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Regulation of mast cell responses in health and disease

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I. INTRODUCTION

Mast cells are primitive immune cells that appear early in evolution and have since evolved into multifunctional cells in vertebrates.¹ They have been long recognized as initiators of IgE-dependent allergic diseases but it is now realized that they also play a fundamental role in innate and adaptive immune responses to infection as well as inflammatory autoimmune diseases.^{2–4} In addition, there is evidence that mast cells participate in inflammatory responses to incipient tumors which may either facilitate or retard tumor growth depending on the type of cancer.^{5–7} Other suspected non-immunological roles for mast cells include promotion of angiogenesis, tissue remodeling, and wound healing.^{8–11} As such, mast cells occupy a precarious position in that their responses to endogenous and exogenous stimuli can be detrimental as well as beneficial to the host.

The scope of the physiologic and pathologic roles noted above illustrate the flexible nature of mast cells which is enabled in part by their ability to release a broad array of bioactive mediators, either preformed and stored in granules such as histamine and proteases, or newly generated such as eicosanoids, cytokines, and chemokines.^{12–14} Mast cells also exhibit phenotypic plasticity which is manifested by differential expression of receptors and granule constituents. The localization of mast cells in tissues as well as their replication and differentiation into distinct phenotypes are typically determined by the chemical environment of their final tissue destination.^{1, 13, 15} KIT ligand (stem cell factor or SCF) is critical for these processes although other growth and chemotactic factors are necessary. Flexibility in function is also conferred through expression of multiple types of receptors.¹⁴ These include Fc, cytokine, tyrosine kinase, and trimeric G protein-coupled receptors.^{12, 16} In addition, mast cells can respond to microbial products through pattern recognition receptors (PRR) which include the Toll-like receptors (TLRs) and the recently recognized nucleotide-binding oligomerization domain (NOD)-like receptor (NLRs).¹⁷ These two families of receptors recognize pathogen-associated molecular patterns (PAMPs) of microbial origin and include both cytosolic and surface-expressed receptors. Many of these receptors can act in concert with the IgE receptor, FcεRI, to substantially enhance mast cell

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responses to antigens or alter the pattern of response such that production of cytokines, for example, predominates over degranulation.^{18, 19} Moreover, mast cells can be negatively regulated through immunoreceptor tyrosine-based inhibitory motif (ITIM)-bearing receptors such as Fc γ RIIb, gp49B1, signal regulatory protein- α (SIRP α), the transforming growth factor- β (TGF β) receptor, along with the non-ITIM-bearing receptor such as CD200.^{20, 21}

All of the above features likely underlie the multifunctional nature of mast cells but little specific information is available as to how mast cells adapt in different immunological/pathological settings even though it is now evident that the relative composition and amount of mediators released from activated mast cells, and the degree to which they home to sites of inflammation, can be profoundly influenced by the extent to which surface receptors interact to engage alternative and complementary intracellular signaling pathways. Therefore, mast cell activation in health and diseases states should be considered in the context of co-stimulatory and inhibitory factors present in the surrounding tissue milieu and not just in terms of specific allergen-mediated processes. In the following sections we review studies that demonstrate potentiation or suppression of Fc ϵ RI-induced responses by activating or inhibitory receptors and the regulation of expression of these receptors by endogenous factors. Although most of these studies were conducted with mast cells in culture, they begin to provide insights as to how mast cell function might be modulated *in situ*. Our intent is to foster further interest in the interplay among mast cell receptors to create a sufficient body of evidence to provide mechanistic explanations for each of the immunological and non-immunological functions attributed to mast cells. Because of the impact on clinical practice, we also discuss receptor-independent mechanisms of mast cell activation by mast cell “secretagogues”, a category that includes opiates and other drugs in addition to antidotes to the biological effects of mast cell products. Finally, we assess the pathophysiological roles of mast cells and their products in health and disease.

