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VIEWPOINT

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# MRGPRX2 signals its importance in cutaneous mast cell biology: Does MRGPRX2 connect mast cells and atopic dermatitis?

Zhao Wang[1,2,3] | Magda Babina[1,2,3]

[1]Department of Dermatology and Allergy, Allergy Center Charité, Charité – Universitätsmedizin Berlin, Berlin, Germany

[2]Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany

[3]Berlin Institute of Health, Berlin, Germany

**Correspondence**
Magda Babina, Department of Dermatology and Allergy, Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.
Email: magda.babina@charite.de

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## Abstract

The discovery of MRGPRX2 marks an important change in MC biology, explaining non-IgE-mediated clinical phenomena relying on MCs. As receptor for multiple drugs, MRGPRX2 is crucial to drug-induced hypersensitivity. However, not only drugs, but also endogenous mediators like neuropeptides and host defense peptides activate MRGPRX2, suggesting its broad impact in cutaneous pathophysiology. Here, we give a brief overview of MRGPRX2 and its regulation by microenvironmental stimuli, which support MCs and can be altered in skin disorders, and briefly touch on the functional programs elicited by MRGPRX2 ligation. Studies in Mrgprb2-deficient mice (the murine ortholog) help illuminate MRGPRX2's function in health and disease. Recent advances in this model support the long-suspected operational unit between MCs and nerves, with MRGPRX2 being a vital component. Based on the limited evidence for a major contribution of FcεRI/IgE-activated MCs to atopic dermatitis (AD), we develop the hypothesis that MRGPRX2 constitutes the missing link connecting MCs and AD, at least in selected endotypes. Support comes from the multifold changes in the MC-neuronal system of AD skin (eg greater density of MCs and closer connections between MCs and nerves, increased PAR-2/Substance P). We theorize that these deregulations suffice to initiate AD, but external triggers, many of which activating MRGPRX2 themselves (eg *Staphylococcus aureus*) further feed into the loop. Itch, the most burdensome hallmark of AD, is mostly non-histaminergic but tryptase-dependent, and tryptase is preferentially released upon MRGPRX2 activation. Because MRGPRX2 is a very active research field, some of the existing gaps are likely to be closed soon.

**Abbreviations:** AD, Atopic dermatitis; c48/80, Compound 48/80; CCL, C-C motif chemokine ligand; EC50, Half maximal effective concentration; FANTOM5, Functional annotation of the mammalian genome 5; FcεRI, High-affinity IgE receptor; GM-CSF, Granulocyte-macrophage colony-stimulating factor; GPCR, G protein coupled receptor; HDM, House dust mites; HDPs, Host defense peptides; LTC4, Leukotriene C4; MC, Mast cell; MCP1, monocyte chemoattractant protein 1; $MC_T$, Mast cells expressing tryptase; $MC_{TC}$, Mast cells expressing tryptase and chymase; Mrgprb2, Mas-related G protein–coupled receptor-b2; MRGPRX2, Mas-related G protein–coupled receptor-X2; NGF, Nerve growth factor; PAR-2, Protease activated receptor 2; PBcMCs, Peripheral blood-derived cultured MCs; PGD2, Prostaglandin D2; RA, Retinoic acid; SCF, Stem cell factor; SP, Substance P; STAT6, Signal transducer and activator of transcription 6; TAC1, Tachykinin Precursor 1; Th, T helper; TNF-α, Tumor necrosis factor-α; TRPV1, Transient receptor potential cation channel subfamily V member 1; TSLP, Thymic stromal lymphopoietin; VEGF, Vascular endothelial growth factor.

