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INVITED REVIEW

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Non-IgE mediated mast cell activation

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Summary

Mast cells (MCs) are innate immune cells that are scattered in tissues throughout the organism being particularly abundant at sites exposed to the environment such as the skin and mucosal surfaces. Generally known for their role in IgE-mediated allergies, they have also important functions in the maintenance of tissue integrity by constantly sensing their microenvironment for signals by inflammatory triggers that can comprise infectious agents, toxins, hormones, alarmins, metabolic states, etc. When triggered their main function is to release a whole set of inflammatory mediators, cytokines, chemokines, and lipid products. This allows them to organize the ensuing innate immune and inflammatory response in tight coordination with resident tissue cells, other rapidly recruited immune effector cells as well as the endocrine and exocrine systems of the body. To complete these tasks, MCs are endowed with a large repertoire of receptors allowing them to respond to multiple stimuli or directly interact with other cells. Here we review some of the receptors expressed on MCs (ie, receptors for Immunoglobulins, pattern recognition receptors, nuclear receptors, receptors for alarmins, and a variety of other receptors) and discuss their functional implication in the immune and inflammatory response focusing on non-IgE-mediated activation mechanisms.

KEYWORDS

alarmins, aryl hydrocarbon receptor, ATP, CD151, CD37, CD48, CD53, CD63, CD81, CD9, complement, endothelin receptors, Fc receptor, free light chain, glucocorticoid receptor, GPCR, IL-1, IL-33, integrins, MAS-related GPCR, mast cell, neuropeptides, neurotensin, nucleotide oligomerization domain-like receptors, pattern recognition receptor, PPAR, retinoic acid-inducible gene-I-like receptors, sphingosine-1 phosphate, substance P, Toll-like receptor, vitamin D receptor

1 | INTRODUCTION

Mast cells (MCs) can be found in virtually all tissues, but they are most abundant in those exposed to the external milieu such as the intestinal tract, the airways, and the skin. This strategic location in close proximity to blood vessels and nerves allows MCs to relay signaling of harmful pathogens or other stimuli from the microenvironment to recruit and activate other members of the innate and adaptive immune system and initiate immunoregulatory functions.[1] MCs are well-known for their pivotal role in allergic responses, where allergens trigger MC activation by crosslinking IgE bound to the high affinity IgE receptor (FcεRI) leading to initiation of the allergic cascade. In addition, MCs express a great armamentarium of receptors (see Table 1) enabling them to respond to a wide variety of cellular, viral, and bacterial triggers. In this review, we discuss the expression of different classes of receptors on MCs and their contribution to non-IgE-dependent MC activation.

This article is part of a series of reviews covering Mast cells and Basophils and their functions appearing in Volume 282 of *Immunological Reviews*.

TABLE 1 Summary of different classes of receptors expressed by mast cells

Immunoglobulin receptors		
Surface IgG receptors	FcγRI	CD64 (IFNγ induced)
	FcγRIIA	CD32A
	FcγRIIB	CD32B
	FcγRIIIA	CD16A
Surface Ig-free light chain receptor (FLCR) (unidentified)		
Pattern recognition receptors (PRRs)		
Toll-like Receptors (TLRs)		
Surface	TLR2/TLR1 or TLR2/TLR6	
	TLR4	
	TLR5	
Endosomal	TLR3	
	TLR7	
	TLR8	
	TLR9	
	TLR10	
C-type lectin receptor (CLRs)		
Surface Dectin-1		
Surface CD48		
Retinoic acid-Inducible Gene-I (RIG-I)-like Receptors (RLRs)		
Cytoplasmic	RIG-I	(Retinoic acid-Inducible Gene-1)
	MDA-5	(melanoma differentiation gene 5)
	LGP2	(laboratory of genetics and physiology 2)
Nucleotide Oligomerisation Domain (NOD)-like receptors (NLRs)		
Cytoplasmic	NOD1	
	NOD2	
	NLRP3	
Nuclear receptors		
Glucocorticoid receptor (GR)		
Hormone receptors	Estrogen	EαR
		EβR
	Progesterone	PR
		PR
	Testosterone	AR (NRC3C4)
Aryl hydrocarbon receptor (AhR)		
Vitamin D receptor (VDR)		
Peroxisome proliferator-activated receptors	PPARβ/δ	
	PPARγ	
G-protein-coupled receptors (GPCRs)		
MAS-related GPCRs	MRGPRX2 (MRG-protein-coupled receptor X2)	Human
	MRGPRB2	Mouse
	MRGPRB3	Rat
Complement receptors	C3aR	
	C5aR	
Endothelin receptors	ET_A	
	ET_B	
Neuropeptide and neurotransmitter receptors	NTSR1 (Neurotensin receptor 1)	
	CRHR-1 (corticotropin-releasing hormone receptor)	
	NK-1R (neurokinin-1 receptor)	
	CLR (calcitonin-like receptor)	

TABLE 1 (Continued)

	VPAC2 (Vasointestinal peptide and pituitary adenylate cyclase-activating peptide receptors 2)	
	VPAC1 (Vasointestinal peptide and pituitary adenylate cyclase-activating peptide receptor 1)	
	ADRB2 (beta2 adrenergic receptor)	
Lipid mediator receptors		
Sphingosine 1 phosphate (S1P) receptors	$S1P_1$	
	$S1P_2$	
Prostaglandin D2 receptors	PTGDR-1 (DP, D prostanoid receptor)	
	PTGDR-2 (DP2 or CRTH2)	
Prostaglandin E2 receptors	EP1 (E prostanoid receptor)	
	EP2	
	EP3	
	EP4	
Leukotrienes (LTs) receptors	CYSLTR1 (Cysteinyl leukotriene D4 receptor)	
	CYSLTR2	
	GPR99 (G-protein-coupled receptor 99)	
	GPR17 (G-protein-coupled receptor 17)	
	BLT1R (B4 leukotriene receptor 1)	
	BLT2R	
	PAFR (PAF receptor)	
Purinergic receptors	A2aR (Adenosine 2a receptor)	
	A2bR	
	A3R	
	P2Y (P2 purinoceptor subtype Y)	
Other GPCRs	Chemokine receptors (not discussed)	
	ADGRE2 (Adhesion G-protein-coupled receptor E2) or	
	EMR2 (EGF-like module-containing mucin-like hormone receptor-like 2)	
Alarmin receptors		
Interleukin receptors	IL-1 receptor (IL-1R)	Interleukin-1 receptor
	IL-33 receptor (ST2)	Interleukin-33 receptor
Purinergic receptors	P2Y receptors	Purinergic 2Y receptors
	P2X receptors (P2X7)	Purinergic 2X receptors (P2X purinoceptor 7)
RAGE	RAGE/AGER	The receptor for advanced glycation end-products
Other receptors		
Integrins	CD29	Integrin Beta 1
	CD49d	Integrin subunit alpha 4
	CD49e	Integrin subunit alpha 5
	CD61	Integrin Beta 3 (Platelet Glycoprotein IIIa)
	CD51	Integrin, Alpha V (Vitronectin Receptor)
	α1β1	Very Late Antigen I (VLA1)
	α2β1	Very Late Antigen 2 (VLA-2), GPIa-IIa, CD49b
	α4β7	Lymphocyte Peyer's patch adhesion molecule, LPAM-1
Tetraspanins	CD9	Tetraspanin 29 (TSPAN-29)
	CD37	Tetraspanin 26 (TSPAN-26)
	CD53	Tetraspanin 25 (TSPAN-25)
	CD63	Tetraspanin 30 (TSPAN-30)
	CD81	Tetraspanin 28 (TSPAN-28)
	CD82	Tetraspanin 27 (TSPAN-27)
	CD151	Tetraspanin 24 (TSPAN-24)

2 | ALLERGEN-SPECIFIC MC ACTIVATION

The most well-known pathway of antigen-specific activation of MCs is via the high affinity IgE receptor (FcεRI). Binding of allergens to receptor-bound IgE results in receptor crosslinking and the activation of MCs to release granule content, and produce lipid mediators and cytokines.[2] However, alternative pathways and Fc receptors can also modulate or contribute to antigen-driven stimulation of MCs.

2.1 | IgA

Although the high-affinity receptor for IgA is found expressed on neutrophils, eosinophils, monocytes and macrophages, dendritic cells, no expression of FcαRI (CD89) has been detected on MCs.[3] In transgenic mice expressing human FcαRI on myeloid cells it was demonstrated that IgA could reduce development of allergic symptoms in the airways after intranasal IgE-complex treatment. However, this IgA-mediated modulation of receptor activation may be more relevant to other CD89 expressing immune cells.[4]

2.2 | IgD

Currently, no evidence exists for specific IgD receptors on MCs. A study with KU812, an immature human basophilic cell line, showed IgD binding, which, however, was not saturable and could be inhibited by IgG1, IgM, and IgE, which strongly indicated that binding was related to an unspecific receptor.[5] In a study by Chen et al, circulating IgD bound to basophils through a calcium-mobilizing receptor and upon IgD crosslinking induced antimicrobial, opsonizing, inflammatory, and B-cell stimulating factors including cathelicidin, IL-1, IL-4, and B-cell-activating factor BAFF. In the same study, MCs isolated from lung tissue and HMC-1 and LAD-2 MC lines showed IgD binding, which was not inhibited by IgG or IgE and only slightly by IgA. LAD-2 cells upregulated IgD binding upon exposure to IL-3 and/or IL-4. IgD binding was abrogated by pretreatment of the MCs with trypsin or papain, but not by pepsin.[6]

2.3 | IgG

MCs express Fc receptors for IgG, via which IgG-immune complexes can directly stimulate MC activation or upon co-crosslinking with other receptors may inhibit MC activation. The expression of FcγR on MCs is dependent on species and environmental conditions. Murine MCs express FcγRIIB and FcγRIIIA. Most human MCs express FcγRIIA, whereas expression of FcγRI can be induced by IFN-γ and crosslinking of the receptor leads to MC activation.[7,8] Interestingly, MCs in skin of psoriasis[7] and intestine of IBD patients[9] were found positive for FcγRI expression. FcγRIIB is present on MCs cultured from cord blood,[10] but not on skin-derived MCs.[11] FcγRI, FcγRIIA, and FcγRIIIA are immunoreceptor tyrosine-based activation motif containing (ITAM), activating receptors and crosslinking of these receptors leads to MC degranulation and secretion of lipid mediators and cytokines.[12-14] FcγRIIB contains an immunoreceptor tyrosine-based inhibitory motif and co-ligating of FcγRIIB with activating ITAM-containing receptors negatively regulates MC activation (reviewed in 15-18).

2.4 | IgG4

IgG4 antibodies are thought to have a protective role in allergy and successful immunotherapy is commonly associated with higher serum IgG4 levels. IgG4 antibodies bind with high affinity (K_A: $3.4 \times 10^7\ M^{-1}$) to FcγRI equaling IgG1 (K_A: $6.5 \times 10^7\ M^{-1}$). IgG4 has a moderate affinity for FcγRIIa/b (K_A: $2.5 \times 10^5\ M^{-1}$), comparable to the affinity for binding of IgG1 to these receptors.[19] It has been suggested that IgG4 inhibits MC activation through activation of a negative-signaling pathway involving FcγRIIb, however, experiments with a chimeric IgG4 antibody in IgE-mediated basophil activation did not support such a negative-signaling contribution.[20] Presently, it is not known if IgG4 is able to elicit signaling via the FcγRI.

2.5 | Ig light chains (FLC)

Immunoglobulin-free light chains are produced in excess during antibody synthesis and are released by plasma cells into the extracellular environment. FLC can be found in all body fluids and increased concentrations are detected in various inflammatory diseases such asthma, COPD, hypersensitivity pneumonitis and idiopathic pulmonary fibrosis, food allergy, non-allergic rhinitis, rheumatoid arthritis, viral myocarditis, multiple sclerosis, and cancer.[21-32] FLC bind to MCs via an undetermined receptor. Experiments in common γ-chain-deficient animals showed that Fc receptors were not involved in FLC-driven allergic responses.[33] Crosslinking of FLC induces MC activation.[33,34] Blocking FLC-mediated MC activation showed the importance of this pathway in murine disease models and inhibited the development of contact sensitivity, asthma, and tumor growth.[24,27,33] Activation of MCs via FLC may be an alternative mechanism to elicit antigen/allergen-induced inflammatory responses.