II. MEDIATORS RELEASED AND GENERATED BY MAST CELLS

A. Preformed Mediators in Granules

The acute reactions that occur as a result of mast cell activation are initiated as a consequence of degranulation and the generation of lipid-derived mediators, whereas more chronic mast cell-mediated symptomology is an outcome of the delayed generation of chemokines, cytokines and growth factors which follow enhanced gene expression.^{22, 23} The process of degranulation occurs within seconds of mast cell activation and the initial rapid phase is essentially complete within 5–10 minutes.²⁴ Although mast cell proteases such as tryptase, chymase and carboxypeptidase, constitute the major components of mast cell granules,^{25–27} histamine is the predominant granule mediator of acute reactions to mast cell activation.

Histamine is localized primarily, but not exclusively, in mast cells and basophils although its link to anaphylactic and inflammatory reactions was suspected long before its recognition as a major constituent of mast cells (reviewed in¹²). Histamine is sequestered in mast cell granules by proteoglycans such as heparin and chondroitin E. On release, it readily diffuses through tissues and the circulatory system but does not penetrate the CNS. It is rapidly inactivated by histamine N-methyl transferase and diamine oxidase. Histamine acts through at least four G protein-coupled histamine (H1 through H4) receptors (reviewed in^{28, 29}). H1 receptors reside primarily on bronchial smooth muscle, endothelial cells, and certain neurons, and are largely responsible for bronchoconstriction, increased vascular permeability leading to hives and allergic rhinitis through separation of endothelial cells, itching, and pain. H2 receptors are located on vascular smooth muscle and gastric parietal cells and thus mediate vascular dilatation and gastric secretion. Collectively, the H1 and H2 receptors contribute to the wheal and flare reaction in skin. H3 receptors are present

primarily in the CNS whereas H4 receptors are expressed on immunocompetent cells including basophils, mast cells,³⁰ and eosinophils³¹ and mediate chemotaxis. In total, the primary effects of histamine release from mast cells and basophils are increased vascular permeability, vasodilatation and bronchial constriction, which are readily reversed by antihistamines. The sedative side effect of classical antihistamines (H1 blockers) is now attributed to reversal of the normal CNS function of histamine in provoking wakefulness and was obviated by the introduction of antihistamines that do not penetrate the CNS. Antagonists of H3 and H4 receptors are under preclinical and clinical investigation as potential therapeutic agents for various CNS disorders but also for the treatment of allergic rhinitis, asthma, pruritis in atopic dermatitis, and inflammatory pain.³¹

Rodent mast cells also contain significant quantities of 5-hydroxytryptamine (5HT, serotonin) within the granules, which can induce inflammatory skin reactions in mice³² and bronchoconstriction in rats.³³ It appears to be a minor component in human mast cells.³⁴ Whether the amounts present are sufficient to impact mast cell function in humans is unclear, but there are reports of effective therapy with the anti-serotonergic agent, cyproheptadine, in patients with some forms of urticaria,³⁵ bullous lesions³⁶ and irritable bowel syndrome, the latter being attributed to immunologically-induced release of serotonin from mast cells.³⁷

Mast cell proteases constitute between 30–50% of the total protein content of mast cells; thus in terms of mass, they represent the major group of mediator released by exocytosis.^{25, 26} Although β -tryptase is the major protease expressed in mast cells, several other proteases and their respective homologs are also present in human and rodent mast cells.²⁶ However, their expression in mast cells is heterogeneous depending largely on the phenotype and distribution of mast cells within the tissues. In the human for example, mast cells present in the mucosal tissues contain primarily tryptase, whereas those present in the skin and submucosa additionally contain chymase and carboxypeptidase.³⁸ Within the granules, the proteases are complexed to proteoglycans which are thought to stabilize the proteases and to regulate their function.²⁶ Although mast cell proteases, released from activated mast cells, have been implicated in allergic inflammation and tissue remodeling,²⁶ recent evidence suggests that they may also have a protective role for example against parasitic infection^{39, 40} and snake and insect venoms⁴¹, and indeed proteases may also help protect against allergic inflammation.

