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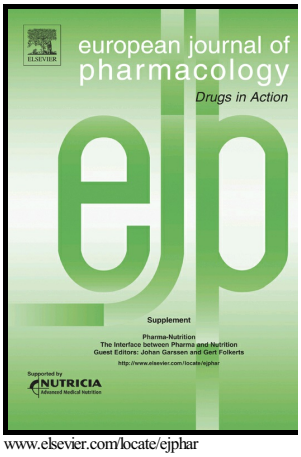

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Non-IgE mediated mast cell activation

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Abstract

Mast cells are crucial effector cells in allergic reactions, where IgE is the best known mechanism to trigger their degranulation and release of a vast array of allergic mediators. However, IgE is not the only component to stimulate these cells to degranulate, while mast cell activation can also result in differential release of mediators. There is a plethora of stimuli, such as IgG, complement components, TLR ligands, neuropeptides, cytokines, chemokines and other inflammatory products, that can directly trigger mast cell degranulation, cause selective release of mediators, and stimulate proliferation, differentiation and/or migration. Moreover, some of these stimuli have a synergic effect on the IgE-mediated mast cell activation. Because of the ability to respond to a large repertoire of stimuli, mast cells may act as a versatile cell in various physiological and pathological conditions. In this review, we discuss current knowledge on non-IgE stimuli for (human) mast cells.

1. Introduction

Mast cells are thought to play a pivotal role in allergy and other inflammatory diseases. While IgE is thought to have a central role in mast cell activation by cross-linking of the high affinity FcεRI (Okayama et al., 2008), also non-IgE mediated mast cell activation may be of importance in the pathophysiology of various inflammatory conditions.

Mast cells are located in close contact with external environment, where they can recognize and be activated by invasive pathogens through complement- and pattern recognition receptor (PRR)-dependent pathways (Marshall, 2004). They are also located close to sensory nerve endings, where they are triggered by a pleotropic variety of neuropeptides, such as substance P, corticotrophin-releasing hormone (CRH) and neurotrophins, suggesting that mast cells are involved in neuro-inflammatory diseases (Kulka et al., 2008). Moreover, mast cells can respond to various inflammatory products, such as IgG, cytokines, chemokines, adenosine, sphingosine-1-phosphate (S1P) and lysophosphatidic acid (LPA), indicating the potential importance of mast cell activation in the initiation and propagation of inflammation in chronic inflammatory diseases. Apart from these endogenous

stimuli, some exogenous molecules can also directly activate mast cells, causing drug side-effects or exacerbating allergic conditions in individuals. In this review, we will discuss various non-IgE stimuli and their targets in mast cell activation with a strong focus on their effects in human mast cells.

2. Immunoglobulins

2.1 Stimulation via IgG

IgG1 bind to its high affinity receptor FcγRI and crosslinking by antigen results in mast cell activation. Immune complexes of IgG1 also bind with high affinity to the FcγRIII, but this receptor is only expressed on rodent and not on human mast cells. It has been reported that FcγRI is up-regulated on human peripheral blood $CD34^+$-derived mast cells (hPDMC) treated by IFN-γ (Woolhiser et al., 2001). Activation of IFN-γ-treated mast cells with IgG1 results in 40% β-hexosaminidase (β-hex) release, but only 3-8% degranulation is observed by cross-linking of IgG2/IgG3/IgG4 (Woolhiser et al., 2001). While β-hex release mediated by FcεRI reaches its peak within a minute, FcγRI aggregation requires more than 15 min to reach its maximum response (Woolhiser et al., 2001). In addition, FcγRI exerts a synergetic effect on FcεRI-mediated mast cell degranulation (Woolhiser et al., 2001). In addition to FcγRI, expression of FcγRII is also found on hPDMC surface, but FcγRII aggregation does not result in mast cell degranulation as evidenced by histamine release (Okayama et al., 2001). The IgG-induced mast cell activation provides a possible link between mast cells and inflammatory diseases such as scleroderma, inflammatory bowel disease (IBD), fibrosis, vasculitis and synovial inflammation, etc. (Woolhiser et al., 2001).

2.2 Stimulation via immunoglobulin free light chains

In addition to the intact immunoglobulins, immunoglobulin free light chains (IgLCs) have been reported to elicit immediate mast cell-dependent hypersensitivity in mice, which can be blocked by the specific antagonist F991 (Redegeld et al., 2002). IgLCs are increased in various inflammatory diseases, such as systemic lupus erythematosus, rheumatoid arthritis, asthma, chronic obstructive pulmonary diseases (COPD), rhinitis, cow's

milk allergy, inflammatory bowel disease (IBD) and cancer, and these increases largely correlate with disease activity (Groot Kormelink et al., 2012; Groot Kormelink et al., 2011; Groot Kormelink et al., 2014; Groot Kormelink et al., 2009; Hampson et al., 2014). Moreover, IgLCs have also been shown to play a crucial role in mast cell activation in mouse models of IBD, asthma, food allergy, and cancer (Groot Kormelink et al., 2014; Kraneveld et al., 2005; Rijnierse et al., 2010; Schouten et al., 2010). However, currently no information of the effects of IgLCs on human mast cells is available in the literature.