3 | PATTERN RECOGNITION RECEPTORS

MCs are key players in innate immunity and serve as first-line effectors in a number of pathogen attempts to contaminate the host. MCs are able as well to respond to danger signals emitted by the injured tissues. To provide these protective functions, MCs are armed with a number of receptors for pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), or pattern recognition receptors (PRRs). They can activate and/or prime them upon ligand binding, either intracellularly or at the cell surface. The large PRR profile presents an important means by which MC participate in host defense against pathogens and tissue injuries in addition to their well-recognized

involvement in allergy. This section will focus on the expression by MCs of some of these PRRs, with an emphasis on Toll-like receptors (TLRs), the lectin-like receptor CD48, and the NLRP3 inflammasome. Signaling elements of such receptor engagement will also be discussed.

3.1 | Toll-like receptors in MCs

MCs express a wide variety of TLRs in humans, mice, and rats. Mouse MCs derived in vitro from bone marrow, fetal liver or skin, or peritoneal stem cells have been shown to express TLR1 to -9 at least at the mRNA and functional levels. TLR-1/2/4/5/6 are expressed on the MC surface and recognize some PAMPs derived from the wall and/or outer membrane of microbiota from different species, whereas endosomal TLR-3/7/8/9 recognizes some virus-derived or host-derived nucleic acids such as CpG-enriched DNA and single stranded RNA (ssRNA).[35] Concerning their function, the degree of maturation of the MC or its localization will influence the kind of mediators released upon engagement.[1,35,36]

Importantly, with the exception of some TLR2 ligands, engagement of most of these receptors does not induce MC degranulation, but leads to cytokine/chemokine and/or cysteinyl-leukotrienes and other eicosanoids production, with a particular profile of these mediators for each receptor. Moreover, their engagement may have as well some impacts on other receptor-mediated MC activation to limit or amplify their functions (FcεRI, LL-37, substance P).

3.1.1 | Surface TLRs

TLR2

TLR2 is a receptor for peptidoglycans (or PGN) mainly derived from Gram-positive bacteria (like *Staphylococcus aureus*). TLR2 can bind other PAMPs and DAMPs like several sugars and glycoproteins derived from viruses and parasites and host-derived proteins (HMGB1).[35] TLR2 builds heterodimers with other TLRs: TLR1 and TLR6. These associations lead to differential specificities: TLR2/1: Pam3CSK4 and triacylated lipopeptides derived from bacteria and mycobacteria, and TLR2/6: Pam2CSK4, FSL1, and MALP2 (as synthetic ligands) and diacylated lipopeptides from mycoplasma and yeasts (zymosan) or group B Streptococcus derivatives (LTA).[35] TLR2 expression (along with TLR1 and TLR6) is proven in mouse, rat, and human MCs at the mRNA, protein, and functional levels.[35,37-40] Unlike TLR4 engagement, TLR2-mediated activation induces MC degranulation in vitro and in vivo in some experimental settings,[40,41] but not in some others.[35,38,42-44] TLR2 also stimulates cytokine, chemokine, and eicosanoid production by MCs. Depending on the TLR2 ligand used, the profile of secreted mediators may vary, but the engagement of this receptor can lead to the production of: IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-17, TNFα, IFNγ, GM-CSF, CysLTs, LTB4, and PGD2 (the latter in mouse peritoneal-cell-derived MC).[35,38,41,45] TLR2-mediated MC stimulation in the skin leads to inflammatory responses related to MC degranulation such as increased vascular permeability.[41] TLR2 engagement also participates in receptor crosstalk enhancing cytokine production induced by IgE-dependent signals in vitro.[43] Conversely, TLR2-mediated MC activation with LTA was also reported to decrease FcεRI expression on the cell surface, desensitizing MC to further IgE-mediated activation.[46] In other experimental settings, the use of PGN or Pam3CSK4 did not lead to downregulation of surface FcεRI expression.[45] TLR2 ligands can as well affect MC responses to LL37-mediated MC activation.[43-45] On the opposite, MC stimulation through substance P leads to increased TLR-2 expression and sensitivity, at least in the human MC line LAD2.[47] Depending on the nature of TLR-2 engagement (ie, depending on the ligand, TLR2, TLR2/1, or TLR2/6), TLR2 will signal through the same MyD88-dependent signaling pathway as the one described below for TLR4. This will result in MAPK (JNK, p38), NF-κB, and AP-1 activation and downstream cytokine production.[35] In LAD2 cells, it has recently been described that TLR2/TLR1 engagement through Pam3CSK4 induces IL-8 secretion through this pathway, which partially depends on G alpha 0 protein (GNAO1), PI3-Kinase activation, and the calcium-dependent NFAT activation.[48] A recent study in LAD2 cells showed that TLR2 engagement with either PGN or Pam3CSK4 leads to IL-8 secretion involving ERK and JNK activation, but which is inhibited by p38 activation.[44] In the latter study, both PGN and Pam3CSK4, induced a low calcium signal without inducing MC degranulation, and both ligands could reduce the LL37-induced calcium signal and subsequent IL-8 secretion.[44] Thus, some discrepancies about the effects of TLR-2 ligands on MC degranulation or TLR2 relationship with other MC receptors are found in the literature. While some of them may be explained by culture conditions (recombinant IL-3 and SCF vs conditioned medium for BMMCs; IL-4 and IgE priming for human MCs) or the type, the dose and the origin of TLR2 ligands used (PGN/LTA/Pam2CSK4/Pam3CSK4), further studies will be needed especially in vivo with clean genetic mouse models to validate the use of TLR2 ligands in decreasing allergic responses.

TLR-4

TLR4 is the receptor for lipopolysaccharides (or LPS) mainly derived from Gram-negative bacteria (*Escherichia coli*). TLR-4 can bind to other PAMPs and DAMPs as well, like several sugars and glycoproteins derived from viruses and parasites and host-derived chaperone proteins (HMGB1, HSP60, HSP70) or oxidized low-density lipoproteins.[36,49] TLR4 is expressed ex vivo by all tested mouse MCs (derived from bone marrow (BMMCs),[50,51] from peritoneal cells (PDMCs)[50], on fetal skin and endogenous peritoneal MCs[50]), both at the mRNA and protein levels. In vivo, the use of MC deficient animals reconstituted with wildtype (WT) or TLR4-mutated or -deficient MCs demonstrated that the MC-dependent responses to LPS in vivo required TLR-4.[52,53] Primary rat MCs express TLR4 both at the mRNA and protein levels (9). Human MCs express TLR4 as well, either MC lines (LAD2, HMC1) or MCs derived from cord blood, peripheral blood, and primary MCs isolated from skin and lung.[40,54,55] TLR4 engagement on MCs does not induce degranulation, but leads to inflammation-related mediator secretion. The profile of secreted mediators depends on the experimental conditions, the origin of MCs used and the kind of mediators examined. They include TNFα, IL-5, IL-6, IL-10,

IL-13, IL-1β, GM-CSF, CCL1, CCL2, CCL3, CXCL2, and as well of cysteinyl leukotrienes (CysLTs).[35,36] To signal efficiently, TLR4 needs to associate with the co-receptors CD14 and MD-2, both of which are expressed by MCs.[42,49,53] On a signaling perspective, TLR4 engagement activates the myeloid differentiation primary response 88 (MyD88)-dependent signaling pathway. The TRIF-dependent pathway (MyD88-independent), requiring internalization of TLR4 after its engagement, is not elicited in MCs since these cells do not internalize TLR4.[35] MyD88 is linked to TLR4 by the adapter molecule TIRAP. Engagement of TLR4, through Myd88 activation, will lead to IRAK family members and PDK1 activation, ultimately leading to the activation of MAPK family members (p38, JNK) and to phospholipase A2 (PLA2) activation and cysteinyl leukotriene (CysLTs) and other eicosanoid production which can be amplified and/or inhibited by the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) activation. This pathway induces the activation of the transcription factors AP-1, NF-κB, and IRF-5, leading to the production of cytokines and chemokines.[35,36] A recent study demonstrated that TLR4/Myd88-mediated IL-13 production by BMMCs is dependent on BLT2 (the receptor for leukotriene B4 or LTB4) through the activation of NF-κB.[56] This important point may indicate that production of other cytokines upon TLR-4 engagement may depend on an CysLTs or LTB4 autocrine or paracrine mechanism.[56] Further studies will be needed to demonstrate this point. Most of the studies on TLR4 in MCs were conducted ex vivo and in vitro, demonstrating that LPS-mediated MC activation induces cytokine/chemokine production without degranulation, either in mouse or human cells. In both species, TLR4 engagement also potentiates heterologous receptor engagement effects such as FcεRI.[1,35,36] However, in vivo in mice, LPS injection also increases IL-10 systemically diminishing FcεRI expression on MCs, thereby desensitizing them to subsequent anti-IgE treatment and limiting their degranulation ability and the extent of anaphylaxis.[57] This phenomenon demonstrated in mice was induced only by LPS.[57] As in anaphylaxis worsening of symptoms in patients upon in infection is frequently observed, other PAMPs and other PRRs than LPS may also participate in this effect.[58] Conversely, LPS intranasal exposure along with an OVA-induced asthma model clearly leads to a BLT2-dependent increase in IL-13 production by MCs worsening the histological outcome of the protocol, as it was demonstrated in vitro in parallel.[56] Taken together these recent insights in the crosstalk between TLR-4 and FcεRI on MCs suggest that it may limit IgE-dependent MC degranulation in vivo. However, stimulation of TLR4 may also lead to increased MC-related long-term tissue damage, which questions the putative therapeutic benefits of using such an axis in clinics.

TLR5

TLR5 is a receptor for flagellin, the main component of bacterial flagellum from both Gram-positive and Gram-negative bacteria.[59] TLR5 expression in mouse MCs is not evidenced. Indeed, its mRNA has not been found neither in BMMCs nor in the MC/9 cell line.[1,35,42,50-52] However, flagellin has some effects on BMMCs and mouse intestinal MCs through a mechanism that needs to be identified.[60] TLR5 expression has been evidenced at the mRNA, protein, and functional levels in rat and human MCs.[37,46,54] In human MCs, very few studies are available about TLR5 engagement functional outcomes and none of them are dedicated to this receptor. IL-1β and TNFα are the only cytokines which are known to be induced in huMC after such stimulation.[37,46,54] The TLR5 signaling is known to be MyD88-dependent, although some alternative pathway may be elicited like for TLR4.[59,61] In LAD2 cells, the TLR5 signaling has not been specifically studied, but flagellin does not induce downregulation of FcεRI expression, but can induce ERK1/2 phosphorylation.[46,54]

3.1.2 | Endosomal TLRs

TLR3

TLR3 is a receptor for double-stranded RNA (dsRNA) derived from viruses like mouse cytomegalovirus (mCMV)[62] or Newcastle disease virus (NDV)[63] and can also be engaged with polyinosine-polycytidylic acid (polyI:C), a synthetic ligand mimicking dsRNA.[35,54,61] TLR3 is expressed in MCs from mouse, rat, and human origin at the mRNA, protein and/or functional levels.[35,37,54,61] TLR3 engagement in mouse and human MCs does not induce degranulation but can inhibit degranulation in some experimental settings.[54,55,63] TLR3-mediated MC activation elicits the production of type I interferon (IFNα/β), IL-6, TNFα, IFNγ and the chemokines CCL2, CCL4, CCL5, CXCL1, CXCL2, and CXCL10.[35,50,54,62-64] This profile of secretion allows MCs to recruit pro-inflammatory cells such as CD8 + T cells.[63] TLR3 transduces signal through a MyD88-independent/TRIF-dependent pathway that leads to p38, JNK, and NF-κB activations in a TRAF6-dependent manner and to IRF3 phosphorylation in a TRAF3-dependent manner and downstream inflammatory cytokine/chemokine and type I interferon productions.[54,62,63,65]

TLR7

TLR7 is a receptor for single stranded RNA derived from viruses and can be engaged also with synthetic ligands belonging to the imidazoquinoline compound family like imiquimod or resiquimod (R848).[35,50,66] TLR7 is expressed in MCs from mouse, rat, and human origins at the mRNA, protein, and functional levels.[35,37,50,54,55,66] Like for other TLRs, TLR7 engagement does not induce MC degranulation, but it induces the secretion of CysLTs, IFNβ, TNFα, IL-6, CCL2, CCL3, CCL5, CXCL2.[35,37,50,54,55,66] No in vivo data exist using TLR7-deficient MCs. TLR-7 engagement initiates receptor crosstalk decreasing FcεRI-mediated MC degranulation.[67] Like TLR3 and TLR9, TLR-7 is expressed intracellularly, in the endosomal compartment of MCs[37,50] and signals through a MyD88-dependent pathway.[61] To our knowledge, no data are available in the literature concerning TLR7 signaling specifically in MCs. In other cell types, like plasmacytoid dendritic cells (pDCs), it induces the activation of NF-κB and IRF7 transcription factors through a TIRAP/MyD88/IRAK/TRAF6 pathway.[61]

TLR8

TLR8 binds to ssRNA derived from viruses and has an endosomal expression. TLR8 is expressed at least at the mRNA level in murine and

human MCs, including BMMCs,[52] but also in rat peritoneal MCs.[68] In human MCs, TLR8 expression was shown at the mRNA and protein levels in HMC1[54] and LAD2 cells[47] and very faintly in peripheral blood derived human MCs.[54] Probably due to its specificity, which is close to TLR7s, no specific functional and/or signaling studies on this receptor in MCs are yet available.