B. Eicosanoids and Reactive Oxygen Species

The bioactive eicosanoids, leukotriene C₄ (LTC₄), LTB₄, prostaglandin D₂ (PGD₂) and, under specific circumstances, PGE₂, are generated and released almost simultaneously with the granule-associated mediators. The initiating process in the generations of these molecules is receptor-mediated activation of phospholipase (PL) A₂, with consequential hydrolyses of arachidonyl-containing phospholipids, primarily phosphatidylcholine, yielding free arachidonic acid.⁴² This is subsequently metabolized through the actions of 5-lipoxygenase and cyclo-oxygenase to respectively generate LTs and PGs. These eicosanoids individually or together can profoundly affect processes associated with the allergic response for example, bronchoconstriction, increased vascular permeability, cellular infiltration and immune suppression.⁴³ Reactive oxygen species, generated as byproducts of eicosanoid generation, have been implicated in mast-cell dependent inflammatory reactions.⁴⁴

C. Cytokines and Chemokines

Mast cells generate a wide variety of both cytokines for example: IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, IL-33, GM-CSF and TNF α ; and chemokines including CCL2, CCL3, CCL5

and CXCL8.^{22, 23, 45–48} However, in contrast to degranulation and eicosanoid release, this is a delayed process taking several hours before significant levels of cytokines and/or chemokines are detected to be secreted from activated mast cells. Although it has been proposed that mast cells may store specific cytokines, for example TNF α , in their granules, at least in the human, this appears to be minimal compared to the levels generated *de novo* following mast cell activation.⁴⁶ As will be discussed elsewhere in this review, under specific circumstances, for example, as part of an innate immune reaction, both cytokines and chemokines can be generated and released in the absence of degranulation. This suggests that cytokines and granule components have evolved to play different roles in the body's defense mechanisms against, parasites, toxins and other harmful bioactive agents and organisms. Nevertheless, along with granule components, secreted cytokines manifest pathophysiology associated with allergic inflammation^{22, 23, 49–51} and may also contribute to angiogenesis and cellular hyperplasia associated with tumorigenesis.¹⁰

D. Thymic Stromal Lymphopoietin (TSLP)

TSLP is now recognized as an important mediator in inflammatory responses to allergens, pathogens and trauma by directing the immune system towards Th₂ responses.^{52, 53} Myeloid dendritic cells are thought to be a key target for TSLP although the possibility exists that mast cells play a similar role. The major sources of TSLP are epithelial cells at barrier surfaces, keratinocytes, dendritic, and stromal cells while its receptor (TSLPR) is expressed on a variety of immune cells including human mast cells,⁵⁴ eosinophils, macrophages, dendritic cells, B cells, and T cells.⁵³ However, functional binding of TSLP to TSLPR requires cooperation of IL-7R α , and in some respects TSLP shares functional similarities with IL-7 although both cytokines target different cells in human and mouse.⁵² Nevertheless, TSLP is produced in significant quantities in lungs of patients with asthma,⁵⁵ human primary small airway epithelial cells in response to TLR ligands, and skin explants from patients with atopic dermatitis.⁵⁴ TSLP from all these sources potentially stimulate human mast cells to produce inflammatory cytokines without inducing degranulation or eicosanoid production.⁵⁴ Conversely, IL-4-primed human mast cells in culture produce and store TSLP on stimulation via Fc ϵ RI. Moreover, bronchial mast cells in atopic asthmatic patients accumulate TSLP and appear to be a significant source of TSLP in bronchial tissue in asthmatics.⁵⁶ TSLP, so produced, is released spontaneously and following Fc ϵ RI aggregation but is rapidly degraded, in part by mast cell proteases, presumably limiting its actions to nearby cells.

Other evidence for a critical role for TSLP in atopic asthma is that the accumulation of TSLP in bronchial mast cells correlates with airway hypersensitivity in asthmatics⁵⁶ and that TSLPR-deficient mice do not develop allergic airway disease.^{55, 57} An interconnecting link between TSLP and mast cells is the fact that, like dendritic cells,⁵⁸ mast cells can both respond and produce TSLP and serve as an additional source of TSLP under pathogenic conditions.