3. Complement factors

The anaphylatoxins C3a and C5a, byproducts of complement activation, can cause degranulation and chemotaxis of human mast cells via C3aR and C5aR, respectively (Ali, 2010; Hartmann et al., 1997). In particular, they induce degranulation mainly in MC_{TC} mast cells, such as skin mast cells, but not in lung mast cells since MC_T mast cells are the predominant cell type present in the lung (Ali, 2010). In addition, C3a can exert synergic effects on IgG-mediated degranulation of hPDMC (Woolhiser et al., 2004) and induce chemokine release from LAD2, such as MCP-1/CCL2 and RANTES/CCL5 (Venkatesha et al., 2005). C5a can induce degranulation in human heart mast cells (Genovese et al., 2010) in addition to the skin mast cell. It can also induce plasminogen activator inhibitor-1 (PAI-1) production by human mast cells (skin mast cells and HMC-1), implying a role for C5a in modulating the balance between proteases and protease inhibitors (Wojta et al., 2002).

Complement C1q, known to coat the surfaces of microbes during infection, can induce IL-6 secretion from mouse peritoneal mast cells via $\alpha_2\beta_1$ integrin in listeria monocytogenes- and zymosan-induced mouse peritonitis (Edelson et al., 2006), but no information is present on effects of C1q on human mast cells.

4. Toll-like receptor ligands

Toll-like receptor (TLR) ligands include not only pathogen-associated molecular patterns (PAMPs) of all classes of microbiotas, but also danger-associated molecular patterns (DAMPs) (Goutagny et al., 2012). Generally, TLR-

1/2/4/5/6 are expressed on the cell surface, mainly being involved in bacteria and fungi recognition, whereas TLR-3/7/8/9, specializing in virus recognition, are located in the cytosol (Goutagny et al., 2012). TLRs are widely expressed by mast cells. For instance, TLR1-4 and TLR6-9 have been identified at the mRNA level with TLR2/4/9 at the protein level in murine mast cells. In human mast cells, protein levels of TLR1-9 with the exception of TLR-8 have been identified. However, it should be noted that expression of TLRs in human mast cells is distinct among different locations (e.g. cord-blood, peripheral blood, skin, and lung), some of which can only be detected at the mRNA level (Sandig and Bulfone-Paus, 2012). In general, TLR activation would not lead to mast cell degranulation, but distinct TLR ligands stimulate differential release of mast cell-derived mediators and cytokine production (Marshall, 2004).

4.1 TLR2 and TLR4 ligands

It has been reported that TLR2 and TLR4 ligands can cause differential release of mediators in both murine and human mast cells. While PGN (a TLR2 ligand) causes mouse bone marrow-derived mast cells (BMMCs) to release TNFα, IL-6, IL-4, IL-5 and IL-13, but not IL-1β, LPS (a TLR4 ligand) stimulates BMMCs to produce TNFα, IL-6, IL-13 and IL-1β, but not IL-4 and IL-5 (Supajatura et al., 2002). Furthermore, PGN can cause degranulation in both murine and human mast cells, while LPS does not (Supajatura et al., 2002; Varadaradjalou et al., 2003). However, different from murine mast cells, human cord-blood derived mast cells (hCBMC) require the priming of IL-4 and soluble CD14 to release TNF-α when stimulated by LPS (Varadaradjalou et al., 2003). Furthermore, different TLR2 stimuli have also been shown to induce release of distinct mediators by hCBMC. For instance, both PGN and zymosan can induce generation of cysteinyl leukotrienes (CysLTs), whereas Pam3CSK4 does not (McCurdy et al., 2003). Both TLR2 and TLR4 can interact synergistically with FcεRI to augment activation of murine mast cells, suggesting infection may contribute to allergic diseases via TLR signaling (Qiao et al., 2006). It has been shown that oxidized low-density lipoprotein (ox-LDL), via TLR4, can cause the human mast cell line

HMC-1 to secrete cytokines (TNF-α, MCP-1 and IL-6), showing a novel pathological link between TLR4 and mast cells in atherosclerosis (Meng et al., 2013).

4.2 TLR3, TLR7 and TLR9 ligands

Poly I:C (a TLR3 ligand), R-848 (a TLR7 ligand) or CpG (a TLR9 ligand) can dose-dependently stimulate murine fetal skin-derived mast cells (FSMC) to produce pro-inflammatory cytokines (e.g. TNF-α and IL-6) and chemokines (e.g. RANTES, MIP-1α, and MIP-2) (Matsushima et al., 2004b). In particular, both murine and human mast cells (hPDMC and human mast cell lines) produce type I IFNs following TLR3 activation by double-stranded RNA (Kulka et al., 2004) and produce cytokines and lipid mediators in respond to TLR9 ligands (Sandig and Bulfone-Paus, 2012).

5. Pathogens and their components

Pathogens can activate mast cells in both direct and indirect ways (Marshall, 2004). The direct interaction is primarily mediated by pattern recognition receptors (PRRs), including TLRs (as discussed in 4) by Toll-like receptor ligands, C-type lectins such as Dectin-1, retinoic acid-inducible gene-I-like receptors (RLRs) and the glycosylphosphatidylinositol-anchored protein CD48 (Abraham and St John, 2010; Urb and Sheppard, 2012). For instance, Dectin-1 can induce leukotriene production from hCBMC in response to fungal zymosan (Olynych et al., 2006); RLRs together with TLR3 stimulate LAD2 cells to produce type-I IFNs and chemokines by interacting with vesicular stomatitis virus (VSV) (Tsutsui-Takeuchi et al., 2014); CD48 activates mast cell by recognizing fimbriated Escherichia coli (in mBMMCs), Mycobacterium tuberculosis (in RBL-2H3 and mouse peritoneal mast cells) or Staphylococcus aureus (in hCBMC) (Malaviya et al., 1999; Munoz et al., 2003; Rocha-de-Souza et al., 2008). The indirect mechanism includes Fc-receptor- and complement-receptor-mediated interaction. The binding of Fc-receptors with pathogen-specific antibodies or antibodies interacting with super-antigens (e.g. S. aureus protein A, P. magnus protein L and protein Fv) leads to degranulation and production of newly generated mediators

from human heart mast cells (Genovese et al., 2003; Genovese et al., 2000). Many forms of infection can activate complement pathways where C3a and C5a are generated, resulting in mast cell activation as discussed earlier (Marshall, 2004). In addition, toxins produced by bacteria, such as C. difficile toxin A, cholera toxin and staphylococcal enterotoxin B, have also been reported to directly induce murine mast cell activation (Calderon et al., 1998; Komisar et al., 1992; Leal-Berumen et al., 1996).