KEYWORDS
allergy, atopic dermatitis, itch, mast cell, MRGPRX2

## 1 | INTRODUCTION TO PSEUDO-ALLERGIC ACTIVATION BY MRGPRX2: A SHIFT TO NON-IGE DEPENDENT HYPERSENSITIVITY

The discovery of MRGPRX2 marks a significant change in mast cell (MC) biology.[1,2] Its identification helps explain MC activation independently of the adaptive immune system. MRGPRX2 is expressed only by $MC_{TC}$-type MCs, predominantly residing in the skin.[1,3,4] The comprehensive transcriptome data from the FANTOM5 consortium revealed that across ≈900 cell and tissue samples, MRGPRX2 was confined to (skin) MCs, qualifying it as a "MC (and even $MC_{TC}$) private gene".[3] In contrast, $MC_T$-type MCs lack MRGPRX2 expression[5] and do not respond to secretagogues acting via MRGPRX2, for example compound 48/80 (c48/80).[6]

MRGPRX2 is activated by a plethora of substances, including cationic drugs, neuropeptides and host defense peptides, which trigger pseudo-allergic reactions, mediate neurogenic inflammation but can also mount antimicrobial defenses,[2,7] for example by binding host defense peptides (HDPs) like cathelicidin (LL-37) and β-defensins.[4,8] Opioids, a drug class contributing to pseudo-allergy, can also target MRGPRX2,[9] and we have demonstrated that MRGPRX2 is the dominant opiate receptor also in human skin MCs (Babina et al, in revision). Other natural or synthetic compounds can activate the receptor, including cathepsin S, antimicrobials, phenothiazine antipsychotics, gold chloride, mucunain and radiocontrast media.[10]

As a G protein coupled receptor (GPCR), MRGPRX2 employs a different activation mode compared to the high-affinity IgE receptor (FcεRI). FcεRI-triggered activation requires three components, the antigen, antigen specific IgE and FcεRI itself, and is initiated by a cascade of tyrosine kinases.[11,12] Conversely, MRGPRX2 triggers exocytosis directly after agonist binding (two-component system) in a Gi and/or Gq-dependent manner.[13] The routes also differ regarding granule exteriorization, whereby FcεRI triggers delayed secretion with more irregularly shaped and bigger granules due to granule-granule fusion, while MRGPRX2 mediates the rapid discharge of small individual granules.[14]

There is substantial inter-individual variability in the responsiveness of skin MCs to canonical MRGPRX2 ligands.[15] Moreover, degranulation by c48/80 and substance P (SP) was almost perfectly correlated, while no correlation was found with FcεRI aggregation.[15] The two major degranulation networks of skin MCs therefore appear to work separately without interconnections at some late events of granule tethering, docking or fusion.[14]

The identification of the mouse ortholog (Mrgprb2) of human MRGPRX2 and creation of the respective knockout mouse finally allowed to study the in vivo significance of the receptor. Mrgprb2 responded to basic secretagogues, whereby Mrgprb2-null mice were completely protected from the adverse effects of these substances.[2] This mouse is now extensively used in various models to delineate MRGPRX2/b2 importance in health and disease. For example, through interaction with sensory neurons, the receptor was shown to regulate itch, hyperalgesia and skin inflammation,[16-18] while on the other end of the spectrum, it executed antimicrobial functions to safeguard health.[7,19]

## 2 | MRGPRX2 MODULATION BY SCF, IL-4, IL-33 AND RETINOIC ACID

The interaction and mutual regulation of receptor networks is an important means by which cells integrate the numerous signals they concurrently receive in their natural habitats, and MCs can change functional phenotypes on exposure to diverse environmental signals. While conditions modulating FcεRI-triggered secretion were broadly covered by the literature, no information was available on the alternative pseudo-allergic route when we started our studies.

Major MC growth and regulatory factors are SCF, IL-4 and IL-33. The SCF/KIT axis promotes MC differentiation, survival, adhesion, chemotaxis and mediator production from early precursors to fully mature MCs.[11,20,21] IL-4, on the other hand, is the signature cytokine of type-2 immunity, IgE-mediated hypersensitivity and can increase proliferation and several MC attributes.[22-25] IL-33 acts as an "alarmin" released from damaged or injured cells, initiating inflammation, but also Th2-skewed immunity; one of its major target cells is the MC, on which it exerts potent phenotypical and functional effects.[26,27] Finally, retinoic acid (RA) has a crucial function in the skin (both as endogenous hormone and therapeutically), and it is skin MCs that are highly enriched with components of the retinoid network vis-à-vis all major skin cells; consequently, skin MCs are potently reshaped by RA.[28]