E. Angiogenic and Other Diverse Mediators

In keeping with their functional versatility, activated mast cells are also a source of angiogenic peptides such as angiopoietin-1, FGF, VEGF (see also **Section VI D**), and renin⁵⁹ which, by promoting localized angiotensin formation in cardiac, lung, and kidney, can induce ischemia/reperfusion arrhythmia,⁶⁰ bronchoconstriction,⁶¹ and renal disease.⁶² In addition, reactive oxygen and reactive nitrogen oxide species have been implicated in mast cell-related inflammatory conditions.⁴⁴ Angiopoietin-1, FGF, and VEGF are all expressed in mast cells as is renin which in cardiac tissue is expressed exclusively in mast cells. In addition to renin, angiotensin-II is produced as a result of release of mast cell

chymase and this mechanism may be more important than the renin-angiotensin system in the generation of angiotensin following mast cell activation.⁶³

III. MAST CELL ACTIVATING LIGANDS, RECEPTORS, AND SIGNALING

A. The High Affinity Receptor for IgE, FcεRI

The role of the high affinity IgE receptor in mast cell activation, and the mechanisms by which this receptor regulates mast cell biology, has been extensively reviewed over the past few years. For this reason, we present a summary of these topics to provide a point of reference for later discussions. Readers are referred to the following selected reviews for more detailed information.^{16, 64–67}

The FcεRI, which belongs to the immunoreceptor superfamily, comprises a single chain IgE-binding α subunit, a signal transducing/amplifying tetramembrane-spanning β subunit, and a signal-transducing γ chain homodimer subunit,⁶⁴ which is also responsible for relaying transmembrane signaling for the FcγRI and FcγRIII IgG receptors.⁶⁸ The FcεRI allows mast cells to be activated in an antigen-specific manner following Th2 cytokine-driven production of antigen-specific IgE by B lymphocytes and subsequent binding of the IgE to the FcεRI. Cell activation is initiated upon binding of antigen to its specific recognition sites on the IgE resulting in receptor aggregation and thence downstream signaling.⁶⁴ These signaling events are sufficient to ensure the generation and/or release of all three major classes of mast cell mediators¹⁶ and mast cell chemotaxis (Figure 1).⁶⁹ However, FcεRI may also influence mast cell biology independently of a direct response to antigen.^{70, 71} In this regard, monomeric (non-aggregated) IgE has been described to promote mast cell survival,^{72, 73} induce mast cell migration⁷⁴ as well as the generation of the cytokines.^{73, 75} Unlike aggregated IgE, monomeric IgE failed to activate the necessary signaling pathways required to induce degranulation and cysteinyl leukotriene production in cultured human mast cells⁷⁵ although modest degranulation and LTC₄ production has been noted in freshly isolated human lung mast cells.⁷⁶

The ability of antigen to induce the release of all major categories of inflammatory mediators from mast cells and to promote mast cell chemotaxis, requires the coordinated activation of sequential, parallel, and interacting signaling pathways that generate the divergent processes required for these multiple responses (Figure 2). The more receptor-proximal signaling events generally share common signaling elements whereas the more distal events show significant divergence. It is the divergence in these signaling pathways that may allow chemotaxis or release one category of mediators in the absence of others. Although the pathways regulating mast cell activation are complex they can be condensed into the following major signaling nodes or axes: 1. FcεRI β and γ chain phosphorylation leading to Syk recruitment/activation; 2. the LAT/ PLCγ₁-calcium/protein kinase C (PKC) axis; 3. the phosphoinositide 3-Kinase (PI3K)-axis; 4. MAP kinase pathways and transcriptional regulation. These axes are discussed in subsequent sections below. Overall, such signaling can be additionally thought of in terms of a primary activation signaling pathway, which can either be upregulated by a secondary amplification/maintenance pathway, or downregulated by inhibitory signaling pathways.¹⁶ This concept could facilitate the understanding of how co-receptors that modify mast cell function can differentially exert their influence on FcεRI-mediated responses.