6. Antimicrobial peptides

Antimicrobial peptides (AMPs), including human β-defensins (hBD-1/2/3/4) and LL-37, are predominately expressed in epithelial tissues, where they participate in the innate host defense by killing invading microbiota (Niyonsaba et al., 2001). In addition to microbicidal activities, they also participate in inflammatory responses by recruiting and activating mast cells. Data from both murine and human studies showed hBD-2/3/4 and LL-37, but not hBD-1, can stimulate mast cells to mobilize intracellular Ca^{2+}, release histamine, prostaglandins and various cytokines in a G protein-dependent pathway (Chen et al., 2007; Niyonsaba et al., 2001; Niyonsaba et al., 2010; Schiemann et al., 2009). In later studies, some novel AMPs have also been discovered to stimulate human mast cells, such as catestatin, a neuroendocrine peptide which exhibits antimicrobial activity in the skin (Aung et al., 2011) and pleurocidin, which can induce mast cell activation through the N-formyl-peptide receptor 1 (FPRL1) receptor (Pundir et al., 2014).

7. Neuropeptides

7.1 Corticotropin-releasing hormone

Corticotropin-releasing hormone (CRH) is typically secreted from the hypothalamus under stress, but it can also be secreted locally from nerve endings, where it exerts pro-inflammatory effects (Alysandratos et al., 2012). Human mast cells express CRH receptors, through which CRH leads to selective secretion of vascular endothelial growth factor (VEGF) by human mast cells (HMC-1 and hCBMC), which can be blocked by the CRH-R1 antagonist

antalarmin (WCao et al., 2005). In addition, CRH also induces expression of FcεRI on human mast cells (LAD2 and hCBMC) and augments IgE-induced release of VEGF (Asadi and Theoharides, 2012). The CRH-induced mast cell activation may contribute to the worsening of various inflammatory conditions by stress, such as multiple sclerosis, atopic dermatitis, autism spectrum disorders, psoriasis and coronary artery disease (Alevizos et al., 2014; Alysandratos et al., 2012; Asadi and Theoharides, 2012; Esposito et al., 2002; WCao et al., 2005).

7.2 Neurotensin

Neurotensin is another neuropeptide secreted locally under stress. It can trigger degranulation and VEGF release from human mast cells (LAD2 and hCBMC), which can be enhanced by CRH and blocked by a neurotensin-receptor (NTR) antagonist SR48692 (Alysandratos et al., 2012). Interestingly, neurotensin induces expression of CRH receptor-1 on LAD2 cells and vice versa, CRH increases NTR expression on mast cells (Alysandratos et al., 2012). The mutual interaction between neurotensin and CRH in mast cells may contribute to allergy symptoms that worsen with stress, such as autism spectrum disorders (ASD) (Asadi and Theoharides, 2012).

7.3 Neurotrophins

Neurotrophins (NTs), including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5), are known as potent regulators of neuronal survival and function (Tam et al., 1997). They exert biological effects through two types of receptors: p75 and the tropomyosin-related kinase family receptors (Trks). Trks are high affinity receptors for all mature NTs: TrkA for NGF, TrkB for BDNF, TrkC for NT-3, TrkA/TrkB also for NT-3 and NT-4/5 (Peng et al., 2013). Several studies indicate that both murine and human mast cells (HMC-1, hCBMC and human intestinal mast cells) express functional Trks protein, but not p75 (Lorentz et al., 2007; Tam et al., 1997). NGF has been shown to promote *in vitro* growth and differentiation of both murine and human mast cells (hCBMC) (Kanbe et al., 2000; Kawamoto et al., 1995; Welker et al., 2000), and serves as a chemoattractant for rat peritoneal mast cells (Sawada et al.,

2000). In addition, it has also been reported to induce histamine release from human placental mast cells in the presence of phosphatidylserine (Purcell and Atterwill, 1994). NT-3, another NT family member, promotes maturation of both fetal mouse skin mast cells and human intestinal mast cells (Lorentz et al., 2007). However, unlike NGF, NT-3 cannot induce mast cell degranulation (Theoharides et al., 2012). Generally, these studies indicate a main role of NTs in the development and survival of mast cells.

7.4 Substance P

Substance P (SP) is a neuropeptide that belongs to the tachykinin family of peptides and is secreted by nerves and inflammatory cells. It has been reported to stimulate both degranulation and chemokine production of mast cells (Kulka et al., 2008), which might be involved in the pathogenesis of various neuro-inflammatory diseases, such as psoriasis and multiple sclerosis (Theoharides et al., 2012). In addition, SP can enhance the innate immune response to bacterial infections by upregulating TLR2 expression on mast cells (LAD2) (Tancowny et al., 2010). On the other hand, SP can also downregulate FcεRI expression on human mast cells (LAD2 and hPDMC), implying its role in the modulation of IgE-mediated allergic diseases (McCary et al., 2010). It has been established that SP activation of murine mast cells is NK1R mediated (Kulka et al., 2008; van der Kleij et al., 2003). However, it is not clearly known which receptors are responsible for human mast cells, as the NK1R selective antagonist only partially blocks the effects of SP in human mast cells (Kulka et al., 2008). It is suggested that SP may also activate human mast cells via MRGPX2 (Kulka et al., 2008; Tatemoto et al., 2006).

