin peptide 9–20 (PAMP9-20) or
317 the compound 48/80 in mice resulted in histamine-independent itch, as it was not alleviated
318 by histamine receptors antagonists. They further showed that MrgprB2 stimulation was
319 associated with the release of high amounts of tryptase (but less histamine and serotonin)
320 compared to canonical IgE stimulation that resulted in the release of high a mounts of
321 histamine and serotonin (but less tryptase), such differential release of mediators then resulted
322 in the activation different population of neurons. In mouse models of two common skin
323 diseases, allergic contact hypersensitivity (ACD) and atopic dermatitis (AD), mice deficient in
324 MrgprB2 showed significantly less pruritus (Meixiong, Anderson, et al., 2019). Finally, the
325 authors found that the skin of patients suffering from ACD was particularly enriched in
326 PAMP(1-20), underlining the potential translational value of these findings. The effective

327 communication between Mrgprs-expressing neuronal and immune cells was also highlighted
328 using intravital calcium imaging of mice carrying a genetically-encoded calcium tracer into
329 sensory neurons, as activation of mast cells via MrgprB2 resulted in the further activation of
330 MrgprD⁺ and MrgprA3⁺ itch sensory neurons (Meixiong, Anderson, et al., 2019). In another
331 study, Li Zhang, McNeil *et al.* proposed that anti-microbial peptides such as β -defensin
332 (Defb14) could induce itch behavior via MrgprB2. This hypothesis was confirmed in
333 MrgprB2-deficient mice (Li Zhang & McNeil, 2019b). Unexpectedly, the same group
334 observed that β -defensin could also activate MrgprA3/C11 and their ortholog MRGPRX1,
335 suggesting that different Mrgprs could eventually share common ligands.

336 Recently, Serhan, *et al.* uncovered a new mechanism regulating type 2 (allergic) skin
337 inflammation that is governed by a subpopulation of skin-projecting *Tac1*⁺ (SP-producing)
338 TRPV1⁺ nociceptors and MrgprB2⁺ dermal mast cells (Serhan et al., 2019). SP deficiency
339 (*Tac1*^{-/-}) and selective depletion of TRPV1⁺ nociceptors protected mice from the development
340 of a model of type 2 skin inflammation that shares many pathological features with the human
341 AD. Same observations were made when mice were deficient in mast cells or carried a
342 truncated and non-functional form of MrgprB2. Imaging of isolated *ex vivo* DRG neurons
343 revealed that common domestic allergens found in most AD patients, the house dust mites *D.*
344 *farinae* and *D. pteronyssinus*, were able to directly activate neurons via their cysteine protease
345 activity. Combining genetic models and intravital imaging, the authors finally showed that
346 TRPV1⁺ SP-producing nociceptors formed physical and functional clusters with MrgprB2⁺
347 mast cells capable to detect allergens and drive the development of AD-like inflammation in
348 the mouse (Serhan et al., 2019).

349 Another recent study using different models of allergen exposure decrypted a similar
350 mechanism of activation, having SP as the main actor that activated CD301b⁺ dendritic cells
351 via expression of MrgprA1. SP-activated dendritic cells migrated to the draining lymph node

352 where they initiated a type 2 immune response (Perner et al., 2020). This study strongly
353 suggests that, albeit expressed on different immune cells, MrgprB2 and MrgprA1 could share
354 the SP as a common ligand in the skin.

355 Immune cells can also release inflammatory mediators capable to activate Mrgprs, for
356 example the 5-oxoETE that is formed by the oxidation of 5-HETE by the 5-
357 hydroxyeicosanoid dehydrogenase (5-HEDH) (Y. Zhang et al., 1996), a microsomal enzyme
358 that is highly selective for 5(S)-HETE and requires NADP⁺ as a cofactor (Erlemann et al.,
359 2007). 5-HEDH is found in neutrophils as well as in a variety of other inflammatory and
360 stromal cells, including monocytes (Erlemann et al., 2007), dendritic cells (Stamatiou et al.,
361 2004) and mucosal epithelial cells (Erlemann et al., 2007). However, more studies would be
362 needed to develop a clear picture of the role of immune cell-derived Mrgprs agonists in the
363 regulation of neuroimmune interactions.