Since early signalling events and subsequent mechanisms of granule discharge differ between the FcεRI- and the MRGPRX2-route, we hypothesized that environmental signals may have divergent consequences on the two degranulation networks.[14,15] SCF priming, reportedly facilitating FcεRI-dependent activation,[11] indeed supported FcεRI-driven secretion, while the same treatment simultaneously dampened c48/80- or SP-elicited degranulation.[15]

Regulation of the two routes by SCF and IL-4 was further studied in our Exp. Dermatol. paper related to this viewpoint.[29] MCs from tissues like skin and gut are typically expanded in the presence of SCF and IL-4.[25,30,31] We found that this altered microenvironment boosts the FcεRI route compared to ex vivo MCs but simultaneously

**TABLE 1** Modulation of human skin MC responses by specific stimuli

| Condition | FcεRI (mRNA) | FcεRI (protein) | FcεRI mediated degranulation | MRGPRX2 (mRNA) | MRGPRX2 (protein) | MRGPRX2 mediated degranulation | Reference |
|---|---|---|---|---|---|---|---|
| SCF (priming, 30 min) | n.d. | n.d. | Up | n.d. | n.d. | Down | [15] |
| SCF (chronic; effect measured upon removal for 16 h) | Unchanged | Up | Up | Down | Down | Down | [29] |
| IL-4 (chronic; effect measured upon removal for 16 h) | Up | Slightly up (but n.s.) | Up | Slightly down (but n.s.) | Down | Down | [29] |
| Retinoic acid (chronic, 7 d) | Unchanged | Unchanged | Up | Down | n.d. | Down | [32] |
| IL-33 (priming, 30 min) | n.d. | Unchanged | Up | n.d. | Unchanged | Up | [34] |
| IL-33 (chronic, 5 wk) | Down | Down | Down | Down | Down | Down | [33,34] |

Abbreviations: n.d., not done; n.s., not significant.

curbs the MRGPRX2 pathway, creating a perfectly inverted image between the two.[29]

By selectively removing and re-adding SCF, IL-4 or both, we determined that SCF was the dominant factor in this setting, while IL-4 had an additive effect in attenuating the MRGPRX2 pathway or in enhancing FcεRI function. The findings are summarized in Table 1.

Similarly, MCs treated with RA decreased MRGPRX2 gene expression and restricted histamine release triggered by c48/80, while FcεRI-mediated degranulation was slightly enhanced,[32] further emphasizing a frequently opposite regulation of these routes (Table 1).

For IL-33, a dichotomy between chronic and acute effects was discovered, whereby "chronic" indicates long-term contact with the cytokine (weeks), while "acute" denotes a short IL-33 burst given minutes prior to the stimulus (priming). In the chronic setting, IL-33 attenuated the FcεRI route (slightly)[33] and the MRGPRX2 pathway (more profoundly).[34] In stark contrast, IL-33 primed for increased degranulation elicited by both routes when administered directly before stimulation.[33,34]

In conclusion, although this does not uniformly apply to all conditions, we may summarize that positive regulators of the lineage more commonly attenuate MRGPRX2 function, while simultaneously augmenting FcεRI functionality.

## 3 | FUNCTIONAL PROGRAMS ELICITED VIA MRGPRX2

MC activation occurs in different phases. Acute activation is detectable within minutes resulting from granule exteriorization and the slightly shifted (but still rapid) generation of lipid mediators, while late phase responses are also orchestrated by newly synthesized cytokines.[12,35] While degranulation is effectively elicited via MRGPRX2 in skin MCs,[15] induction of the other mediator classes is less clear. Of the lipid mediators produced by MCs, especially prostaglandin D2 (PGD2) and leukotriene C4 (LTC4),[36,37] only little release of PGD2 was detectable after MRGPRX2 activation, and its level was substantially lower than after FcεRI aggregation.[14,38,39]