8. Cytokines

8.1 Stem cell factor (SCF)

SCF is a well-known cytokine that plays an essential role in supporting mast cell proliferation, differentiation and survival by interacting with the c-kit receptor (CD117) (Lewis et al., 2013). It has also been widely studied as a potential activator of mast cells. Earlier studies demonstrated that 100ng/ml SCF alone can induce serotonin

release from mouse peritoneal mast cells (Coleman et al., 1993), but fails to stimulate degranulation from human PDMC (Hundley et al., 2004). However, it has been reported in a later study that 30ng/ml SCF alone can drive histamine release from human lung mast cells, and at 100ng/ml is effective in generation of CysLTs and PGD2, which can be blocked by the c-kit inhibitor imatinib (Lewis et al., 2013). SCF can also act in synergy with FcεRI-mediated signaling pathways in human PDMC (Hundley et al., 2004).

8.2 IL-3

It is well-known that IL-3 is a major growth and differentiation factor for murine mast cells (Bischoff, 2007). By contrast, most human mast cells respond poorly to IL-3, and human mast cells isolated from lung, skin, uterus, kidney or tonsils do not express the IL-3 receptor (Bischoff, 2007; Gebhardt et al., 2002). Although IL-3 is widely used as a growth factor for the *in vitro* culture of human mast cells derived from blood precursors, reports on IL-3R (IL3Rα, CD123) expression on these mast cell populations remain conflicting. For instance, while Dahl et al. reported that expression of the IL-3R increased during culture of hCBMC from CD133+ progenitors (Dahl et al., 2004), the group from Jensen detects no CD123 expression on mast cell populations developed from CD34+ and CD133+ peripheral blood and CD133+ cord-blood, respectively (Jensen et al., 2014). However, IL-3 has been shown to regulate growth of human intestinal mast cells (Gebhardt et al., 2002). Furthermore, it can selectively enhance histamine and LTC4 release from IgE-activated human intestinal mast cells (Gebhardt et al., 2002).

8.3 IL-4

IL-4 is a key cytokine of the Th2 type immune response, which serves as an important factor for class switching of B cells to produce IgE in both humans and rodents, and is produced locally in various allergic inflammation (Xia et al., 1997). Priming of mature human mast cells with IL-4 shifts IgE-dependent cytokine production toward increased Th2 cytokines, such as IL-3, IL-5 and IL-13, and decreased IL-6, which can be blocked by the MEK inhibitor PD98059 (Lorentz et al., 2005). It induces maturation of fetal-derived human mast cells and hCBMC by

increasing FcεRI expression and chymase synthesis (Bischoff and Sellge, 2002). In addition, IL-4 can synergize with adenosine or lysophosphatidic acid to augment human CBMC activation (Hua et al., 2011; Lin and Boyce, 2005). Interestingly, IL-4 exerts opposite effects on mast cell growth. For instance, it favors SCF-driven proliferation of mature human mast cells derived from intestine and lung, but reduces the number of mast cells derived from immature progenitors in the presence of SCF (Bischoff and Sellge, 2002).

8.4 IL-9

IL-9 is a pleiotropic cytokine mainly derived from activated T cells and mast cells (Wiener et al., 2004). One of the main functions of IL-9 is to promote mast cell proliferation (Shiohara and Koike, 2005). In addition, combined with antigen-specific IgE or ionomycin, it can increase cytokine production by mouse BMMCs (Wiener et al., 2004). A recent study showed that IL-9 alone can stimulate human LAD2 to secrete VEGF without degranulation or the release of other mediators, which can be inhibited by the STAT-3 inhibitor (Sismanopoulos et al., 2012). As IL-9 and its receptor are significantly elevated locally in patients with atopic asthma and atopic dermatitis, these results suggest a pathological link between IL-9 and mast cells in the development of atopic diseases (Shimbara et al., 2000; Sismanopoulos et al., 2012).

8.5 IL-33

IL-33 belongs to the IL-1 superfamily and acts as an alarmin in both host defense and allergic responses (Saluja et al., 2015). It is expressed primarily by stromal cells, such as epithelial cells, and released upon cell damage (Wang et al., 2014). IL-33 modulates various aspects of mast cell function, including adhesion, survival, maturation and activation, through activation of the cell surface ST2 (IL-1RL1). For instance, (1) adhesion: IL-33, together with IL-1β, enhances the adhesion of human CBMC to fibronectin (Iikura et al., 2007); (2) survival: IL-33 attenuates human skin mast cell apoptosis through the anti-apoptotic molecule B-cell lymphoma-X large (BCLXL), raising the possibility of IL-33/ST2 axis as a potential target to limit mast cells in chronic inflammatory

diseases (Wang et al., 2014); (3) maturation: the addition of IL-33 to *in vitro* cultures accelerates the maturation of $CD34^+$ mast cell precursors into tryptase-containing cells (Allakhverdi et al., 2007); (4) activation: IL-33 exacerbates antigen-induced arthritis activating mast cells in a murine model (Xu et al., 2008); it can also synergize with IgE or IgE-independent agents, such as adenosine, C5a, SCF, NGF, PMA and TSLP, in the activation of HMC-1 (Silver et al., 2010). However, it should be noted that long exposure to IL-33 in *in vitro* cultures can lead to a hypo-responsive phenotype of both human and mouse mast cells (Sibilano et al., 2014).