364 **Conclusion and perspectives: Mrgprs as potential therapeutic targets to treat**
365 **inflammation, pain and itch sensations**

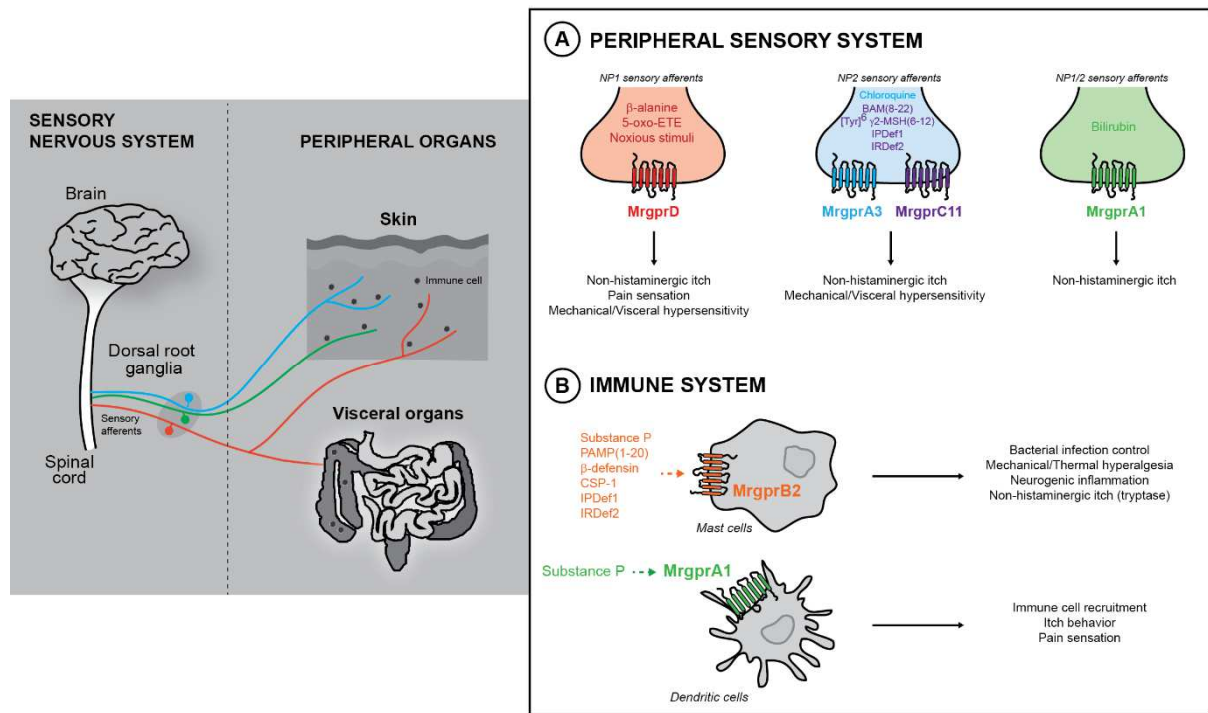
366 Mrgprs have emerged as substantial players in the biology of itch and pain, as well as
367 in the onset and development of inflammation in the skin and in visceral organs. Despite the
368 significant progresses made in the past few years on Mrgprs biology, there is still a lot to be
369 discovered about their physiological and pathological functions. Many Mrgprs are still orphan
370 receptors with no identified endogenous or chemical ligands. For the moment, very few
371 agonists or antagonists have been described; the “deorphanisation” of additional Mrgprs is an
372 exciting area of investigation and should bring invaluable informations on the molecular
373 mechanisms that govern neuroimmune crosstalks and their roles in health and diseases.