TLR9

TLR9 is an endosomal receptor for CpG-DNA from bacterial, mycobacterial, and viral origins.[35] Synthetic CpG oligodeoxynucleotides (ODNs) mimicking these DNAs are used as ligands in most of the studies on TLR9.[35,61] TLR9 expression has been demonstrated at the mRNA, protein, and functional levels in MCs from mouse, rat, and human origins.[35,37,47,50,54] TLR9 engagement in MCs from mouse, rat, and human origins does not induce MC degranulation in any of the MCs studied, but it induces the secretion of CysLTs, IFNα, IFNγ, TNFα, IL-1β, IL-6, CCL2, CCL5, and CXCL2.[35,36,50,54] Like TLR3 and TLR7, TLR9 is expressed on endosomes in MCs[37,50] and signal through a MyD88-dependent pathway.[61] No in vivo data are available for TLR9 function in MCs and its signaling is poorly described in this cell type. In other cell types, like plasmacytoid dendritic cells (pDCs), it induces the same signaling pathways as the one described for TLR7.

TLR10

TLR10 receptor and its ligand are not well described. There are no mouse homologs for this TLR, and in human its expression has been detected preferentially in germinal center B cells and NK cells.[69] In human MCs, its expression at the mRNA level has been detected in lung and skin MCs.[55] However, no other elements are available in the literature on this TLR expression and function in MCs.[35,36]

3.2 | CLR: C-TYPE LECTIN RECEPTOR family member expressed in MCs: DECTIN-1

Dectin-1 is a cell surface expressed receptor from the C-type lectin receptor (CLRs) family. Dectin-1 is able to bind zymosan, a component of the cell wall of Saccharomyces cerevisiae as TLR-2 does. Specific ligands are domains rich in β-glucans present in most of the fungal pathogens (β-1,3-glucans) like Candida albicans, Aspergillus fumigatus but also in some bacteria, viruses, helminths, and protozoa.[61,70,71] Dectin-1 is mainly expressed by dendritic cells (DCs) but can also be found on monocytes, macrophages, neutrophils, and MCs.[71] Its expression has been demonstrated at the mRNA, protein, and functional levels in mouse, rat, and human MCs.[71-73] Dectin-1 engagement in MCs from these species does not induce MC degranulation, but induces reactive oxygen species (ROS) generation, the secretion of CysLTs (LTC4), and the production at the mRNA and/or protein of TNFα, IL-3, IL-4, IL-13, CCL2, and CCL7.[71-74] Dectin-1 can promote C albicans phagocytosis by MCs and its destruction through NO production in a TLR-2 and dectin-1-dependent pathway.[74] Dectin-1 possesses in its intracytoplasmic tail a hemi-immunoreceptor tyrosine-based activation motif (hemi-ITAM) since it is composed of just 1 YXXL motif instead of the usual 2.[61] Upon engagement of Dectin-1, this hemi-ITAM becomes phosphorylated by a Src family kinase(s) (SFK) allowing the recruitment of the spleen tyrosine kinase (Syk).[72] Syk then induces PLCγ2 activity leading to the formation of inositol 1,4,5-trisphosphate (IP3) together with diacylglycerol (DAG).[61,72] IP3-mediated Ca^{2+} release from the endoplasmic reticulum induces a CRAC-dependent Ca^{2+} influx and consequent NFAT activation.[61] Dectin-1/Syk-dependent activation of NFAT has been confirmed in MCs, controlling the production of IL-3, CCL2, IL-4, and IL-13, but not TNFα.[72] In DCs, Ca^{2+} and DAG will also activate PKCδ leading to canonical NF-κB activation through the formation of a CARD9/Bcl-10/MALT-1 complex in dendritic cells.[61] In these cells, Syk also controls noncanonical NF-κB activation through NF-κB-inducing kinase (NIK).[61] Concerning MCs, Dectin-1 engagement leads to the induction of the non-canonical NF-κB family member IκBζ promoting TNFα production.[72] In MCs, the activation of PKCδ and the formation of the CARD9/Bcl-10/MALT-1 complex has not been studied yet.[61,72]

3.3 | CD48

CD48 is a glycosyl-phosphatidyl-inositol (GPI)-anchored cell surface receptor belonging to the CD2 family. CD48 is expressed on the surface of T and B cells, NK cells, DCs, monocytes, neutrophils, eosinophils, and MCs. CD48 represents a co-stimulatory molecule that binds to CD2 and CD244 (2B4) which enable cell-cell interactions with T cells and NK cells.[75] CD48 also binds to the type 1 fimbrial FimH adhesin, which is responsible for D-mannose-sensitive adhesion of the FimH-expressing bacteria. This specificity for FimH has been demonstrated initially in the RBL-2H3 MC cell line and mouse BMMCs[76] but was found on MCs from mouse, rat, and human origins.[75-79] Engagement by FimH-expressing *E. coli* induces MC degranulation, TNFα secretion, and endocytosis of the bacteria in caveolar-like structures at the MC plasma membrane (lipid rafts).[79] The CD48 signaling pathway induced by FimH binding is poorly known. However, being a GPI-anchored molecule and aggregating upon engagement in lipid rafts, all the signaling molecules needed to induce MC degranulation and TNFα production will be present and active. We did not find signaling studies upon CD48 engagement in MCs, but CD48 engagement collaborate with FcεRI to increase IL-8 production by MCs.[75]

3.4 | MC Cytoplasmic PRRs

3.4.1 | Retinoic acid-Inducible Gene-I (RIG-I)-like Receptors (RLRs)

RIG-I, melanoma differentiation gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2) are 3 DExH/D box helicases, which are cytoplasmic viral dsRNA sensors notably for dengue (DENV), hepatitis C viruses (HCV), Influenza A virus (IAV), and vesicular stomatitis virus (VSV).[61,80-82] RIG-I, MDA5, and LGP2 expression has been demonstrated in MCs from mouse, rat, non-human primate, and human origins.[80,82,83] Unlike VSV,[80] DENV and IAV induce MC degranulation in a RIG-I and MDA5-dependent manner.[81,82] Upon DENV MC

infection, RIG-I and MDA5 also controls the production of IFNα, TNFα, IL-6, CCL2, CCL3, CCL5, CXCL10, CXCL12, and CX3CL1.[82,84] This profile of cytokine/chemokine production leads to the recruitment of NK and NK T cells to the site of infection.[82] BMMC and LAD2 cell infection by VSV induces, in a RIG-I and MDA5 dependent, but TLR3-independent manner, production of IFNα, IFNβ, IL-6, and CXCL10[80,85] and of CCL5, CXCL11, and IL-15, although its dependency on RLRs has not been demonstrated, yet.[85] BMMC infection by IAV induces, in a RIG-I dependent manner, the production of LTB4, IL-6, CCL2, and CCL4.[81] RLRs signal through their CARD domains, RIG-I and MDA5 activate the adaptor MAVS (mitochondrial antiviral signaling protein), which self-polymerizes and recruits TRAF2, -5, and -6. These ubiquitin ligases are required for the activation of TBK1 and the formation of the IKK complex.[61] These kinases activate transcription factors such as NF-kB, IRF3, and IRF7 leading to the production of type I IFN, proinflammatory cytokines, and IFN-stimulated genes (ISGs).[61] However, the RLRs signaling pathway has not really been studied in MCs per se, albeit Graham et al described that RIG-I and MAVS were necessary for the MC response to IAV.[81] While CARD9 was dispensable, STING and STAT6 were partially responsible for IAV-induced production of inflammatory cytokines and chemokines by MC.[81]

3.4.2 | Nucleotide Oligomerisation Domain (NOD)-like receptors (NLRs)

The NLRs family of PRR is divided into 3 subfamilies: the NLR family containing CARD (caspase recruitment domain) NLRC1-5, among which are NOD1 and NOD2 (NLRC1 and 2); the NLR family containing a PYD domain (NLRP1-9 and NLRP11-14) and the NLR family apoptosis inhibitory proteins (NAIP1,2,5,6).[61] Among this family of PRRs, only the expression and/or function of NOD1, NOD2, and NLRP3 have been studied in MCs.[86-91] These 3 NLRs are cytoplasmic and involved in the recognition of bacterial outer membranes or cell walls (PGN) such as γD-glutamyl-meso-diaminopimelic acid (iE-DAP), M-TriDAP for NOD1, muramyl dipeptide (MDP) for NOD2 and NLRP3.[61,88] NLRP3 also senses bacterial mRNA, the antiviral compound R837 and some endogenous danger signals such as monosodium urate crystals, asbestos, silica, and aluminum salts.[92] These NLRs are rarely activated alone in a cellular response to PAMPs or DAMPs, and their activation are often sustaining and/or reinforcing the cellular response mediated by other PRRs.[61] Indeed, NOD1 and NOD2 can be activated by peptidoglycans like TLR2 is, and NLRP3 can be activated by bacterial mRNA as other PRRs are (see above).[61]

NOD1 and NOD2

NOD1 and NOD2 expression has been demonstrated at the mRNA, protein and/or functional levels in MCs from mouse, rat, and human origins.[86,87,89-91] NOD2 is increased in intestinal human MCs from Crohn's disease (CD) patients and seems to play a central role in disease pathophysiology.[89] NOD1 engagement by its synthetic ligand M-TriDAP in cord blood derived MCs (CBMCs) does neither induce degranulation nor eicosanoids secretion. However, it promotes the production of IL-8, TNFα, CCL3, and CCL4 (but not of IL-1β, GM-CSF, and CCL2).[86] No data exist on the effects of NOD2 activation in MC, but NOD2 knockdown in HMC1 cells blocked PGN-induced degranulation.[90] Concerning signaling, in other cell types it is known that NOD1 and NOD2 engagement induces association with the Receptor-interacting serine/threonine-protein kinase 2 (RIPK2) via CARD domain interactions, resulting in the formation of a signaling complex that mediates NF-κB and MAPK activation.[61] In CBMCs, the use of chemical inhibitors indicated that M-TriDAP-induced cytokine production that was dependent on p38 activation, but independent of other MAPK or PI3K pathways.[86]

NLRP3

The inflammasome is a cytoplasmic multiprotein complex that promotes proinflammatory cytokine maturation in response to PAMPs and/or DAMPs. NRLP3 forms an inflammasome with the adaptor protein, apoptosis-associated speck-like protein containing a CARD (ASC) in response to a variety of PAMPs or DAMPs. This induces secretion of interleukin (IL)-1β and IL-18 via the processing of their precursors through a caspase-1 and proteasome-dependent mechanism.[88] Interestingly, mutations in the NLRP3 genes are found in a population of patients with CAPS (Cryopyrin-associated periodic syndromes).[88,93] These CAPS patients develop an urticarial-like skin disorder due to a dramatically increased IL-1β and IL-18 expression in their skin.[93] NLRP3 is expressed at the mRNA, protein, and functional levels in MCs from mouse and human origins.[88,92,94] NLRP3 expression is low in unstimulated mouse BMMCs and fetal skin-derived MCs but increased after LPS or TNFα exposure along with the adaptor protein ASC and the cytokine IL-1β.[88,92] NLRP3 engagement with R837 does not induce MC degranulation.[92] By itself, this stimulation does not lead to cytokine (IL-1β) production, but enables LPS-induced IL-1β production.[92] Interestingly, mouse MCs bearing the same mutations in the Nlrp3 gene as CAPS patients also show an increased production of IL-1β as what is observed in patient skin MC[88,92] and mice bearing the mutations develop a skin phenotype mimicking this in CAPS patients. After adoptive transfer into MC-deficient animals, only those reconstituted with Nlrp3-mutated MCs develop the disease.[88] NLRP3 engagement after MC exposure to LPS or TNFα is known to lead to an Asc-dependent NF-κB activation.[61,88,92]