8.6 Other cytokines

In addition to SCF, IL-3, IL-4 and IL-9, other cytokines such as IL-5, IL-6, and GM-CSF, have also been demonstrated to augment the SCF-dependent proliferation of hCBMC (Bischoff and Sellge, 2002; Ochi et al., 1999). Particularly, IL-6 can markedly reduce apoptosis of human mast cells derived from fetal liver when SCF is withdrawn (Kambe et al., 2001). IL-10 can promote proliferation of human mast cells (hCBMC) in combination with SCF and IL-6 (Ochi et al., 1999).

9. Other inflammatory mediators

9.1 ATP/ADP

High levels of the "danger signal" ATP and other nucleotides are released actively upon stimulation or by passive leakage from injured or dying cells (Bulanova and Bulfone-Paus, 2010). They exert biological effects through activation of P2 purinoceptors which comprise the P2X and P2Y family. While P2X (P2X1-7) are ATP-gated ion channels, P2Y receptors (P2Y1, 2, 4, 6, and 11-14) are G protein-coupled receptors (Kurashima et al., 2012). Mast cells express various P2 receptors that trigger degranulation, mediator release, chemotaxis and apoptosis, which has been thoroughly reviewed by Bulanova at al (Bulanova and Bulfone-Paus, 2010). In particular, a recent study has shown that ATP induces mBMMCs to release PAD2 enzyme and citrullinated proteins through the P2X7 receptor (Arandjelovic et al., 2012). PAD2 and citrullinated proteins, which are increased in the synovial fluid of

patients with rheumatoid arthritis (RA), are closely linked with inflammation in RA synovial tissues (Arandjelovic et al., 2012). In addition, the ATP-P2X7-mediated mBMMC activation is also associated with colitis and Crohn's disease (Kurashima et al., 2012). However, the effects of ATP-P2X7 axis on human mast cells has been less studied and still remains unclear (Bulanova and Bulfone-Paus, 2010).

9.2 Adenosine

Adenosine, a metabolic by-product of ATP, can induce a biphasic effect on IgE-induced mast cell degranulation. The enhancing effect occurs at low (10^{-7}-10^{-5} M) concentrations through A3AR, whereas inhibition occurs at high (10^{-4}-10^{-3}) concentrations by triggering A2aAR (Okayama et al., 2008). Furthermore, the enhancing effect can only be found in human lung mast cells, but not in human skin mast cells, explaining why adenosine induces mast cell-mediated bronchospasm in asthmatics without causing urticaria (Gomez et al., 2011).

9.3 Cysteinyl leukotriene (CysLTs)

CysLTs (LTC4, LTD4 and LTE4) are highly potent peptide-conjugated arachidonic acid-derived mediators and are closely associated with allergic inflammation (Laidlaw and Boyce, 2012). LTD4 has been reported to promote proliferation of hCBMC through transactivation of the c-kit tyrosine kinase (Jiang et al., 2006). In addition, LTC4 and LTD4 can induce cytokine and chemokine production by IL-4-primed hCBMC, which can be completely blocked by a selective CysLT1 antagonist MK571 (Mellor et al., 2002). While LTD4 is more potent for inducing calcium flux in LAD2, LTE4 is more potent for inducing proliferation and chemokine release (Paruchuri et al., 2008). In addition to CysLT1 and CysLT2 receptors, ADP-reactive purinergic ($P2Y_{12}$) receptor is newly found to be required for LTE4-induced chemokine and PGD2 production in LAD2 cells (Paruchuri et al., 2009).

9.4 Endothelin-1

Endothelins (ETs) were initially identified as a potent vasoconstrictive peptides derived from endothelial cells (Matsushima et al., 2004a). They can also be synthetized and bound by many cell types and serve as a mast cell activator (Hultner and Ehrenreich, 2005). There are three different ET peptides ET-1, ET-2 and ET-3, and two ET receptors ET_A and ET_B (Matsushima et al., 2004a). ET-1 can potently induce mouse fetal-skin mast cell degranulation and cytokine release via the ET_A receptor (Hultner and Ehrenreich, 2005). It has also been reported to mediate anti-arrhythmic effects by activating mast cells in a rat model (Walsh et al., 2009).

9.5 Histamine

Histamine generated by mast cells can in turn modulate their functions via H1, H2 and H4 receptors (Thurmond et al., 2008). It has been reported that histamine can induce chemotaxis of murine mast cells both *in vitro* (Hofstra et al., 2003) and *in vivo* (Thurmond et al., 2004), which can be blocked by a selective H4R antagonist JNJ7777120 (Thurmond et al., 2004). In particular, H4R is found to be highly expressed on human mast cells (Jemima et al., 2014). It has been reported that histamine enhances CXCL12 chemotactic activity on human mast cell precursors via H4R (Godot et al., 2007). Both histamine and 4-methylhistamine (selective H4R agonist) can induce degranulation, CysLTs and LTB4 production, various pro-inflammatory cytokines and chemokines release by human mast cells (LAD2, HMC-1 and hCBMC) (Jemima et al., 2014).

9. 6 Lysophosphatidic acid

Lysophosphatidic acid (LPA), a prominent lipid component of serum, has pleiotropic effects on cell development, cardiovascular inflammation and cancer (Lundequist and Boyce, 2011). Human CBMCs express receptors for LPA, including LPA1, LPA2, LPA3, LPA4 (GPR23) and LPA5 (GPR92) at the mRNA level. LPA potently accelerates human CBMC proliferation and differentiation *in vitro*, which involves LPA1 and/or LPA3 receptors, and PPAR-γ (Bagga et al., 2004). This might be one of the mechanisms for mast cell hyperplasia after platelet activation or vascular leakage (Lin and Boyce, 2005). In addition, LPA has also been shown to stimulate IL-4 priming of human

CBMC to produce chemokines, such as MIP-1β, IL-8 and MCP-1 in a LPA2 receptor-dependent manner (Lin and Boyce, 2005). LPA5, the most abundant LPA receptor in human mast cells (LAD2 and hCBMC), is responsible for the majority of LPA-induced MIP-1β generation (Lundequist and Boyce, 2011). LPA is also a major constituent of modified low-density lipoprotein (LDL). It is suggested that locally high concentrations of LPA can mediate mast cell activation in atherosclerotic plaque destabilization (Bot et al., 2013).