374 Because Mrgprs are found to be expressed in both sensory nervous and immune
375 systems, it is interesting to speculate that a sustained co-evolutionary communication has

376 occurred to promote mutually beneficial biological events. Immune cells and nociceptors are
377 distributed in all tissues, especially those located at the interface between the host and the
378 environment. Studies described in this review showcased an important number of interactions
379 between Mrgprs-expressing cells and other cells involved in the regulation of pain, itch and
380 inflammation in different organs. Both chronic and acute diseases are often associated to
381 various mechanisms that involve GPCRs and notably Mrgprs. Skin diseases such as AD and
382 ACD, as well as visceral disorders (such as IBS) are thought to be accompanied by Mrgprs-
383 driven inflammation. New antagonists for MRGPRD and MRGPRX1 are currently being
384 investigated in pre-clinical trials as novel anti-itch drug targets. In line with these molecules,
385 the design of new MRGPRX2 antagonists could constitute an innovative line of treatment in
386 the context of pain, itch and allergic inflammation. Finally, it is important to keep in mind that
387 translational studies of neuroimmune interactions in human tissues will constitute a major (but
388 nevertheless difficult) challenge in the field, due to the remote anatomical location of sensory
389 neuron cellular bodies in DRG or other related ganglia.

390

391 **Figures, tables and legends**



392

393 **Figure 1. Mrgprs-expressing cells belong to the peripheral sensory and immune systems,**
 394 **and are involved in pruriception, nociception and inflammation.** Isolectin B4-positive
 395 small-diameter afferents neurons that express Mrgprs innervate the skin and the visceral
 396 organs and can be classified into three distinct classes. **A**, MrgprD is mainly expressed by
 397 nociceptors belonging to the NP1 subpopulation (**red**) and is activated by β -alanine and 5-
 398 oxo-EETE causing non-histaminergic itch, mechanical and visceral hypersensitivity. MrgprA3
 399 and MrgprC11 are Mrgprs expressed by pruriceptors belonging to the non-peptidergic family
 400 2 (NP2, **blue**) and are activated by CQ and BAM(8-22) and $[Tyr^6]$ γ 2-MSH(6-12)
 401 respectively. Their activation drives itch and may modulate pain. MrgprA1-positive sensory
 402 neurons (both NP1 and NP2 population) (**green**) are activated by bilirubin and are strongly
 403 linked to pruritus. **B**, Immune cells were also found to express Mrgprs. MrgprB2⁺ mast cells
 404 can be activated by diverse ligands such as PAMP(1-20), β -defensin and SP resulting in non-
 405 histaminergic itch and pain behavior. CSP-1 can also bind to MrgprB2 resulting in the control
 406 of bacterial infection. Tick-derived salivary protein IPDef1 and IRDef2 also activate MrgprB2
 407 and drive local inflammation. Additionally, binding of SP to mast cell-MrgprB2 or dermal

408 dendritic cell-MrgprA1 promotes skin inflammation and onset of type 2 immune response.
 409 *Abbreviations: Mrgpr: Mas-related G protein-coupled receptor, NP: non-peptidergic, 5-oxo-*
 410 *ETE: 5-oxoeicosatetraenoic acid, BAM(8-22): Bovine Adrenal Medulla, PAMP(1-20):*
 411 *proadrenomedullin peptide 1-20, SP: Substance P, CSP-1 : Competence Stimulating Peptide*
 412 *I.*