4 | G-PROTEIN-COUPLED RECEPTORS (GPCRS)

G-protein-coupled receptors or GPCR comprise a family of over 800 genes encoding proteins with 7-transmembrane spanning helical domains.[95] GPCRs are associated with a trimeric GTP-binding protein (G protein) composed of Gα and Gβγ subunits. Upon activation, GDP dissociates from Gα allowing GTP to bind, resulting in dissociation from Gβγ.[96] Gα can be grouped into 4 classes: Gs, Gi, Gq, and $G_{12/13}$ that couple to different signaling effectors.[96] Gs is coupled to the activation of adenylate cyclase, whereas Gi to its inhibition. Gq is coupled

to the activation of PLCβ and $G_{12/13}$ couples to various effectors such as PLCε or RhoGEFs. While Gi is inhibited by Pertussis toxin, Gs is sensitive to inhibition by Cholera toxin. The Gβγ subunits also regulate intracellular effectors such as PLCβ. Receptors can be desensitized through the G-protein-coupled receptor kinase (GRK)-arrestin pathway whereby GRK binds and phosphorylates the activated receptors, which allows recruitment of β-arrestin preventing further GPCR activation and promoting internalization and cytoplasmic β-arrestin-dependent signaling.[97] In the following section, we will focus on several types of these GPCRs expressed in MCs and detail their roles.

4.1 | MAS-related GPCRs

It has been known for more than 70 years that many basic compounds, including a large number of drugs, can induce the release of histamine in the body.[98,99] This basic principle is conserved in mammals and birds and even in lower organisms.[100,101] Furthermore, it became apparent that the major histamine-releasing cells are MCs.[102] Besides certain drugs, many of these basic secretagogues correspond to endogenous or exogenous peptides such as, for example, neuropeptides (Substance P, vasointestinal peptide, neurotensin, somatostatin), antimicrobial peptides (LL-37, β-Defensins, catestatin, etc.), toxins (mastoparan, sarafotoxins, helodermin).[103] Albeit-specific receptors exist for certain of these peptides (see below), some of them as well as other cationic agents interact with a new subfamily of GPCRs related to the MAS1 oncogene with encoding genes being called Mas-related gene (MRG) and receptors being called MAS-related GPCRs.[101,103] These receptors are expressed abundantly in the neuronal system in dorsal root ganglia, but MCs are the only other cells that express the MRGPRX2 (MRG-protein-coupled receptor X2) isoform in humans or their orthologs MRGPRB2 and MRGPRB3 in the mouse and rat.[103] They are mostly associated with the tryptase/chymase positive MCs (MC_{TC}) that are predominant in the skin, whereas tryptase only positive MCs (MC_T) do not express this receptor.[101,103,104] MRG GPCRs couple to both Gi and Gq as signaling studies showed that they contained both pertussive toxin-sensitive (Gi) and insensitive components (Gq).[103] They are relative insensitive to desensitization as MRGPRX2 is resistant to LL-37-induced receptor phosphorylation, desensitization, and internalization and silencing of either GRK2 or GRK3 had no effect on LL-37-induced MC degranulation.[103]

Tatemoto et al[104] provided the first description of MRGPRX2 in MCs and its reactivity to various peptides such as the synthetic compound 48/80 or endogenous peptides including substance P (SP) and vasointestinal peptide (VIP). The first in vivo study using mutant mice carrying a null mutation was reported in 2015.[101] It confirmed that MRGPRB2 is the mouse MC basic secretagogue receptor causing histamine release, inflammation and airway contraction. Furthermore, it was shown that most classes of approved peptidergic drugs associated with allergic-type injection-site reactions, pseudo-allergic, or anaphylactoid reactions activate MRGPRB2 in WT but not in mutant mice. Thus, certain nicotinic receptor antagonist, non-steroidal neuromuscular blocking drugs (NMBDs), including tubocurarine and atracurium and antibiotics such as new generation ciprofloxacin all induced MC responsiveness via MRGPRB2. This calls for considering the structural characteristics of MC-activating peptides in the design and development of peptidergic drugs to avoid accompanying side effects.[105] While, these pseudoallergic reactions may represent a problem for drug development, MRG GPCRs also have important physiological functions. The reactivity with antimicrobial peptides participates in MC-driven innate host responses enhancing vascular permeability and recruitment of neutrophils. It also contributes to direct bacterial killing as MC activation via LL-37 exerted potent antimicrobial effects through the release of extracellular traps against *Enterococcus faecalis*, a pathogen that has emerged as an important cause of life-threatening multidrug-resistant bacterial infections.[106] MRG GPCR activation may also be useful in vaccination strategies providing an adjuvant effect.[107] Given its reactivity with neuropeptides such as SP and VIP, the receptor represents also a component of the communication between the neuronal and immune system participating, for example, in neurogenic inflammation responsible for pain and itch[108] in agreement with their localization close to nerve endings that release these peptides. Taken together, the description of this new receptor explains to a large extent the extraordinary capacity of MCs to respond to a diverse array of compounds of different origin that have the characteristics of being charged positively.

4.2 | Complement receptors

Well before the discovery of IgE, Friedberger[109] coined the term "anaphylatoxin" as a serum substance, which could be the result of cleavage of a serum component as a possible explanation for the effects of the toxin introduced in the famous experiments by Portier and Richet describing anaphylaxis. Later studies by Z. Ovary and colleagues in the 1950s showed that complement components participated in passive cutaneous anaphylaxis in the rat.[110] Two biologically and chemically distinct anaphylatoxins, called C3a and C5a[111] were found to be generated and able to induce histamine release by rat MCs.[112] Their receptors, C3aR and C5aR, are typical GPCRs that couple to the Gi family of heterotrimeric G proteins.[113,114] Some populations of rodent and human MCs express these receptors inducing degranulation and hypersensitivity reactions in vivo. They correspond to MCs of the serosal type in mice or MC_{TC} in humans, although no systematical studies have been performed.[115] In humans they are particularly enriched in the skin and associated with chemotactic and histamine-releasing activities.[116-119] They could also be demonstrated in certain human MC lines.[115] In rodents, rat peritoneal MCs are directly activated by C3a and C5a,[112], whereas in mice expression was inducible upon stimulation by the IgE receptor.[120] Some studies, however, challenged the notion of specific receptors by MCs by the fact that highly cationic degradation products of C3a may produce MC responsiveness in a manner similar to other cationic peptides that we now know to interact with specific receptors.[121,122] However, recent work by Galli and coworkers clearly demonstrated the involvement of specific receptors in MC-driven inflammatory responses based on the use of C3aR- and C5aR-deficient

MCs.[123] By measuring the magnitude of passive cutaneous anaphylaxis (PCA) reactions following intradermal injections of C3a or C5a they reported an important contribution to skin swelling, albeit some MC-independent skin swelling occurred with C5a in agreement with its larger distribution, notably on neutrophils. Interestingly, they reported also an important cross-talk with IgE receptor mediated PCA responses as mice reconstituted with either C3aR or C5aR deficient MCs showed less severe responses. Complement activation, which occurs in many types of inflammatory responses, may therefore be an important contributor to inflammatory pathologies driven by MCs.

4.3 | Endothelin receptors

Several other GPCRs have also been described to potently induce MC degranulation and the MC-mediated inflammatory responses. Endothelin (ET) is a 21 aa peptide endowed with potent vasoconstrictor functions released by many cells. Two related peptides ET-2 and ET-3 differ, respectively, by 2 and 6 aa.[124] They are normally kept in tight balance, but during an inflammatory response ET has been implicated in a wide spectrum of pathological processes in different tissues and organs. Given the broad tissue distribution of MCs it was important to analyze potential interactions. MCs express the ET_A GPCR, whereas the expression of ET_B GPCR is minimal or non-existent.[125] Functional studies showed that MC degranulate in response to ET-1. This induces a feedback control limiting endogenous ET-1 toxicity as MC-derived proteases, in particular carboxypeptidase A, hydrolyze ET-1 to a biologically inactive peptide.[126] This protective feedback contributes to an increased survival of mice in a model of severe sepsis as MC-deficient mice reconstituted with ET_A-deficient MC show a lower survival rate.[127] MCs through their ET-degrading activity may therefore contribute to the maintenance of physiological ET levels. Conversely, ET-1 can also have aggravating functions, notably by enhancing IgE-mediated anaphylaxis.[125]

4.4 | Neuropeptide and neurotransmitter receptors

Neurotensin (NT) is a tridecapeptide expressed in the brain and in the GI tract.[128] In the brain, it functions primarily as a neurotransmitter and in the GI tract it controls gastric acid secretion and motility. However, NT is also known for its interaction with immune cells such as lymphocytes and MCs.[129] MCs produce NT on their own.[130] Soon after the discovery of NT, it was reported that MCs bind NT.[131] Further studies in mice showed that they predominantly express NTSR1[132] a GPCR that couples to both Gi and Gq.[133] NT binding induces degranulation and VEGF production,[134] albeit the degranulating activity seems to be lower than through ET-1.[132] In addition, NT induces expression of corticotropin-releasing hormone receptor CRHR-1,[134] a GPCR that couples to multiple types of G proteins.[135] NT and CRH are released under stress supporting a NT-CRH crosstalk at the neuronal-immune interface. Several chronic inflammatory skin disorders such as psoriasis, atopic dermatitis can worsen with stress. As NT serum levels are elevated in these diseases, they may contribute to the aggravation of symptoms.[108] Conversely, MCs can also reduce NT toxicity in septic peritonitis induced by cecum ligation and puncture reducing NT levels and NT-induced hypotension.[132,136] Interestingly, this effect does not require MC degranulation, but was, at least partly, dependent on the expression of NTSR1. The NT-degrading activity was associated with enhanced expression of neurolysin in its plasma membrane form. NT reduction could also depend on its increased uptake by MC-expressed NTSR1.

Other neuropeptides have been reported to activate MC or modulate their responses. These peptides, released from the brain or locally in tissues from nerve endings participate in the crosstalk with immune cells among which MC are prime effectors. These peptides include, for example, SP known to induce MC degranulation and chemokine production thereby participating in a neurogenic MC inflammatory axis.[137] Early studies using NK-1R KO mice showed that the neurokinin receptor-1 (NK-1R) was necessary to induce MC-dependent edema formation.[138] Its expression was inducible in cultured BMMC by IL4 and SCF or in nasal mucosa MC during allergic rhinitis, which may be relevant in inflammatory conditions.[139,140] Interestingly, new studies found that SP also interacts with MRGPRX2 albeit with somewhat lower affinity (0.5 nM vs 100 nM) and much lower affinity (50 μM) in the case of mouse MRGPRB2.[141] NK-1R antagonists inhibit mouse MRGPRB2, but fail to inhibit human MRGGBX2, which may account for the failure of NK-1R antagonists in some clinical investigations as compared to studies in the mouse. In addition, it was shown that SP-induced itching was not due to the interaction of SP with NK-1R, but involved the activation of MRGPRA1 expressed on sensory neurons.[142] Hence much needs to be learned about the interactions between the neuronal and the immune system and its involvement in pathophysiology.