9.7 Sphingosine-1-phosphate

Sphingosine-1-phosphate (S1P) is a biologically active metabolite of plasma-membrane sphingolipids, which is essential for immune-cell trafficking (Rivera et al., 2008). It is elevated in many inflammatory diseases, such as asthma and autoimmunity (Rivera et al., 2008). In contrast to its weak effect on degranulation of murine mast cells, S1P potently induces degranulation of human mast cells (LAD2, skin mast cells and hCBMC) (Oskeritzian et al., 2008; Oskeritzian et al., 2010). It also stimulates production of cytokines and chemokines by human mast cells (LAD2, skin mast cells and hCBMC) (Oskeritzian et al., 2008; Oskeritzian et al., 2010). Mast cells express $S1P_1$ and $S1P_2$ receptors (Kuehn and Gilfillan, 2007). The $S1P_1$ receptor modulates mast cell chemotaxis in a pertussis toxin-sensitive manner, and the $S1P_2$ receptor regulates mediator releases in a pertussis toxin-insensitive manner (Kuehn and Gilfillan, 2007; Oskeritzian et al., 2014; Oskeritzian et al., 2010). The effect of $S1P_2$ can be attenuated by its antagonist JTE-013 (Oskeritzian et al., 2010). Interestingly, the concentrations of S1P required for mast cell degranulation are higher than those required for migration and the high concentrations of S1P also inhibits migration (Kuehn and Gilfillan, 2007). Sphingosine kinases-1 and -2 (SphK-1 and -2) are the enzymes that produce S1P from sphingosine. Several studies have shown that SphK1 plays a pivotal role in IgE-induced mast cell degranulation in both murine allergic models and human mast cells (LAD2 and hCBMC) (Oskeritzian et al., 2014; Price et al., 2013). This effect can be attenuated by a specific SphK1 inhibitor, SK1-I (Price et al., 2013).

10. Chemokines

Seven chemokines (CXCL1, CXCL5, CXCL8, CXCL14, CX3CL1, CCL5 and CCL11) have been demonstrated to induce migration of human mast cells from different origins (HMC-1, primary mast cells derived from blood precursors or tissues) (Juremalm and Nilsson, 2005). Interestingly, apart from the effect on migration of chemokines, some chemokines have been reported to selectively induce mediator release from mast cells (Juremalm and Nilsson, 2005). For instance, CXCL12 can specifically induce secretion of de novo synthesized IL-8 from HMC-1, suggesting CXCL12-activated mast cells play a role in recruiting neutrophil *in vivo* (Juremalm and Nilsson, 2005). CCL11 is able to enhance the secretion of IL-13 from hCBMC upon IgE activation (Juremalm and Nilsson, 2005). The effects of chemokines on mast cells have been excellently reviewed by Juremalm et al (Juremalm and Nilsson, 2005). In fact, in addition to chemokines, other inflammatory factors can also induce mast cell migration, such as SCF, S1P, PGE2, leukotrienes, adenosine and complement factors, etc.

11. Exogenous molecules and drugs

Compound 48/80 is a canonical basic secretagogue, which activates mast cells through the G-protein-coupled receptor Mrgprb2/MRGPRX2 (McNeil et al., 2014). Interestingly, a recent study showed that mast cells can also be directly activated by most FDA-approved peptide drugs associated with allergic-type injection-site reactions (ISR) and small molecule-drugs containing a tetrahydroisoquinoline (THIQ) motif or the structural feature of C48/80 via Mrgprb2/MRGPRX2 (McNeil et al., 2014). Mercuric materials are widely found in drugs and used as preservative in vaccines (Kempuraj et al., 2010). It has been reported that mercuric chloride (HgCL2) can stimulate VEGF and IL-6 released by LAD2 and hCBMC, suggesting a potential role of HgCL2-induced mast cell activation in the disruption of blood-brain-barrier and brain inflammation (Kempuraj et al., 2010). In addition, estrogens can induce degranulation and enhance IgE-mediated responses in HMC-1, suggesting that estrogenic environmental pollutants might promote allergic responses in allergic individuals who are exposed to allergens (Narita et al., 2007).

12. Pharmacological intervention

The critical role of mast cells in allergic responses and other inflammatory diseases prompts researchers to look for pharmacotherapy to inhibit specific mast cell activation. The best known mechanism of mast cell activation is through the cross-linking of FCεRI, which subsequently induces the downstream phosphorylation of several Src kinases (e.g. Lyn, Syk, Fyn, and Hck) (Sibilano et al., 2014). Thus, blockage of Syk/Fyn leads to the complete loss of degranulation and cytokines secretion from mast cells (Sibilano et al., 2014). As described above, mast cells can also be activated by diverse non-IgE stimuli. Frequently, for these stimuli their responsible receptors and downstream signaling pathways may be the designated therapeutic targets. For instance, SCF-mediated mast cell migration and activation can be blocked by the c-kit inhibitor imatinib. The IL-33/ST2 axis can serve as a potential target to limit mast cell activation in many chronic inflammatory diseases. It should be noted that some activators such as S1P, adenosine and LPA, have multiple receptors on mast cells, which triggers diverse or opposite responses (Kuehn and Gilfillan, 2007). Thus, it is necessary to study extensively a receptor subtype and its downstream signaling in order to selectively modulate its specific function in mast cells. However, some responsive receptors on mast cells are still not clearly identified, such as receptors for immunoglobulin free light chains (IgLCs), antibacterial peptides (AMPs), LTE4, etc. The pharmacological intervention in mast cell activation will also be further discussed in other reviews of this Special issue.