MC cytokines are involved in multiple processes and can contribute to chronic inflammation.[11,12,30,40] Cytokine induction by MRGPRX2 is a controversial issue. While multiple entities were found to be stimulated via MRGPRX2, including TNF-α, GM-CSF, IL-8, CCL2/MCP-1 and IL-31,[19,41-45] most of the studies were performed with LAD2 cells. In CD34+ peripheral blood-derived cultured MCs (PBcMCs), one study detected cytokines after stimulation with neuropeptides and c48/80,[41] while another study found only low levels of VEGF after SP stimulation, though parallel IgE/anti-IgE resulted in high levels of all cytokines tested.[14] The inconsistencies may partially stem from differences across MC subsets (and/or donors). It will be important to analyse this issue in skin MCs, and we have therefore started to compare cytokine outputs in these cells and hope to present the findings soon.

## 4 | IMPLICATION OF MRGPRX2 IN THE CROSSTALK BETWEEN MCS AND NEURONS

It has long been known that histamine and serotonin (5-HT) from degranulated MCs activate histamine receptors (H1R and H4R) and 5-HT receptors (5-HTR2 and 5-HTR7) on neurons (histamine in mouse and man, serotonin limited to mouse).[46] However, in some chronic disorders, like allergic contact dermatitis, histamine blockage is ineffective, and PAR-2 plays a more relevant role.[47-49] Meixiong et al[17] compared Mrgprb2-mediated and FcεRI-mediated activation in a mouse model of allergic contact dermatitis finding that tryptase but not histamine forms the major constituent in the context of pseudo-allergic/neurogenic exocytosis, and that tryptase, activating PAR-2 on neurons, can elicit histamine-independent itch.[46] Among the multiple neuropeptides, SP is the most exhaustively studied entity. Serhan et al[16] reported that degranulating MCs are mostly adjacent to activated neurons and found that HDM (house dust mite) extracts induce TRPV1+ Tac1+ nociceptors to release SP, which then activates Mrgprb2 on skin MCs.

Together, there is a functional link between nerves and MRGPRX2. The next paragraph tests the hypothesis that atopic dermatitis can be initiated or maintained by a feedforward loop between cutaneous MCs and sensory neurons in response to exogenous elicitors or even autonomously.

## 5 | IS THERE A ROLE FOR MRGPRX2 IN ATOPIC DERMATITIS?

Although deregulations in the MC compartment are believed to contribute to AD pathology, as MCs are increased in lesions and show signs of degranulation,[50,51] the mechanisms by which MCs contribute and their modes of activation are surprisingly ill-defined. As indicated by its name, AD has a connection with atopy (disposition to produce increased levels of total or allergen-specific IgE), but whether IgE is a driver or rather a bystander remains poorly understood. Possibly, IgE has varying roles in the distinct AD endotypes, which are also characterized by the immune polarization of T-cell subsets (Th1/Th2/Th17/Th22), combined with differential changes in barrier proteins like filaggrin and loricrin.[52] Clearly, IgE is not an indispensable element because AD can be intrinsic, that is not associated with increased IgE, and therefore, quite paradoxically, atopy is not an essential criterion for diagnosis.[51] It is unresolved to what extent IgE contributes to AD precipitation in extrinsic AD, that is the more common form associated with elevated IgE levels. Since barrier impairment is a hallmark of the disease, increased sensitization via the skin could alternatively lead to enhanced IgE production secondary to allergen permeation.[53] In support of this, patients with extrinsic AD have more pronounced barrier defects than those with intrinsic AD.[54] There is also limited improvement of AD with IgE-directed strategies (Omalizumab), especially in patients with pure AD and the same applies to specific immunotherapy (reviewed in[55-58]). In addition, AD occurrence in infancy can precede sensitization, and exacerbations of AD by food allergen ingestion have been reported but are not prevalent (especially in older children and adults).[59] Infantile AD is also more common of the intrinsic type.[60] A Th1-prone subtype as well as presence of contact allergy (especially to metals) is far more frequent in intrinsic AD.[61] Interestingly, intrinsic AD also shows more overlaps with psoriasis (including Th1 and Th17/22 dominance) than with extrinsic AD.[52] Further evidence for a rather small causative effect of IgE comes from AD mouse models, which are typically independent of IgE and B cells.[50] This is well exemplified by STAT6 deficiency: while STAT6-sufficient mice develop skin lesions, Th2 cytokines and IgE responses, their STAT6-null counterparts, that have no detectable IgE, still display comparable skin lesions.[62,63] Besides immune dysregulations and defects in the epidermal barrier,[64,65] alterations in the nervous system are also well-documented in the literature, though they are less commonly highlighted in AD reviews. Emerging evidence suggests that MCs and neurons form operational units,[46,65,66] as outlined above.