Other neurogenic peptides reported to activate MCs include calcitonin gene-related peptide (CGRP), somatostatin, vasoactive intestinal peptide (VIP), and many others.[108,143,144] Most of them are endowed with histamine-releasing activity with some also showing modulatory effects on histamine release. For several of these, specific receptors are present on MCs. These include, for example, CGRP, a 37 aa peptide produced as a consequence of alternative splicing of the calcitonin gene. It has a wide ranging physiological and pathophysiological activities, including in migraine, cardiac failure, hypertension, and sepsis.[145] The GPCR for this neuropeptide is somewhat unusual as it is composed of 3 subunits including the 7-transmembrane calcitonin-like receptor (CLR), the receptor activity-modifying protein 1 (RAMP1), and the receptor component protein (RCP) allowing G protein coupling.[146] The CLR was found to be localized to granular cells in the dura mater, the outer layer of the meninges of the rat[146] and upon activation by CGRP promotes histamine release from dural MCs.[143] As CRGP is elevated in serum and saliva during migraine attacks, this supports an important role of MCs in migraine pathology.[146] Concerning VIP, a 28 aa peptide, MCs have been reported to synthesize and release a truncated form of VIP (VIP_{10-28}) on their own[147,148] and to express VPAC2 receptors and possible also VPAC1 receptors in certain subpopulations.[137,149] In the gut it can be released from sympathetic cholinergic nerves[150] and was recently shown to

regulate intestinal barrier function during stress increasing the permeability via the activation of MCs.[151]

Adrenaline or epinephrine, is another hormone and neurotransmitter, that is, released in response to stress promoting the acceleration of heart beats, blood pressure but also bronchodilatation. Its receptor, the beta2 adrenergic receptor, also known as ADRB2 was the first GPCR to be cloned.[152,153] Due to its bronchodilatory effect, ADRB2 agonists have been used in the treatment of asthma for more than 50 years. However, other effects have also been described and these include among others inhibition of histamine release by MCs.[154] Indeed, evidence for the expression of the ADRB2 receptor inducing cAMP elevations in MCs was reported already in 1975.[155] Their effect has been mostly tested on human lung MCs. The studies show that both short- and long-acting ADRB2 receptor agonists are effective inhibitors of MC activation although there are differences in the degree of inhibitory activity attained with a given agonist. Tolerance effects have also been observed, which may be influenced by genetic variants of the ADBR2, but also by cellular interactions between MCs and smooth muscle cells, which can induce desensitizing phosphorylation events of the ADBR2.[156]

4.5 | Lipid mediator receptors

MC are also activated by certain bioactive lipid mediators via GPCRs. The best studied mediators are Sphingosin-1-phosphate (S1P), prostaglandins, leukotrienes, and PAF synthesized, respectively, from Sphingomyelin, phospholipids, and ether-linked phospholipids.[157]

S1P is a bioactive lipid, which exhibits a sharp gradient between the circulation (μM) and in tissues (nM), that is, maintained by S1P degrading enzymes in tissues. This gradient promotes chemotaxis of immune cells from lymphoid organs to the circulation via expressed S1P receptors.[157] During an inflammatory response, activated MCs, via sphingosine kinase, produce and release S1P through membrane transporters leading to its upregulation in tissues. MCs express 2 out of the 5 known S1P GPCRs, $S1P_1$,and $S1P_2$. The $S1P_1$ receptor mediates chemotaxis toward antigen or stem cell factor (SCF) in an autocrine manner.[158] The $S1P_2$ receptor also enhanced IgE-induced degranulation albeit this was largely dependent on the type of MCs examined.[157] S1P may also have receptor-independent effects as a signaling effector as suggested by studies in Sphingosine kinase 2 knock out cells, which do not produce S1P. These cells show profound defects in different functional responses including degranulation and calcium mobilization.[159] A clear study using MCs cells deficient in both S1P receptors to distinguish between these effects is still missing.

Concerning prostanoids, MCs have been reported to be responsive to PGD_2 and PGE_2. They are themselves important producers of PDG_2 and hence may affect MC functions in an autocrine manner.[160] PGD_2 acts through prostaglandin D2 receptor 1 and 2 (PTGDR1-1 and -2) also known as DP1 and DP2 (or as chemoattractant receptor-homologous molecule expressed on TH2 cells, CRTH2) GPCRs.[160] DP2 is expressed in BMMC and MC lines and responds to stimulation with agonists with chemotaxis and the upregulation of CD23 and CD30, as well as CD62L shedding, whereas no effect on degranulation is observed.[161] A recent study in mice uncovered a role of the DP1 receptor as being important for the maturation of MC through a PGD_2-DP1 mediated crosstalk with fibroblasts.[162] Fibroblasts produce PDG_2, which through the interaction with DP1 on immature MC induces the expression of maturation markers such as, for example, MC proteases. PGD_2 also reduced responses to systemic or passive anaphylaxis supporting an important role of this lipid mediator and DP1 in MC function. Human MC and MC lines were shown to express DP2, however, the GPCR was observed mostly intracellularly.[163] In agreement functional studies showed that they were unresponsive to stimulation with agonists.

In contrast to PGD_2, PGE_2 is not majorly produced by MC. It was noticed, however, that PGE_2 had a beneficial effect in clinical studies reducing airway inflammation.[164] Evidence for expression of all 4 PGE_2 receptors EP1 to EP4 has been reported depending on the MC type and species.[165-167] While EP1 and EP3 had activating functions involving Gi, the EP2 and EP4 were found to have inhibitory activity involving Gs signaling.[167] Indeed, while EP1- and EP3-specific agonists activated cells for degranulation and eicosanoid production, the EP2- and EP4-specific agonists led to cAMP accumulation and inhibited generation of several mediators including TNF and PGD_2 induced by FcεRI with a dominant effect of EP2 over EP4.[165-167] In addition, EP2 has been found to mediate the closure of the intermediate conductance calcium-activated K^+ channel $K_{Ca}3.1$ in human lung MCs by a Gs-mediated mechanism that was cAMP-independent.[168] Further studies showed that the global outcome of PGE_2 signaling depended on the ratio of EP2 and EP3 receptors, which differed between isolated and cultured primary mouse and human MCs and MC lines.[165-167,169] Hence, the use of specific EP2 agonists instead of PGE_2 may be a useful strategy to limit airway responsiveness avoiding the cross-effects of the use of PGE_2.

Leukotrienes (LTs), both LTB4 and cysLTs such as LTC4, LTD4, and LTE4[170] are eicosanoid lipid mediators derived from arachidonic acid through the lipoxygenase pathway. Their biological effects are mediated by various GPCRs: cysLTs interact with CYSLTR1 and CYSLTR2 with CysLT2R binding LTC4 and LTD4 with equal affinity, but binding LTD4 with a 10-fold less affinity than CysLTR1. Another receptor GPR99, homologous to G-protein-coupled purinergic receptors, more specifically interacts with the stable metabolite LTE4.[170] An additional constitutively active receptor, GPR17, forms heterodimers with CYSLTR1 and exerts an inhibitory role in the absence of ligand binding. LTB4 acts through BLT1R and BLT2R (also called LTB4R 1 and 2) with, respectively, high- and low-affinity.[171] Cultured primary MC and human MC lines have been shown early on to express both CYSLTR1, CYSLTR2.[171-174] Cultured murine MC were also found to express BLT1 and BLT2.[175] Interestingly, CYSLTR2 can form heterodimers with CYSLTR1 thereby diminishing its expression, down-modulating the mitogenic response of MCs in response to cysLTs.[176] More recently a study performed on isolated rat peritoneal MCs provides evidence that MCs express in addition GPR17.[171] Although membrane expression is evident, all receptors were also found intracellularly close to the nucleus. In addition, human lung MCs express

GPR99 that is upregulated in response to allergic stimulation[177] Functionally, both cysLT and LTB4 were able to activate MCs inducing early signaling event such as p38 and Erk phosphorylation as well as expression of mRNAs for certain cytokines, PGD2 release, and proliferation.[171,176,178] LTB4 represents also a chemoattractant for MC progenitors.[179]

Recently, platelet-activating factor (PAF) has been shown to be implicated in the pathogenesis of anaphylaxis in murine models[180] and in humans, where PAF levels are markedly increased.[181] The major metabolizing enzyme, PAF acetyl-hydrolase, showed reduced levels in patients with anaphylaxis.[182] Many cell types produce PAF including MCs.[183] It acts through the PAFR, a GPCR highly expressed on platelets causing platelet aggregation. Concerning MCs, PAF was initially described to induce degranulation of skin MCs, however, this effect appeared to be indirect implying the activation of neurons. More recently, however, it was found that mucosal MCs in the lung or cultured human MC grown from adult peripheral blood progenitors but not skin MCs express a functional PAFR.[184] The authors showed that these MCs degranulate in response to PAF in a Gi-dependent manner. Pretreatment with the PAFR antagonist CV-6209 inhibited this response. Incubation with PAF also induced PGD_2 and a certain number of chemokines and cytokines, albeit in lower amounts than after stimulation through FcεRI. An additive effect on degranulation was observed when MCs were stimulated both with PAF and IgE/Ag. Based on the fact that PAF levels were increased in anaphylactic patients, the authors suggested that PAF may contribute to an amplification loop promoting the generalization of the MC response to an allergen in the body.

4.6 | Purinergic receptors

Other important GPCRs described early on to be expressed on MC include receptors for the purine nucleoside adenosine produced by numerous cell types in response to cell stress and hypoxia that are important under inflammatory conditions.[185] MC express the A2aR, A2bR, and A3R, whereas A1 was absent. A2b and A3 receptors bind adenosine with lower affinity than A2aR. The A2 receptors are known to couple to Gs with A2b also being reported to couple to Gq, whereas the A3 receptors couple to Gi.[186] The importance of the adenosine response by MCs was first advocated by its ability to provoke bronchoconstriction in atopic and asthmatic individuals, but not in normal subjects, a phenomenon referred to as adenosine hyperresponsiveness (AHR)[187] and inhibited by MC degranulation blockers.[188] However, further studies with MCs showed that adenosine can mediate both activating and inhibitory functions.[189] At least from animal studies it appears that it is the A3R, which is responsible for the hyperresponsiveness as AHR develops in MC-deficient mice reconstituted with WT, but not with $A3R^{-/-}$ MCs. On the contrary the inhibition of degranulation may involve A2a and A2b receptors.[189,190] However, the situation seems to be complicated as these studies were not confirmed in human cells implicating the A2bR, whereas the A3R was rather attributed an inhibitory function.[191] However, disparities were also found between different MC populations.[192] Therefore, further studies are necessary to identify the exact contribution of adenosine receptors.

4.7 | Other

In addition to the above-mentioned receptors MCs express numerous other GPCRs. This includes, for example, a large number of chemokine receptors. These are a large family of GPCRs that are classified according to the location of the first 2 cysteines in their sequence: CC, CXC, C, and CX3C (where X stands for any amino acid). The MC expression profile largely depends on the type of MC examined: progenitor cells vs mature MCs or MC subtypes. Besides inducing bona fide MC chemotactic responses, chemokine receptors have also been implicated in the cross-talk with other receptors synergistically enhancing FcεRI-mediated responses such as reported for CCL7.[193] An excellent review on these receptors was recently published.[194]

Another interesting receptor that can be mentioned is the ADGRE2 GBCR, a GPCR composed of an Extracellular N-terminal α subunit with 5 epidermal growth factor (EGF)-like adhesion domains binding dermatan sulfate in the skin and a β subunit containing the classical 7-transmembrane domains. Gain of function mutations (C492Y) in this receptor have recently been reported to be responsible for physical urticarias in response to various stimuli that can be provoked by vibration of the forearm on a laboratory vortex.[195] The physiological role of this receptor, which is lost in mice, is still to be defined, but could relate to the necessity to respond to physical stimuli.