Table 1: ***Triggers of non-IgE mediated human mast cell activation***

Stimuli	Receptor	Mast cell response	Mast cell population	Inhibitor	Reference
Immunoglobulins					
IgG	FcγRI	degranulation	IFNγ-treated hPDMC		(Okayama et al., 2001; Woolhiser et al., 2001)
IgLCs	?	degranulation	mBMMC	F991	(Redegeld et al., 2002)
Complement factors					
C3a	C3aR	degranulation	human skin MCs; LAD2	receptor specific Ab /PTX	(Ali, 2010)
		chemotaxis	human skin MCs; hCBMC; HMC-1		(Hartmann et al., 1997)
		CCL2, CCL5	LAD2		(Venkatesha et al., 2005)
C5a	C5aR	degranulation	human skin/heart MCs		(Ali, 2010; Genovese et al., 2010)
		chemotaxis	human skin MCs; hCBMC; HMC-1		(Hartmann et al., 1997)
Toll-like receptor ligands					
CpG	TLR9	TNFα, IFNγ, IL-1β; CysLTs	hPDMC		(Sandig and Bulfone-Paus, 2012)
Flagellin	TLR5	TNFα, IL-1β	hPDMC		(Sandig and Bulfone-Paus, 2012)
LPS	TLR4	TNFα, IL-5, IL-10, IL-13	IL-4 primed hCBMC in the presence of CD14		(Varadaradjalou et al., 2003)
		TNFα, CCL1, IL-5	IFNγ-treated human lung MCs / hPDMC		(Okumura et al., 2003)
Ox-LDL	TLR4	TNFα, MCP-1, IL-6; increase TLR4 expression	HMC-1		(Meng et al., 2013)
PGN	TLR2	histamine; TNFα, IL-5, IL-10, IL-13, GM-CSF, IL-1β; CysLTs	hCBMC		(McCurdy et al., 2003; Varadaradjalou et al., 2003)
Poly I:C	TLR3	Type I IFNs	hPDMC, HMC-1, LAD2		(Kulka et al., 2004)
Zymosan	TLR2	GM-CSF, IL-1β; CysLTs	hCBMC		(McCurdy et al., 2003)
Pathogens and their components					
Fungal zymosan	Dectin-1	LTB4, LTC4	hCBMC		(Olynych et al., 2006)
S. aureus	CD48/TLR2	IL-8, TNFα	hCBMC		(Rocha-de-Souza et al., 2008)
S. aureus protein A / P. magnus protein L	Fc-receptor	histamine; LTC_4	human heart MCs		(Genovese et al., 2003;

/protein Fv					Genovese et al., 2000)
Vesicular stomatitis virus	RLRs/TLR3	IFNα, IFN β; CCL5, CXCL10, CXCL11, IL-15	LAD2		(Tsutsui-Takeuchi et al., 2014)
Antimicrobial peptides					
β-defensins/LL-37	G protein–coupled receptor	histamine; PGs; IL-31, IL-2, IL-4, IL-6, GM-CSF, NGF; LTC_4	hPDMC , LAD2	PTX/wortmannin (PI3 kinase inhibitor)/U73122 ()/Ro-31-8220 (PKC inhibitor)	(Niyonsaba et al., 2010)
catestatin		migration; degranulation; LTC_4; PGD2, PGE2; GM-CSF; CCL2, CCL3, CCL4	hPDMC , LAD2		(Aung et al., 2011)
LL-37		degranulation	human lung MCs		(Schiemann et al., 2009)
pleurocidin	FPRL1/ G protein–coupled receptor	migration; degranulation; CysLTs; PGD_2; CCL2, CCL4	hPDMC , LAD2	PTX/FPRL-specific inhibitor	(Pundir et al., 2014)
Neuropeptides					
CRH	CRH-R1	VEGF	hCBMC, HMC-1	CRH-R1 antagonist antalarmin	(WCao et al., 2005)
Neurotensin	NTR	degranulation; VEGF	hCBMC, LAD2	NTR-antagonist SR48692	(Alysandratos et al., 2012)
NGF	TrkA	histamine	human placental MCs in the presence of phosphatidylserine		(Purcell and Atterwill, 1994)
		growth, differentiation	hCBMC		(Kanbe et al., 2000; Welker et al., 2000)
NT-3	TrkA-C	maturation	human intestinal MCs		(Lorentz et al., 2007)
Substance P	MRGPX2/ NK1R	degranulation; MCP-1, RANTES, IL-8	hPDMC , LAD2	PTX/wortmannin/ H89 (PKA inhibitor)/antagonist of NK1R (D-Pro4 D-Trp7.9)	(Kulka et al., 2008; Tatemoto et al., 2006)
Cytokines					
SCF	C-kit	proliferation, differentiation, survival	human MCs	C-kit inhibitor imatinib	(Lewis et al., 2013)
		histamine; CysLTs; PGD2	human lung MCs		
		migration	mBMMC		(Huang et al., 2008)
IL-3	IL-3R*	growth	hCBMC, hPDMC, human intestinal MCs		(Dahl et al., 2004; Gebhardt et al., 2002)
		enhance histamine and LCT4 release	IgE-activated human intestinal MCs		(Gebhardt et al., 2002)
IL-4	IL-4R	increases IgE-induced Th2 cytokine	mature human MCs		(Bischoff and Sellge, 2002;