As depicted in Figure 1, various anomalies of AD skin at the level of epithelial/stromal cells, sensory nerves and MCs suggest an intense neuronal-MC communication. On comparison with healthy skin (Figure 1A), AD nerve fibres show greater positivity for Substance P[67,68] and express higher levels of PAR-2,[68,69] which is of relevance to our hypothesis. As for the degree of skin innervation, there is controversy since several studies reported greater nerve density,[70,71] while a newer one, taking into account the whole epidermal volume, found the opposite.[72] The degree of innervation is therefore depicted as unchanged vs healthy skin in Figure 1. Conversely, MC numbers are not only increased in AD skin,[73,74] but the cells are also situated in close proximity to and even within the epidermis[75] and they can invade SP-containing nerve bundles, showing signs of degranulation.[67,76,77] It has been known for a while that AD itch is mostly non-histaminergic[69,70] and that tryptase can activate or sensitize non-histaminergic neurons via PAR-2.[65,69] Tryptase is preferentially released upon MC stimulation of AD vs healthy skin.[69] Interestingly, exactly the same pattern, that is preferential release of tryptase (over histamine), was recently reported for MRGPRX2/b2 stimulation on comparison with the FcεRI-pathway.[17] In addition to tryptase, skin MCs also produce IL-31,[3] which acts as pruritogen and can sensitize and induce elongation of nerve fibres.[65,66] In different models of dermatitis and itch Mrgprb2-null mice were largely protected,[16,17,78] further highlighting the connection between itchy eczema and the pseudo-allergic route. An association with itch is further supported by the identification of MRGPRX2 as significantly increased in itchy AD skin over non-itchy skin from the same patients.[68] The same study revealed not only PAR2 overexpression in AD vis-à-vis healthy skin, but it also demonstrated higher PAR2 expression in itchy vs non-itchy skin from AD patients,[68] providing further support for a crucial role of the Tryptase-PAR2 axis in the development of AD pruritis.

As summarized in Figure 1B, we hypothesize that the changes in the MC-neuronal unit of AD skin, including MC hyperplasia, closer contacts, overexpression of SP (perhaps other neuropeptides), tryptase and PAR2, will lead to a labile equilibrium, that is an equilibrium, to