1. FcεRI β and γ Chain Phosphorylation Leading to Syk Recruitment and Activation—The progression of the signaling events following FcεRI aggregation requires initial phosphorylation of specific tyrosine residues in the immunoreceptor tyrosine-based activation motifs (ITAMs) contained within the β and γ chains of the FcεRI which respectively leads to recruitment of the Src family kinases Lyn^{77–79} and Fyn⁸⁰ to the β chain

and the ZAP 70 family member Syk to the γ chain dimer.^{81, 82} Although Lyn has been suggested to be the tyrosine kinase responsible for this initial phosphorylation, there remains compelling reasons to suspect that other kinases may additionally or alternatively regulate this obligatory response. Namely, in human mast cells and, depending on the genetic background, mouse mast cells Lyn appears to be dispensable and even inhibitory for subsequent mast cell activation.^{83, 84} One explanation could be that Src kinase family members have overlapping functions in mast cell activation. Certainly, in addition to Lyn, other family members including Fyn,⁸⁰ Fgr,^{85, 86} and Hck⁸⁷ have been implicated in mast cell activation albeit by the regulation of different processes. Nevertheless, the recruitment of Syk to the phosphorylated γ chains and its subsequent activation is accepted to be an obligatory step for mast cell activation.

2. The LAT/ PLC γ ₁-Calcium/ PKC Axis—Recruitment of regulators and components of the subsequent signaling nodes, as defined above, into the receptor-signaling molecule signaling complex is coordinated via a series of constitutive and inducible protein-protein and lipid-protein interactions through a framework of transmembrane (e.g. CBP/PAG, LAT and LAT2) and cytosolic (e.g. SLP 76, Grb2, Gads, Gab2, Vav, Shc) adaptor proteins.^{88, 89} It is thought that such interactions occur within discrete localized regions enriched in glycolipids, termed lipid rafts.^{90–93} Consequently, early signaling events associated with the Fc ϵ RI may be controlled as much by distribution and redistribution of the specific signaling elements within the membrane micro-domains as by posttranslational modification.

The preferential engagement of specific adaptor molecules by individual surface receptors and their capacity to selectively recruit particular signaling elements may underlie the ability of different receptors to independently regulate the release of the individual classes of mediators. The transmembrane adaptor molecule LAT is a major substrate for Syk and a central coordinator of downstream events required for mast cell activation following Fc ϵ RI aggregation. LAT contains multiple tyrosines within the cytosolic tail that, once phosphorylated by Syk and potentially other kinases, recruits PLC γ ₁ and the cytosolic adaptor molecules SLP76 and indirectly Gads, which stabilize this complex. The importance of these interactions is illustrated by the markedly attenuated capacity of antigen to elicit a calcium response, degranulation, and the generation of cytokines in mast cells derived from the bone marrow (BMMCs) of *lat*^{−/−},^{94–96} *slp76*^{−/−},^{97, 98} and *gads*^{−/−} mice.

PLC γ exists as two isoforms, PLC γ ₁ and PLC γ ₂, both of which are expressed and activated upon Fc ϵ RI aggregation in mast cells.^{100–102} However, at least in human mast cells, PLC γ ₁ may be the predominant form.¹⁰³ PLC γ activation leads to the hydrolysis of the membrane-associated phospholipid, phosphoinositide 4, 5 bisphosphate (PIP₂) thus liberating inositol trisphosphate (IP₃) and diacylglycerol (DAG).¹⁰⁴ These products respectively liberate calcium from the endoplasmic reticulum, and activate specific PKC isoforms, critical signals for mast cell activation.^{105, 106} The IP₃-dependent release of calcium from the intracellular stores results in depletion of these stores which is detected by the calcium sensor STIM1 which is critically located in the ER membrane.^{107–109} The subsequent conformational change in STIM1 and its interaction with the calcium transporter ORAI1^{110–112} on the cell membrane allows calcium influx from extracellular stores. Such influx in mast cells may also, in part, be regulated by members of the TRPC family of calcium channels.^{113, 114} The exact contribution of this family of proteins to the calcium signal, however, is still a matter of debate. The calcium signal is essential for a variety of downstream signaling process regulating not only degranulation, but also for generation of other mediators and chemotaxis.^{115, 116} For example, calcium is required for the activation of the calcium-dependent forms of PKC, a family of serine/threonine kinases critical for the generation of all classes of mediators.^{117–121} Calcium is also necessary for the activation of PLA₂ required for the generation of arachidonic acid leading to eicosanoid generation and for activation of

the calcium-regulated transcription factor NFAT which contributes to cytokine generation.¹¹⁵