5 | NUCLEAR RECEPTORS

Contrary to classical plasma membrane receptors, nuclear receptors are ligand-activated transcription factors that sense their ligands intracellularly. The 48 known NR can be classified in 7 subfamilies.[196]. Albeit not all ligands have been identified, they include, for example, steroid, thyroid hormones, and certain other molecules such as lipophilic vitamins.[196,197] NRs can bind to DNA and regulate the expression of adjacent genes as transcription factors. Some NRs bind the ligand in the cytoplasm, which induces dissociation of heat shock protein, homodimerization, and nuclear translocation. Such receptors include, for example, androgen, estrogen, glucocorticoid, and progesterone receptors. Others receptors are located in the nucleus. Usually in this case ligand binding induces dissociation of a repressor or recruitment of a coactivator enabling transcriptional activity. Examples for this type of receptors are, for example, the retinoic acid receptor, retinoid X receptor, or thyroid hormone receptors.[196,197]

5.1 | Glucocorticoid receptors

MC have been known for many years to respond to glucocorticoids.[198] Glucocorticoids are steroid hormones released upon stress with multiple anti-inflammatory roles ranging from immunosuppression, psycho-neuronal effects, effects on fat and protein metabolism, and many others. Corticoids are important options in the treatment of

severe allergies and asthma due to their anti-inflammatory function. At the molecular level, they act by binding to an intracellular cytosolic NR, the glucocorticoid receptor (GR). This receptor after translocation to the nucleus induces the transcription of anti-inflammatory products such as lipocortin-1 (also called Annexin A1) or anti-inflammatory cytokines such as IL-10. Lipocortin-1 inhibits the activity of phospholipase A2 the generator of arachidonic acid thereby blocking production of eicosanoids. It can also block the transcription of pro-inflammatory products. These nuclear actions require at least 30 min of exposure to glucocorticoids. However, additional anti-inflammatory functions of glucocorticoids can also be observed rapidly within seconds to minutes, which excludes a nuclear effect. MCs were shown recently to express the GR in the RBL-2H3 cell line,[198] but also in human uterine MC.[199] Numerous functional consequences of glucocorticoid exposure in MCs have been reported. This includes the effect on a large number of signaling molecules ranging from the downregulation of FcεRI, signaling effectors (PLCγ1, Syk, Erk1/Erk2, p38, and phosphatases such as DUSP1/2), and adapter molecules (LAT, Dok1, SLAP). Only a few of these effects in MC have been studied mechanistically, and many of them may involve classical transcriptional effects. However, short-term effects of glucocorticoids have also been demonstrated in MCs. Thus, MCs degranulation was inhibited 5 min after exposure, correlating with a decrease in membrane capacitance and calcium signaling.[200] Interestingly, a recent study reported that in response to IgE/Ag-mediated activation, the GR gets rapidly recruited to the plasma membrane, where it seemed to interact with membrane-bound factors. The recruitment occurred independently of treatment with corticoids, but could be enhanced in their presence as was also the phosphorylation of Erk.[201] These studies support a role of plasma membrane localization of the GR in addition to its role in the nucleus in MC.

5.2 | Hormone receptors

Receptors for the 3 classes of sex hormones—estrogens, progesterone, and testosterone—have been identified on various immune cells[202] including MCs.[203-206] Female sex hormones interact with the estrogen receptors EαR and EβR and the progesterone receptors PR-A and PR-B, whereas the male sex hormone testosterone acts trough the androgen receptor AR, also known as NRC3C4 (nuclear receptor subfamily 3, group C member 4).[207,208] It has been known for many years that immune responses can vary with gender and the reproductive phase, sex factors regulating, for example, immunoglobulin levels and skin transplantation.[209,210] Furthermore, it is known that asthma and other allergic airway diseases as well as anaphylaxis are more common in women.[211,212] Xenoestrogens such as bisphenol A and phthalates have also gained attention as they were shown to enhance allergic sensitization in animal models and may enhance development of atopic disorders like asthma in humans.[211] Studies in animals showed that IgE levels are higher in allergic female mice compared to syngeneic male counterparts[213] and that ovariectomized female rats developed less airway inflammation compared with sham controls.[214] Concerning MCs, studies in rodent or human MC and MC lines showed that—depending on the dose used, estradiol, progesterone, and testosterone can induce MC degranulation and some other mediators.[215,216] This effect required only short-term incubation suggesting, like for the GR, the occurrence of cytoplasmic signaling.[215,217] Interestingly, a study showed that degranulation was observed in rat peritoneal MCs isolated from female rats,[216] whereas another study on human foreskin MC did not detect degranulation in response to testosterone treatment.[204] Complex effects were seen when rat peritoneal MCs were pretreated with sex hormones before stimulation with either IgE or SP ranging from stimulatory effects (estrogen) to inhibitory effects (progesterone and testosterone).[216] However, no further mechanistic studies have been made. Besides MC degranulation sex hormones may fulfill other functions. It has been reported that estradiol and progesterone regulate the migration of MC from the periphery to the uterus and induce their maturation. In the uterus, MC are important for fetal growth, although their absence can be compensated by NK cells and vice versa.[218] Likewise, MC numbers in testis correlate with estrogen levels promoting fibrosis and deceased spermatogenesis in adults, a phenomenon that may be amplified in cryptorchid testes due to elevated estrogen levels.[219] Together these studies show that sex hormones can significantly affect MC responses and they can differ between MCs of different sex, which at least in some cases may explain experimental differences in various studies. Care should therefore be taken to indicate and choose the sex origin of cells and animals in MC-related experiments and this may also apply for other immune cells.

5.3 | Aryl hydrocarbon receptor

Recently the aryl hydrocarbon receptor (AhR) has also gained attention. This NR represents a cytosolic sensor of natural metabolites including endogenous products such as tryptophan metabolites (kynurenine), heme metabolites (bilirubin), eicosanoids, certain dietary substances such as quercetin (apple), resveratrol (wine), and curcumin (spices) as well as xenobiotics such as dioxin, benzoflavones, benzanthracenes, etc.[220]. Like other NR it becomes activated after the interaction with its ligand in the cytoplasm leading to nuclear translocation activating a series of pro- and anti-inflammatory genes, historically grouped under the acronym DRE (dioxin responsive elements). AhR is expressed in different immune cells and was recently shown to be expressed in various murine and human MCs and the RBL-2HR3 MC line.[221-224] The studies showed that incubation with 6-formylindolo[3,2-b]carbazole (FICZ), a strong ligand derived from the tryptophan metabolism, induced degranulation, LTC4 release and cytokine production including IL-6 and IL-13. AhR activation also induces ROS production, which due to the close association of MC with blood vessels and nerve endings, may produce vascular and neuronal inflammatory effects. Prolonged exposure was reported to induce a shift to IL-17 production and impaired degranulation[222] indicating that the associated inflammatory response can change with time of exposure. The effect on MC proliferation and differentiation reported in AhR-null mice[223] was disputed by others[225] albeit studies in

an inflammatory model have not been investigated. Therefore, it will be important to study the role of this receptor in various MC-driven diseases. Notably, the MC reactivity to xenobiotics other than the endogenous ligand has not been studied. Yet, it is known that allergic and airway diseases including COPD are influenced by pollutants and xenobiotics. In particular, long-term consequences are important to study. In this respect it should be noted that increased numbers of IL-17 producing T cells are present in the lungs, sputum, bronchoalveolar lavage (BAL) fluids or sera from asthmatics.[222] They are also present in psoriatic lesions in human skin[226] and atherosclerotic plaques[227] and many other diseases with a MC-rich inflammatory infiltrate. Hence, the activation of IL-17 producing MC through the AhR may represent a contributing factor to disease development.

5.4 | Vitamin D receptor

1,25-Dihydroxyvitamin D3 [1,25(OH)2D3], the active metabolite of vitamin D3 (cholecalciferol) functions by binding to the vitamin D receptor (VDR). It works as a ligand-activated transcription factor that binds to vitamin D responsive element (VDRE) in vitamin D responsive genes. Vit D was originally identified as a key regulator of bone metabolism and calcium homeostasis, but has also been recognized as an important system endowed with immunoregulatory and anti-inflammatory properties.[228] MCs express VDR and interaction with the ligand inhibits IgE-induced degranulation and release of some other mediators and chemokine/cytokine production.[229,230] The effect was more pronounced after pretreatment for 48 hours as compared to 24 hours. However, enhancement of degranulation response was also observed in MC lines.[231] Direct long-term incubation of MC with Vit D3 was also shown to inhibit MC differentiation by promoting apoptosis of MC precursors and VDR-deficient mice showed a slight increase in skin MCs supporting a role in MC development.[232] Likewise, direct incubation of MCs with Vit D3 induces the secretion of certain cytokines such as IL-10, IL-4, and TNF.[233] Furthermore, topically applied Vit D induced the anti-inflammatory cytokine IL-10 by murine skin MCs, which suppresses the inflammatory response associated with chronic UVB exposure of the skin differentiation, and function. Absence of the VDR in MC-deficient mice reconstituted with VDR-deficient MCs abrogated this suppressive function.[233] Hence, activation of this receptor may have an important anti-inflammatory function in MCs.

5.5 | Peroxisome proliferator-activated receptors

The peroxisome proliferator-activated receptors (PPARs) are NR that promote the transcription of target genes by forming heterodimers with the retinoid X receptor (RXR) to induce gene expression by binding to PPAR responsive elements.[234] PPARs are at the crossroads of lipid metabolism and inflammation regulating genes involved in lipid and carbohydrate metabolism, vascular biology, but have also important anti-inflammatory functions.[234] They are activated by endogenous ligands which include fatty acids and their derivatives such as eicosanoid metabolites many of which also signal through membrane receptors creating a lipid signaling network between the cell surface and the nucleus. Among the 3 PPAR subtypes (α, β/δ, and γ) both PPARβ/δ, PPARγ were found to be expressed in murine and human cultured MCs with PPARγ being induced after IgE/Ag stimulation.[235,236] Pharmacological ligands of both types inhibited cytokine production indicating a negative regulatory function. In human LAD-2 MCs LTE_4 induced PGD_2 in a manner that was dependent on PPARγ, which may explain some of the unique function of this eicosanoid in human airways.[237] Other studies using PPARγ-specific ligands and siRNA-mediated knock-down reported an inhibition/acceleration of the maturation of bone marrow progenitors into connective tissue-type MCs (CTMCs) regulating histamine content and expression of several MC proteases.[238] In addition, histamine release as well as the production of LTB_4 and TNF was inhibited after long-term incubation with PPARγ ligands. A retrospective study in humans showed that application of the PPARγ ligand was able to attenuate atopic dermatitis,[239] whereas in mice it rather implicated PPARα and PPARβ/δ.[240] The effect of PPARγ on MC proliferation, maturation was, however, confirmed using a specific ligand showing in addition that the ligand was able to induce apoptosis of MC progenitors.[241] Less work has been performed with PPARβ/δ. A recent study showed that BMMCs and peritoneal MCs from *Ppar*$\beta/\delta^{+/+}$ mice expressed higher levels of FcεRI compared with *Ppar*$\beta/\delta^{-/-}$ mice. Furthermore, the development and maturation of peritoneal MCs was markedly impaired in the KO mice with several proteases, but also beta-hexosaminidase content being significantly diminished in cultured BMMCs.[242] Interestingly, cytokine production was differentially affected depending on the type of stimulus (IgE/Ag, UVB, LPS, or TPA). For example, while *Tnfa* expression was strongly enhanced after IgE/Ag stimulation, it was diminished after UVB stimulation of BMMC from *Ppar*$\beta/\delta^{-/-}$ mice and unchanged in BMMC from *Ppar*$\beta/\delta^{+/+-}$, whereas the reverse was observed for IL-10 production after IgE/Ag and LPS stimulation. Altogether, these data show that MC express certain PPAR isoforms and that these can importantly influence their maturation and response profile warranting further studies on their pharmacological applications in MC-driven diseases.

6 | ALARMIN RECEPTORS

Multicellular animals have developed diverse mechanisms to rapidly detect whether their cells are injured or dead. A complete system for the detection, containment, and repair of damage caused to cells requires warning signals, cellular responses via receptors and signaling pathways, and outputs in the form of physiological reactions. PAMPs are exogenous danger signals derived from a diverse set of microbial molecules. Many self-molecules released from dying cells can also serve as a danger signal to the host. The term “alarmin” refers to such endogenous molecules that signal tissue and cell damage. They share several features: (1) they are rapidly released by necrotic cells, but not by apoptotic cells; (2) immune cells can also be induced to produce and release alarmins without dying; and (3) they can recruit and activate receptor-expressing cells of the immune system; (4) finally, alarmins can either restore homeostasis or provoke uncontrolled

inflammation.[243,244] This group of molecules include the high-mobility group box 1 protein (HMGB1), interleukin (IL)-1α/β, IL-33, S100s, HSPs, and nucleotides. In this section, some of these alarmins will be discussed with a focus on their association with MCs in the context of acute and chronic inflammatory diseases.