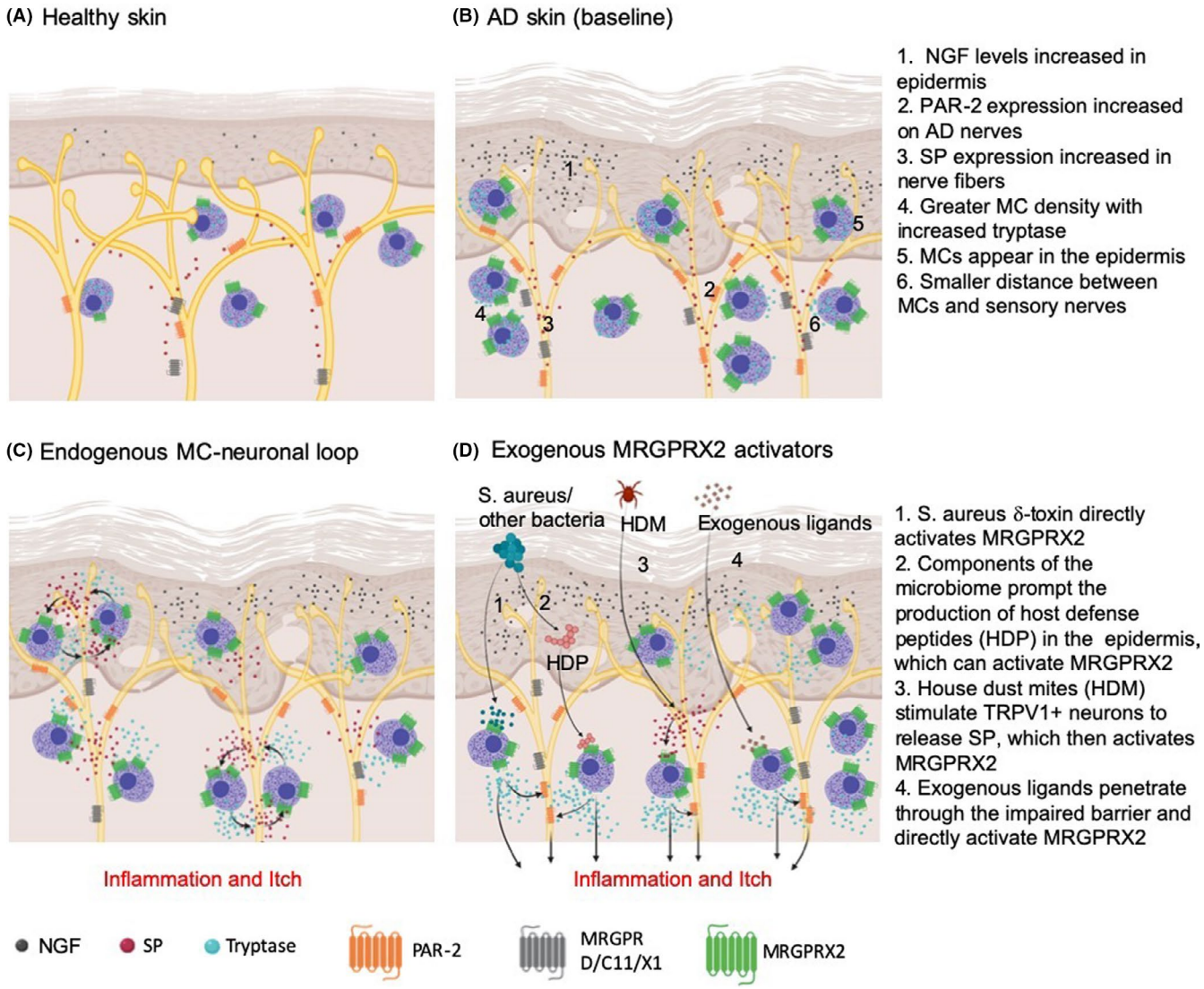


**FIGURE 1** Anomalies in the MC-neuronal axis as the trigger of atopic dermatitis—a hypothesis. (A) Healthy skin with homeostatic levels of MCs in the dermis and normal innervation. (B) AD skin in the absence of triggers, that is at baseline. As explained by the numbers placed next to the figure on comparison to healthy skin, AD skin exhibits the following: (1) enhanced levels of nerve growth factor (NGF) in the epidermis[70]; (2) greater PAR-2 expression on nerves[69]; (3) more SP in nerve fibres[67]; (4) increased MC numbers[73,74] with heightened tryptase[69]; (5) de novo appearance of MCs in the epidermis[75]; and (6) Closer contacts between MCs and sensory neurons.[67,76,77] These changes lead to a labile equilibrium. (C) Any slight disturbance of this equilibrium (such as neuropeptide release due to stress[66]) can start an endogenous MC-neuronal loop, whereby MRGPRX2 becomes activated by endogenous neuropeptides, for example SP,[10] which degranulate MCs and elicit the preferential release of tryptase to induce itch via PAR-2. Various (other) MC mediators, including neurotrophic factors (not depicted for the sake of clarity), may provide support to the neurons, lead to their elongation towards MCs and prompt further release of neuropeptides to maintain the MC-nerve feedforward loop. (D) In addition to the autonomous loop between MCs and nerves, triggers can also enter the skin from the outside and either activate MRGPRX2 directly or via other cells as intermediaries through release of MRGPRX2 ligands. MRGPRX2 is the receptor for a multitude of substances, and therefore, several scenarios are imaginable, also specified next to the figure. (1) *Staphylococcus aureus* (*S aureus*), with which most AD patients are colonized, produces the δ-toxin that can directly activate MCs via MRGPRX2[81]; (2) Components of the microbiome can prompt the production of host defense peptides (HDP) in the epidermis, which will activate MRGPRX2 and induce MC degranulation[4,8]; (3) House dust mites (HDM) stimulate TRPV1+ neurons to release SP, which then activates MRGPRX2[16]; (4) Exogenous ligands such as drugs or substances from the environment penetrate through the impaired barrier and directly target MRGPRX2.[2] In any case, MC tryptase will activate PAR-2 on neurons and lead to itch sensations which can start the itch-scratch cycle. This, together with a number of mediators from MCs, T cells and skin resident cells will bring about skin inflammation. C and D constitute hypotheses but are based on a large body of literature. Since the focus is on the MC-nociceptor regulatory unit and the circular relationship between the two elements, other well-documented deregulations encountered in AD skin have been