Receptor	Human ortholog	Ligand		References
		Endogen	Exogen	
MrgprB2	MRGPRX2	Substance P Platelet factor-4 AG-30/5C β -defensin Cathelicidin LL-37 BAM (8-22;13-22;22) Catestatin Cortistatin Hemokinin-1 Kallidin Neuropeptide FF Oxytocin PACAP (6-27) PAMP(9-20) Somatostatin Substance P VIP Vasopressin Dynorphin A	Ciprofloxacin Levofloxacin Moxifloxacin Ofloxacin Atracurium Rocuronium Tubocurarine Angiopeptin Cetrorelix Hexarelin Icatibant Leuprolide Octreotide Sermorelin Compound 48/80 Mastoparan CSP-CSP1-CSP2 Entf Streptin-1	(Alkanfari et al., 2019; Dong et al., 2001b; Kamohara et al., 2005; McNeil et al., 2015; Pundir et al., 2019; Robas et al., 2003; Subramanian et al., 2013; Subramanian, Gupta, et al., 2011b; Tatemoto et al., 2006; Gaudenzio et al., 2016; Serhan, et al., 2019)
Mrgprc11	MRGPRX1	BAM(8-22) β -defensin SLIGRL [Tyr ⁶] γ 2-MSH(6-12) Neuropeptide FF	IPDef1 IRDef2	(Chang et al., 2009; S.-K. Han et al., 2002; Lembo et al., 2002; X. Li et al., 2020)
Mrgpra3	MRGPRX1	β -defensin	Chloroquine	(Q. Liu et al., 2009; Li Zhang & McNeil, 2019a)
Mrgprd	MRGPRD	β -alanine Alamandine 5-oxoETE Angiotensin(1-7) GABA	ND	(Bautzova et al., 2018; Karnik et al., 2017; Lautner et al., 2013; Qu et al., 2014; Santos et al., 2003; Shinohara et al., 2004; Uno et al., 2012)
Mrgpra1	MRGPRX4	Bilirubin Salusin β Arg-Phe-amide containing neuropeptides (FLRF- amide, FMRF-amide and NPFF)	ND	(Dong et al., 2001c; S.-K. Han et al., 2002; Meixiong, Vasavda, et al., 2019; Z. Wang et al., 2006)
Mrgpra4		Neuropeptide FF ACTH	ND	(Dong et al., 2001c)

413

414 **Table 1. Human and murine Mas-related G protein-coupled receptor ligands.** Table

415 abbreviations: BAM: Bovine Adrenal Medulla, PACAP: Pituitary adenylate cyclase

416 activating polypeptide, PAMP: proadrenomedullin peptide, CSP: competence-stimulating
417 peptide 1, MSH: Melanocyte-Stimulating Hormone, 5-oxoETE: 5-Oxoeicosatetraenoic Acid,
418 GABA: Gamma aminobutyric acid, ACTH: Adrenocorticotropic hormone, ND: not
419 determined.

420 **Author contributions**

421 All authors participated in writing and/or editing the paper.

422

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427

428 **Conflict of interest statement**

429 N.G. is acting as Chief Scientific Officer consultant for Genoskin. He is a member of the
430 advisory board for MaxiVAX. He has served as consultant for Boehringer Ingelheim and
431 Novartis. He has a patent pending for the treatment of type 2 inflammation and mast cell-
432 dependent disorders. N.S., L.B. and N.C. declares no competing interest.

433

434 **List of abbreviations**

435 5-HEDH 5-Hydroxyeicosanoid Dehydrogenase

436 5-oxoETE 5-Oxoeicosatetraenoic Acid

437 ACD Allergic Contact Hypersensitivity

438	AD	Atopic Dermatitis
439	AITC	Allyl Isothiocyanate
440	Ang	Angiotensin
441	BAM	Bovine Adrenal Medulla
442	CQ	Chloroquine
443	CR	Chromosome
444	CVH	Chronic Visceral Hypersensitivity
445	CSP-1	Competence-Stimulating Peptide 1
446	DRG	Dorsal Root Ganglia
447	DTR	Diphtheria Toxin Receptor
448	GPCR	G Protein-Coupled Receptor
449	IBS	Irritable Bowel Disease
450	IL	Interleukin
451	Mrgpr	Mas-Related G Protein-Coupled Receptor
452	MSH	Melanocyte-Stimulating Hormone
453	NP	Non-Peptidergic
454	NPFF	Neuropeptide FF
455	PAMP(1-20)	Proadrenomedullin Peptide 1-20
456	qPCR	Quantitative PCR
457	RT	Reverse Transcription
458	SP	Substance P
459	TRPA1	Transient Receptor Potential Ankyrin 1
460	TG	Trigeminal Ganglia
461	TNBS	Trinitrobenzenesulphonic acid

462 TRPV1 Transient Receptor Potential Vanilloid 1

463

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