6.1 | IL1-R/IL-1

The IL-1 family contains 11 members. IL-1α and IL-1β are 2 classic proteins in this family. Both are highly similar in structure and bind to the same cell membrane receptor IL-1R. IL-1α precursor (pIL-1α) is constitutively expressed in stromal cells, such as epithelial cells lining the gastrointestinal tract, liver, kidney, and skin.[244] In conditions of necrosis or tissue damage, pIL-1α can be passively released or processed by the membrane-bound protease calpain into a mature form and then released into the extracellular space.[244] The pro-inflammatory role of IL-1α and IL-1β has been well-studied in various diseases, only a few studies have shown their direct interaction with MCs and they mainly focused on the role of IL-1 in the cytokine production of MCs. Kandere-Grzybowska et al have reported that IL-1 induces secretion of IL-6 without degranulation from MCs.[245,246] Huitner et al showed that IL-1 can upregulate the production of IL-3, IL-5, IL-6, and IL-9 as well as TNF from activated MCs, indicating that the IL-1-MC axis is associated with allergies and helminthic infections.[247] In a coculture model of IL-4 or double-stranded RNA stimulated bronchial epithelial cells and MCs, Nagarkar et al demonstrated that IL-1 released by stimulated bronchial epithelial cells induces the production of Th2 cytokines in MCs. This implicates that during viral infections, IL-1 released by epithelial cells can exacerbate local inflammation in asthma.[248]

6.2 | ST2/IL-33

Similar to IL-1α, IL-33 is another IL-1 family member widely expressed in stromal cells, such as endothelial cells, fibroblasts, and the epithelial cells of tissues in contact with the environment.[244] It is already translated and stored in the nucleus of the cells and released immediately during emergency conditions such as infection, injury, or inflammation due to other stresses.[249] Once released, IL-33 binds to a member of the IL-1R family, ST2 (also known as IL-1RL1), through which IL-33 can activate both innate and adaptive immune cells. ST2 is particularly expressed in T-helper 2 (Th2) cells and MCs.[249] Upon binding of IL-33, ST2 activation requires the accessory receptor IL-1R3 to function.[244] Once activated, ST2/IL-1R3 triggers signal transduction through a MyD88-IRAK-dependent pathway, leading to activation of NF-κB, C-Jun N-terminal kinase (JNK), and MAPK.[244]

IL-33 can serve as a potent activator of MCs and has been reported to promote survival, maturation, migration, adhesion, and the production of several pro-inflammatory cytokines (eg, IL-4, IL-5, IL-6, IL-8, and IL-13) and chemokines (eg, MIP-1α and MCP-1) in these cells.[250-260] In addition, in the presence of SCF, IL-33 can also induce TNF production in MCs via a MK2/3-, ERK1/2-, and PI3K-dependent pathway.[261] Recently, Taracanova et al have shown that IL-33 and SP together amplify TNF secretion from MCs, which is mediated by the interaction of NK-1R and ST2 receptors.[262] In addition, IL-33 and FcεRI act synergistically in the production of TNFα by MCs.[263] IL-33 promotes ICAM-1 expression in murine MCs and subsequently increased adhesion to LFA-1.[264] Moreover, IL-33 modestly enhances IgE-mediated MC degranulation,[263,265,266] as also shown at the single-cell level.[267] Notably, IL-33 amplifies IgE synthesis and triggers MC degranulation via IL-4 in the absence of specific allergen.[257] There is no ex vivo evidence that IL-33 directly induces MC degranulation without IgE-crosslinking. While most studies supported IL-33 as a potent activator for MCs, Jung et al reported that long-term IL-33 treatment induced a hypo-responsive phenotype of MCs, leading to a substantial reduction in MC activation in response to antigen.[268] These findings suggest that IL-33 can modulate MC activation depending on its exposure time and the presence of other stimuli. Furthermore, it reveals a plasticity in the MC activation phenotype by IL-33 under different inflammatory conditions.

On the other hand, activated MCs can modulate IL-33 activity via the secretion of serine proteases. Human MC chymase and tryptase selectively cleave full-length human IL-33 ($IL\text{-}33_{1\text{-}270}$) and generate the active forms: $IL\text{-}33_{95\text{-}270}$, $IL\text{-}33_{107\text{-}270}$, and $IL\text{-}33_{109\text{-}270}$, which were 30-fold more potent than full-length protein for activation of group-2 innate lymphoid cells (ILC2s) ex vivo.[269,270] It was also shown that cleavage of full-length IL-33 by tryptase contributes to the allergic airway inflammation in vivo.[269] In contrast, mouse MC chymase (MCPT4) has been reported to degrade IL-33, dampening inflammatory responses.[271,272]

During allergic inflammation, IL-33 is rapidly released by damaged epithelial cells lining in the skin, airway or gut. It can exacerbate allergic responses via the activation of MCs. Thus, IL-33 promotes oral anaphylaxis after epicutaneous sensitization by targeting MCs.[265] Involved mechanisms may relate to augmenting IgE-mediated MC degranulation[263,265-267] and the production of Th2 cytokines such as IL-4, IL-5, and IL-13 from MCs.[250,252-254,256,259] In asthma models, IL-33 promotes airway smooth muscle contraction via upregulation of MC-derived IL-13.[273] It exacerbates allergic bronchoconstriction by increasing secretion of serotonin from MCs[266] and IL-33 has also been reported to induce Th17-mediated airway inflammation via MCs. Vice versa, MCs release IL-33 under IgE/antigen stimulation[253,259] and the generation of potent forms by the cleavage of proteases,[269,270] thus leading to a positive feedback of IL-33 activity.

Conversely, IL-33 can also play a protective role in allergic inflammation. In a mouse model of Papain-induced allergy, IL-33-induced production of IL-2 by MCs suppresses inflammation by promoting regulatory T-cell expansion.[274] Similar mechanisms were also demonstrated in a mouse model of oxazolone-induced dermatitis.[275] IL-33 is expressed in synovial fibroblasts from patients with rheumatoid arthritis (RA).[260] In a mouse model of collagen-induced arthritis, IL-33 exacerbated the local inflammation by activating MCs to release various pro-inflammatory cytokines and chemokines.[260] In contrast, IL-33 can also induce an immunomodulatory phenotype of MCs in RA, such that MCs stimulated with IL-33 and IgG lead to the release of IL-10 and histamine.[276] Taken together, IL-33 may retune the immediate responses

of MCs to antigen toward the enduring pro- or anti-inflammatory cytokine production and thus determine the symptoms and severity of allergic and autoimmune diseases.

6.3 | High mobility group box 1 (HMGB1)

High mobility group box 1 (HMGB1) is one of the most abundant non-histone nuclear proteins and is a member of the HMG protein family that contributes to chromatin architecture and modulates gene expression.[244] Upon necrosis or tissue damage, HMGB1 is released from stromal or immune cells. The activity of HMGB1 is complex and multifaceted. On one hand, HMGB1 has 3 different oxidative forms, which enables 3 mutually exclusive functions: alarmin, chemoattractant, or tolerance.[244] On the other hand, HMGB1 can interact with multiple cell surface receptors, such as the receptor for advanced glycation end-products (RAGE) and TLR4.[244] In addition to TLR4 and RAGE, HMGB1 interacts with several other receptors. Indeed, extracellular HMGB1 can interact with IL-1β,[277] CXCL12,[278] and nucleosomes,[279] thereby promoting the activation of IL-1R, CXCR4, and TLR2. HMGB1 exerts a plethora of cell regulatory functions, ranging from maturation, proliferation, motility to inflammation, survival, and cell death.[244] Therefore, HMGB1 has been widely covered in various disease, such as infection, chronic inflammation, and cancer, as recently reviewed by Bertheloot et al.[244] Although surface receptors for HMGB1 are expressed on MCs,[280] there is not much direct evidence showing HMGB1-mediated MC activation. Several studies have shown that neutralization of HMGB1 is able to block production of Th2 cytokines IL-33, IL-25, and GM-CSF in the lung after allergen challenge,[281-283] which could be a hint for the interaction of HMGB1 and MCs.

6.4 | Purinergic receptors

Intracellular ATP is an energy source for many cellular reactions, but it can be released into the extracellular space actively upon stimulation or by passive leakage from injured or dying cells. Once released, it contributes to the efficient triggering of the innate immune system via the activation of purinergic 2 receptors (P2X and P2Y). P2X (P2X1-7) are ATP-gated ion channels and P2Y (P2Y1, 2, 4, 6, and 11-14) are G-protein-coupled receptors (see above).[36] Expression of various P2 subtypes in different MC subsets has been comprehensively reviewed by Bulanova et al.[284] Indeed, ATP can activate MCs and induce a plethora of responses, for example, Ca^{2+} influx, degranulation, cytokine and chemokine release, chemotaxis, and apoptosis.[284] In particular, the function of P2X7 in MCs has been in the spotlight these years. For instance, ATP induced PAD2 (protein arginine deiminase) enzyme activity and protein citrullination in MCs through P2X7, which is associated with the development of autoantibodies against citrullinated self-proteins in rheumatoid arthritis.[285] An increase in the number of MCs expressing P2X7 was reported in the colons of mice with colitis and of patients with Crohn's disease. ATP-mediated activation of P2X7 induces the production of inflammatory cytokines (IL-6, TNF-α, and oncostatin M), chemokines (CCL2, CCL7, and CXCL2), and leukotrienes from MCs, which subsequently exacerbate intestinal inflammation.[286] A recent study also showed that P2X7 is responsible for high concentration of ATP-mediated MC degranulation in LAD2 human MCs.[287] Notably, P2X7 is highly expressed by ex vivo cultured human MCs (HMC-1 and activated CBMC), but no detection of this receptor was found in human primary MCs isolated from lung and skin.[284]

ATP levels are significantly elevated in the airways of asthmatic patients after allergen challenge and in mice in a model of ovalbumin (OVA)-induced asthma.[288] ATP induces expression and release of many pro-inflammatory mediators from MCs, including IL-4 and IL-13,[284] implicating the importance of ATP-mediated MC activation in allergic inflammation. On the other hand, ATP can be converted to adenosine due to the enzymatic activity of extracellular CD39 and CD73.[284] ATP and its derivative adenosine can induce a synergistic response in MCs by P1 and P2 receptor co-activation, which further exacerbates the local inflammation.

7 | OTHER RECEPTORS

7.1 | Integrins

Integrins are αβ heterodimers where the α subunit is non-covalently attached to the β subunit. There are 14 known α subunits and 8 known β subunits and integrins are constituted of different combinations of these subunits.[289] Integrins are expressed on many cell types, and most cells express several integrins.[289] Blood basophils and different MC populations from lung, uterus, skin, human MC line HMC-1, were shown to express the beta1 integrins (CD29), the alpha chain of VLA-4 (CD49 d) and VLA-5 (CD49e), beta 3 integrins (CD61), and the alpha chain of the vitronectin receptor (VNR) (CD 51). No expression of CD18, CD11a, CD11b, CD11c, the alpha chain of VLA-2 (CD49 b), and VLA-6 (CD49 f) was detected,[290] giving rise to the idea that there is a unique expression pattern of integrins on blood basophils and MCs. MC-expressed integrins are thought to play an important role in their migration, homing, and function in inflamed tissue.[290-293]

Integrins serve as receptors for many extracellular matrix proteins like collagen, laminins, cadherins MMP-1 but also for several viral ligands.[294-298] The role of collagen binding α1β1 and α2β1 integrins in several in vivo mouse models of delayed type hypersensitivity (DTH), contact hypersensitivity (CHS), and arthritis has shown the importance of interaction between extracellular matrix and these integrins in inflammation.[299] Antibodies directed against α1 and α2 chains were found to inhibit inflammatory responses as observed by decreased leukocyte infiltration and edema formation. In a *Listeria monocytogenes*- and zymosan-induced peritonitis mouse model, α2 integrin-deficiency exhibited diminished neutrophil and IL-6 responses. α2β1 Integrins were mainly expressed on peritoneal MCs, where the expression is constitutive. It was further demonstrated in MC deficient mouse models that peritoneal MCs expressing α2β1 are crucial for the neutrophil and IL6 response.[300] In the same disease model, they later showed C1q and the collectin family of proteins as novel adhesive ligands for the α2β1 integrin.[295] Binding of α2β1 integrin with C1q complement protein and collectins that share a common collagen-like sequence

with a Gly-X-Y motif, causes activation of MCs. However, this interaction alone was not sufficient enough to cause cytokine secretion. In another study to examine the role of αE and β7 integrin in immune complex mediated tissue injury, $\alpha E^{-/-}$ and $\beta 7^{-/-}$ integrin lacking mice were subjected to peritoneal and cutaneous reverse-passive Arthus reaction and pointed to an important role of α4β7 integrin in the recruitment of MCs. α4β7 integrin is expressed on MCs, whereas αE integrin is not expressed on MCs and has role in modulating function and number of CD8 + T cell. Mice deficient in β7 showed reduced MCs migration in a peritoneal reverse-passive Arthus reaction.[301]