omitted, especially cytokines from skin resident cells (TSLP, IL-25, IL-33) and from T helper cells, the latter also frequently produced by MCs (especially IL-13, IL-22 and IL-17), which can feed into this system at multiple levels. In addition to MRGPRX2, IgE triggered MC activation (which is not in the spotlight here) may play an additional role, especially in extrinsic AD. Not inconceivable, the two receptor systems may variably contribute to distinct subforms of AD

which any small change (such as psychological stress) may prompt the release of neuropeptides and/or MC mediators. Once their concentration reaches a critical threshold, they may endogenously start a nerve-MC-nerve loop, in which neuropeptides act on MCs and MC mediators act on neurons (Figure 1C). Since AD skin contains more Substance P,[67] and the major SP receptor on skin MCs is MRGPRX2,[10] MRGPRX2 seems crucial in this scenario. Neurotrophic factors derived from MCs may further strengthen neuro-MC contacts.[66]

In our theory, the crosstalk can be autonomously sustained to a certain degree, but exogenous stimuli are likely to (additionally or alternatively) feed into this loop (Figure 1D). In fact, components of the skin microbiome can stimulate HDP production in keratinocytes, of which β-defensin and cathelicidin induce MC degranulation via MRGPRX2.[4,8] Furthermore, most patients are colonized with *Staphylococcus aureus*,[79] and its δ-toxin contributes to pathogenesis.[80] It was later discovered that, like many other compounds, δ-toxin activates MCs via MRGPRX2.[81] Furthermore, HDM allergens can activate MRGPRX2 indirectly (via SP release from neurons[16]) and other MRGPRX2 ligands (considering their sheer number) could enter via the impaired barrier to directly stimulate their receptor on MCs, leading to mediator release and subsequent nociceptor stimulation. It is possible, though yet to be proven, that changes in MRGPRX2 itself or elements upstream or downstream thereof (transcription factors, signalling components) may predispose to AD development. Possible deviations in the MRGPRX2 system could be genetic or epigenetic or not imprinted at the level of MCs themselves, but driven by the skin micromilieu (Table 1). In summary, a deregulated MC-nerve unit could be an early event and initiator of AD, at least in subgroups of patients. Additional elements of this unit like Schwann cells could further contribute to pathology.[82] In other manifestations of the disease, such as extrinsic and/or strongly Th2-dependent forms, MRGPRX2 may rather act as a bystander (in analogy with the suggested bystander role of FcεRI, especially in intrinsic AD). This is supported by our finding that IL-4 *dampens* and does not strengthen the MRGPRX2-route in skin MCs (Table 1).