		production; favors SCF-driven proliferation			Lorentz et al., 2005)
		maturation	fetal-derived human mast cells, hCBMC		(Bischoff and Sellge, 2002)
IL-9	IL-9R	VEGF	LAD2	STAT-3 inhibitor	(Sismanopoulos et al., 2012)
IL-33	ST2	survival, adhesion, cytokine production (IL-13, IL-5, IL-6, IL-10, TNF, GM-CSF), chemokine production (CXCL8, CCL1)	hCBMC, hPDMC		(Allakhverdi et al., 2007; Iikura et al., 2007)
		survival	human skin MCs		(Wang et al., 2014)
Other inflammatory mediators					
ADP/ATP	P2Y receptors	calcium influx	hCBMC	P2Y receptor-selective antagonist/PTX	(Bulanova and Bulfone-Paus, 2010; Feng et al., 2004; Schulman et al., 1999)
		eicosanoid; exocytosis	hCBMC		
		enhances IgE-induced degranulation	human lung MCs		
Adenosine	A3AR	(low dose) enhances IgE-induced degranulation	human lung MCs	PTX	(Okayama et al., 2008)
Endothelin-1	ET_A	degranulation; TNF, IL-6, VEGF	mouse fetal-skin MCs		(Matsushima et al., 2004a)
histamine	H4R	degranulation, leukotrienes, various pro-inflammatory cytokines and chemokines	HMC-1, LAD2, hCBMC	H4R antagonist JNJ7777120/ PTX	(Jemima et al., 2014)
LTD4	CysLT1	proliferation	IL-4 primed hCBMC	CysLT1 receptor-antagonist KMK571/PTX	(Jiang et al., 2006)
LTC4/LTD4	CysLT1	IL-5, TNFα; MIP-1β	IL-4 primed hCBMC	CysLT1 receptor-antagonist KMK571/PTX	(Mellor et al., 2002)
LTE4	CysLT1?/ e PPARγ	proliferation; MIP-1β; PGD2; COX2↑	LAD2	CysLT1 receptor-antagonist KMK571 / e PPARγ antagonist GW9662a	(Paruchuri et al., 2008)
LTE4	$P2Y_{12}$/un-identified receptor?	MIP-1β , PGD2	LAD2		(Paruchuri et al., 2009)
LPA	LPA1/LPA3 /PPAR-γ	proliferation, differentiation	hCBMC	competitive antagonist of LPA1 and LPA3 (VPC-32179)/PTX/ e PPARγ antagonist	(Bagga et al., 2004)

				GW9662a	
	LPA2	MIP-β, IL-8, MCP-1	IL-4 priming hCBMC		(Lin and Boyce, 2005)
	LPA5	MIP-β	LAD2		(Lundequist and Boyce, 2011)
S1P	$S1P_1$	chemotaxis	hCBMC, human skin MCs	$S1P_1$ selective antagonist W146/PTX	(Oskeritzian et al., 2010)
	$S1P_2$	degranulation; TNFα, IL-6; CCL2;	LAD2, hCBMC, human skin MCs	$S1P_2$ selective antagonist JTE-013/PTX	(Oskeritzian et al., 2008; Oskeritzian et al., 2010)
Chemokines and other chemoattractant					
Chemokines (CXCL1, CXCL5, CXCL8, CXCL14, CX3CL1, CCL5 and CCL11)	Chemokine receptors	migration	human MCs		(Juremalm and Nilsson, 2005)
CXCL12	CXCR4	IL-8	HMC-1		
CCL11 (Eotaxin)	CCR3	IL-13	IgE-activated hCBMC		
Serotonin (5-HT)	$5\text{-}HT_{1A}$	adherence to fibronectin; migration	hPDMC		(Kushnir-Sukhov et al., 2006)
Urokinase	Urokinase receptor	migration	human lung, uterus, tonsil and skin MCs; HMC-1		(Sillaber et al., 1997)
Exogenous molecules and drugs					
Compound 48/80, drugs with ISR (e.g. icatibant, cetrirelix, and leuprolide, etc.)	MRGPRX2	degranulation	LAD2	PTX	(McNeil et al., 2014)
Estrogen	ER	degranulation	HMC-1		(Narita et al., 2007)
HgCL2		VEGF, IL-6	LAD2, hCBMC		(Kempuraj et al., 2010)

*data of IL-3R (CD123) expression on human mast cells derived from blood precusors is conflicting. ? non-identified receptors.
MCs, mast cells; hPDMC, human peripheral blood-derived mast cells; hCBMC, human cord-blood derived mast cells; mBMMCs, mouse bone-marrow derived mast cells; IgLC, immunoglobulin free light chains; PGN, peptidoglycan; LPS, Lipopolysaccharides; Ox-LDL, oxidized-low density lipoprotein; CysLTs, cysteinyl leukotrienes; CRH, corticotropin releasing hormone; NGF, nerve growth factor; SCF, stem cell factor; FPRL1, N-formyl-peptide receptor 1; RLR, acid-inducible gene-I-like receptors; TLR, toll-like receptor; Trks, tropomyosin-related kinase family receptors; GM-CSF, Granulocyte-macrophage colony-stimulating factor; IFN, Interferon; TNF, tumor necrosis factor; MCP-1/CCL2, Human monocyte chemoattractant protein-1; PGs, prosglandings; VEGF, Vascular endothelial growth factor; MIP-1β/CCL4, macrophage inflammatory protein-1 β; RANTEs/CCL5, regulated on activation, normal T cell expressed and secreted; PTX, Pertussis toxin.

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