Integrin receptors are important to MC function in both IgE-dependent and IgE-independent pathophysiological function. In both conditions, integrin-mediated MC and ECM association is needed for the variety of MC functions.[302,303] Integrin αIIb3β3 has been shown to mediate the cell adhesion to fibrinogen and von Willebrand factor (vWF) on mouse and human MCs and this adhesion enhances the MC function in concert with SCF.[303] Oki et al reported enhancement of proliferation, degranulation, cytokine production, and migration of BMMCs through interaction with fibrinogen, when they transduced the αIIb-deficient BMMCs with αIIb integrin. However, the reverse was observed in the cells transduced with either non-functional αIIb or in the cells deficient for the gene.[302] Members of β1 and β3 subfamily of integrins bind to ECM proteins like fibronectin, laminin, and fibrin that contain Arginine-glycine-Aspartic acid (RGD) sequence. Fowlkes et al showed using a competitive inhibitor of RGD-integrin that mechanical stress induces MC degranulation via this interaction.[304]

7.2 | Tetraspanins

Tetraspanins consist of 4 transmembrane domains with an evolutionary conserved structure, connected both intracellularly and extracellularly by loops.[305-307] They function as molecular scaffold by bringing together different molecules of signaling cascades thereby amplifying their activity.[307] Tetraspanins and associated proteins exhibit several cellular functions, for example, modulation of intercellular immune interactions including adhesion, migration, organizing membrane signaling complexes, facilitate intracellular protein transport, and function as chaperons.[306,308] In recent years, different studies supported evidence for their role in tumor malignancy, infectious diseases, fertilization, angiogenesis, etc.[309]. Tetraspanins are present is almost all human cell types. MCs are reported to express tetraspanins CD9, CD37, CD53, CD63, CD81, CD82, and CD151 on their cell surface.[305] The functional and physiological role of these tetraspanins for MCs is only sparsely investigated. Selected tetraspanins are discussed below with respect to their potential function in MC activation.

7.2.1 | CD9

CD9 was first identified as human leukemia associated and lymphohematopoietic progenitor cell surface antigen p24 by Kersey et al in an attempt to identify the unique structures on acute lymphoblastic leukemia (ALL) bone marrow.[310] CD9 may have a role in cytokine-mediated chemotactic responses of human MCs. Antibody blocking of CD9 in HMC-1 MCs inhibits the IL-16-mediated chemotactic and Ca^{2+} mobilization responses. Because HMC-1 MCs lack CD4 as receptor for IL-16, this shows that CD9 can act as an alternate IL16 receptor.[311] Electron microscopy studies showed that CD9 colocalized with FcεRI and non-T-cell activation linker (NTAL) and the crosstalk between CD9 and NTAL in MC activation and chemotaxis was investigated.[312] Antibody-mediated crosslinking of CD9 activates the MCs in a manner different from that known for the MC activators stem cell factor (SCF) and IgE/Ag. Binding of the CD9 antibody to bone marrow-derived cultured MCs (BMMC) caused increased degranulation which was paralleled with increased intracellular calcium and NTAL phosphorylation. Since CD9 is now known to have effects on both chemotaxis and non-IgE-mediated degranulation of MCs, it will be important to look at it as a prospective target in MC-driven diseases.

7.2.2 | CD37

CD37 has been mostly documented on developing B cells, except plasma cells. HMC-1 MCs express CD37,[313] but its function in these cells is yet to be explored. On the other hand, cultured human MCs, whereas positive for tetraspanins CD53, CD63, and CD81, do not express CD37.[313] CD37 mediates apoptotic signals in B cells[314] and regulates β2 integrin-mediated adhesion and migration of neutrophils.[315]

7.2.3 | CD53

The direct function of CD53 on MCs is not known, but some studies in MC-related diseases such as asthma[316] and rheumatoid arthritis,[317] pointed to a potential functional role of this member of the tetraspanin family.

7.2.4 | CD63

Initially, CD63 was recognized as 53 kD highly glycosylated protein and platelet activation marker.[318] Later, it was confirmed as ME491, that has been defined as a stage-specific antigen in melanoma, which is highly expressed in early stages of tumor progression and weakly on advanced stages.[318,319] In MCs and basophils, CD63 is expressed at the cell surface and at the membrane of secretory lysosomes, including serotonin-containing granules that during activation fuse with the plasma membrane. CD63 is extensively used as an activation marker of basophils, because non-activated basophils have virtually no expression of CD63 on the cell surface.[320] Non-activated MCs show significant expression of cell surface CD63, but its expression is strongly enhanced after stimulation.[321] It was further shown that human CD63 on vesicles and on the cell surface are 2 structurally distinct isoforms.[322] Cell surface expressed CD63-like other tetraspanins- is located in the vicinity of FcεRI. Experiments in CD63-deficient mice and BMMC cultured from these mice showed that absence of CD63 results in reduced release of preformed mediators, but had no effect on production of newly synthesized products such as leukotrienes and

IL-6.[323] Anti-CD63 antibodies may be useful as therapeutic agents in MC-dependent diseases because they were shown to block FcεRI-induced degranulation of MCs.[324]

7.2.5 | CD81

The important function of CD81 in context to MC biology emerged when it was shown that an anti-CD81 mAb downregulated the FcεRI-mediated degranulation of MCs.[325] However, its precise function and role in other pathways of MC activation is not known.

7.2.6 | CD151

CD151 is also a poorly understood tetraspanin family member. In a recent work it has been found to negatively regulate the FcεRI-mediated MC degranulation.[326] In CD151-deficient BMMCs, IgE-receptor triggering resulted in enhanced production of IL-4, IL-13, and TNF-α. CD151 deficiency resulted in enhanced and sustained phosphorylation of extracellular signal-regulated kinase1/2 and protein kinase B.[326]

8 | CONCLUSIVE REMARKS

As evidenced in this review, MCs do not only express IgE receptors inducing allergies but have an extraordinary large repertoire of receptors. This allows them to fulfill their physiologic function as sentinels in tissues at the interface with the external environment or after an inflammatory reaction where they often infiltrate tissues in increased numbers.[327-330] It endows MCs to respond to different environmental cues and mount an adequate response under various physiological and inflammatory conditions. Depending on the tissue, this review shows that MC can adapt their repertoire of receptors and signaling response to meet the diverse functional requirements of their host tissue, highlighting their plasticity. Thus, MCs, depending on their location, can express different set of receptors, albeit the study of their expression in various tissues is still at its infancy. It would need an overarching approach involving many laboratories to study their expression in all MC containing tissues both at homeostasis and under inflammatory conditions. Not only do they express different receptors, but they can also adapt their response as a function of the stimulus. Thus, MCs can exhibit a full-blown response leading to mediator release

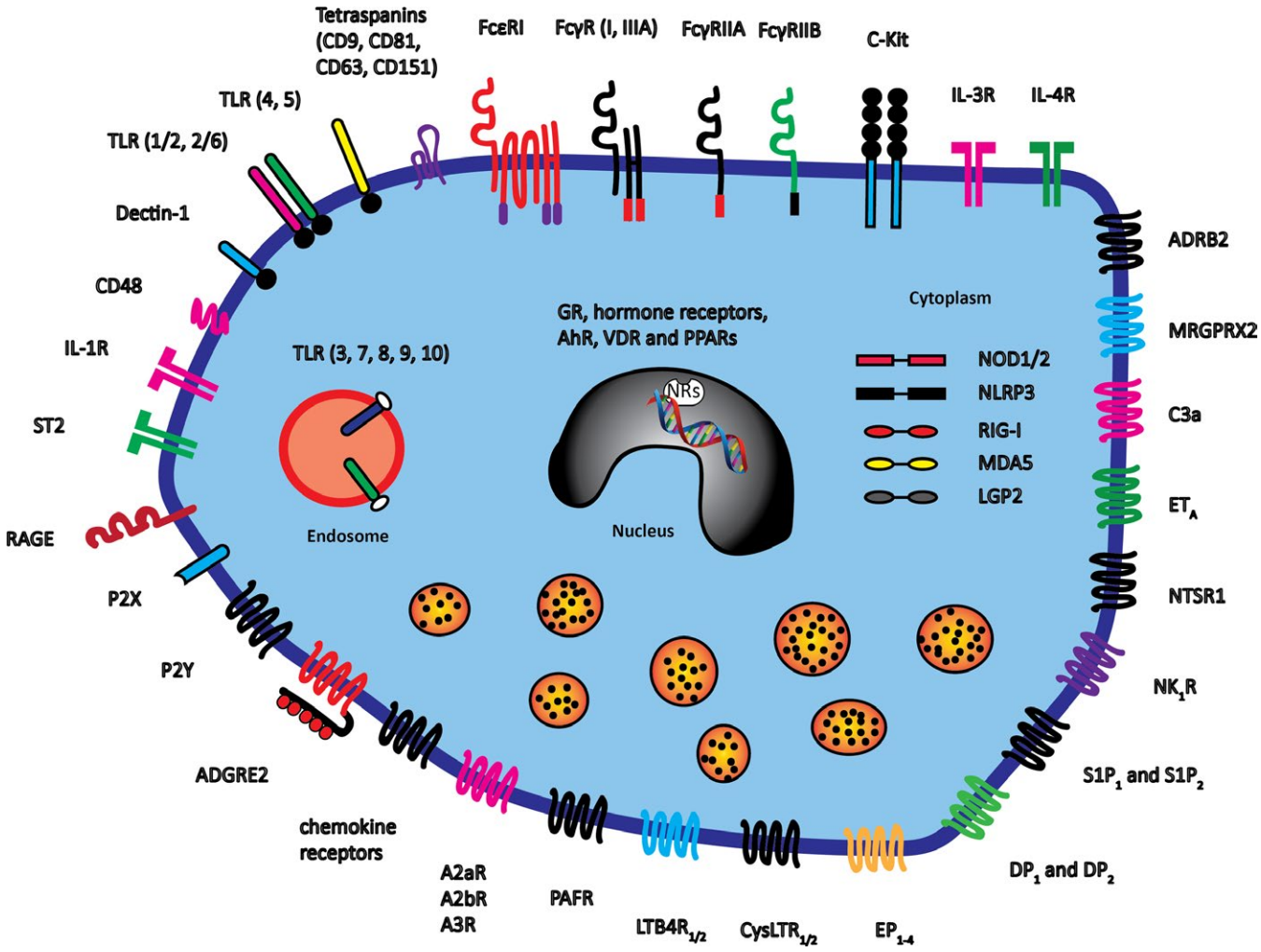

FIGURE 1 Schematic picture of the cellular localization of different receptors expressed by mast cells. Receptors and their ligands involved in non-IgE-mediated activation of mast cells are further discussed in this review

by degranulation as well as a whole panoply of newly synthesized mediators including eicosanoid products and various cytokines and chemokines. Stimulation may also be more subtle inducing only degranulation with little cytokine and chemokine release as often occurring after stimulation through GPCRs or only cytokine and chemokine release as occurring, for example, after stimulation through TLRs. MC responses may also depend on the strength (dose) of the stimulus applied. In addition, analysis of MC responses via these receptors have often revealed a significant cross-talk sometimes enhancing, sometimes inhibiting responses through other receptors. Thus, they have the exquisite capacity to act as exquisite sensors of their microenvironment and adapt the response in a rheostatic manner.[328,331]

Given the large repertoire of receptors expressed by MCs, we were unable to dress a complete list of their expressed receptors. Thus, important receptors such as the KIT receptor, cytokine receptors, or growth factor receptors have not been discussed in this review and readers may therefore refer to other recent reviews. To obtain information on expressed receptors readers may also refer to data obtained in recent transcriptome profiling and deep-sequencing approaches.[332,333] The purpose was rather to provide information of selected families or individual receptors (Table 1 and Figure 1) that have gained recent interest.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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