Future efforts will be required to prove or disprove this model, and answers on how instrumental MRGPRX2 is in AD pathology will likely emerge over the next years. It seems plausible that distinct micromilieus resulting from differentially skewed Th and skin resident cells (the latter producing IL-25, IL-33 and TSLP) may favour MRGPRX2- or FcεRI-dominated AD "endotypes." The better the molecular deregulations of individual AD endotypes are understood, the better the chances of personalized therapeutic approaches.

## 6 | FUTURE DIRECTIONS IN MRGPRX2 RESEARCH

Intense research into MRGPRX2 biology has just begun, and understanding is still at an early stage, though it is one of the "hottest receptors" in the MC field at the moment.[83]

Consequently, the exploration of ligands, acting as agonists (explaining why these substances induce MC-associated symptoms) or antagonists (to therapeutically interfere with MRGPRX2-triggered hypersensitivity) is in full swing. Several molecules discovered as MRGPRX2 ligands could indeed be linked to MRGPRX2-triggered adverse reactions, including the "Red Man Syndrome" due to vancomycin,[81] and injection-site erythema due to icatibant.[13,84]

Structure-function relationships and differences across ligands regarding binding characteristics and signalling cascades form another topic. For example, c48/80 represents a balanced ligand, which activates both the G protein and the β-arrestin pathway, while icatibant and AG-30/5C are G protein biased ligands, which do not induce receptor internalization.[85,86] Identifying these characteristics for a number of ligands will be crucial to estimate the type and duration of signal transduction, as well as receptor desensitization following binding of the respective ligand, whereby distinct ligands may also make variable contributions to diseases like AD.

Like most disease-associated structures, MRGPRX2 can be assumed as a double-edged sword, causing disease or safeguarding health depending on the circumstances. For example, MRGPRX2 can orchestrate host-defenses and facilitate microbial clearance.[7,19] Interestingly, the MRGPRX2 gene has undergone positive selection in human evolution,[87] so other beneficial functions of the receptor will likely be uncovered, as well.

On the other end of the spectrum are severe pseudo-allergic reactions and skin diseases. With the help of primary cells, especially from the skin, genetically modified cell lines, transgenic animals and human in vivo studies, that are only moderately invasive (such as skin tests), it will be possible to determine if and how MRGPRX2 contributes to sensations of itch and pain, and to disorders, in which MCs are supposedly involved but which are not primarily associated with type-I allergy. Apart from anaphylaxis and AD, chronic idiopathic urticaria, for which higher MRGPRX2 levels have been reported,[5] and rosacea (which is inducible by cathelicidin acting via MRGPRX2[88]) represent further entities, which may be caused, at least in part, by an aberrant MRGPRX2 system.

Related to the above is the question what factors actually dictate the differential MRGPRX2 responsiveness across individuals. So far, MRGPRX2 variants have been identified that mainly dampen MRGPRX2 function.[89,90] A plausible hypothesis is that patients susceptible to MRGPRX2 ligands express higher levels or variants of the receptor that conversely facilitate ligand binding and/or signalling. These are key questions for future research.

## 7 | CONCLUSION

Though at an early stage, evidence is accumulating that MRGPRX2 dysregulation contributes to diseases like anaphylaxis, AD, chronic urticaria and rosacea. Since expression of MRGPRX2 is basically confined to $MC_{TC}$-type MCs, the molecular underpinnings underlying this narrow range of expression will help comprehend how cutaneous MCs differentiate and are shaped by the specific microenvironment of the skin. Differences in (epi-)genetic traits either

in the MRGPRX2 gene itself or in genes upstream or downstream thereof will illuminate the differential responsiveness to MRGPRX2-activation across subjects and may provide a fresh view on the aetiology of skin disorders.

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## CONFLICT OF INTEREST

The authors have declared no conflicting interests.

## AUTHOR CONTRIBUTION

MB and ZW performed the literature review and wrote the article.

## ORCID

*Magda Babina* https://orcid.org/0000-0002-4500-7615

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