3. The PI3K/BTK Axis—Although the activation of PLC γ is primarily regulated via the aforementioned process, the maintenance and amplification of this signal is regulated by the PI3K/Btk axis.^{16, 24, 122} PI3K is recruited to the signaling complex following the Fyn-dependent binding of PI3K to Gab2.¹²³ It then promotes membrane localization of specific signaling molecules through the generation of phosphatidylinositol 3, 4, 5 trisphosphate which binds to pleckstrin homology (PH)-domains contained within these signaling molecules.¹²⁴ In this manner, the Tec kinase, Btk is recruited to the cell membrane where it is activated; a response which further increases PLC γ_1 activity and its capacity to reinforce the calcium signal.^{24, 69, 124, 125} Although the initial phase of the calcium signal mediated by PLC γ_1 is unaltered by inhibition of PI3K, the maintenance of this signal is significantly reduced following inhibition of PI3K either by the expression of an inactive form of the enzyme¹²² or through the use of PI3K inhibitors¹⁰³ and in *btk*^{-/-} BMMCs.^{24, 69, 126, 127} The maintenance /amplification of the PLC γ_1 signal following Fc ϵ RI aggregation may be coordinated additionally by the LAT-related transmembrane adaptor molecule LAT2 (NTAL, LAB)^{128, 129} although LAT2 may also regulate an inhibitory pathway for Fc ϵ RI-mediated mast cell degranulation, at least in mouse BMMCs.^{95, 96} Certainly LAT2 knock down in human mast cells¹³⁰ and the RBL 2H3 rat mast cell line¹²⁸ attenuates Fc ϵ RI-mediated degranulation through reduction of the calcium signal. Our studies suggested that LAT2 may be contributing to the PLC γ_1 -mediated calcium signal by indirectly binding PLC γ_1 .¹²⁹ Subsequent studies suggested that this interaction may be occurring through SLP76.¹³¹ As further discussed later, this maintenance/amplification pathway for antigen-mediated responses in mast cells may be the portal by which signaling pathways initiated by other mast cell receptors allow synergistic potentiation of Fc ϵ RI-mediated degranulation and cytokine production.

The experiments utilizing mouse mast cells expressing catalytically inactive PI3K δ and those using PI3K inhibitors further revealed that PI3K regulates not only mast cell degranulation but also generation of reactive oxygen species (ROS), eicosanoid and cytokine production, cell growth and survival, cell adhesion and chemotaxis.^{122, 124, 126} Central to the ability of PI3K to regulate such diverse processes is its pivotal role in the regulation of multiple signal transduction pathways. Although several of the responses mediated by PI3K, for example degranulation and the generation of ROS and eicosanoids, may to a certain extent be explained by downstream activation of Btk^{24, 126} other PI3K-regulated pathways certainly contribute to mast cell homeostasis and function. For example, the ability of PI3K to regulate cell growth, survival, and transcriptional regulation may be partly explained by its regulation of the activities of the mammalian target of rapamycin complex (mTORC) 1 and 2^{132, 133} and GSK3 β ¹³⁴ through the activation of AKT. Other pathways controlling transcriptional regulation in a PI3K-dependent manner undoubtedly also contribute to cytokine and chemokine generation. In this respect, the antigen-dependent activation of the transcription factors NFAT and NF κ B are both dependent on the PI3K/Btk axis as demonstrated in the *btk*^{-/-} BMMCs. Similarly, the ability of co-activating receptors to enhance transcription activity leading to synergistically enhanced antigen-mediated cytokine generation, requires engagement of the PI3K/Btk axis.²⁴ For more in depth discussions on the role(s) of PI3K in mast cell function readers are referred to a recent review article on this topic.¹²⁴

4. MAP Kinase Pathways and Transcriptional Regulation—Receptor-mediated generation of cytokines, chemokines, growth factors and other proteins in mast cells requires activation of the mitogen-activated protein (MAP) kinase pathways and enhanced transcription through the activation of specific transcription factors that interact with the

promoter regions of the encoding genes. All three major MAP kinase pathways (ERK, JNK, and p38 MAP kinase) are activated via the Ras-Raf pathway in antigen-stimulated cells as discussed in detail in a previous review.⁶⁶ The transcription factors activated include fos and c-jun which are components of the dimeric API complex,^{19, 125, 135} NFAT,^{18, 19, 136–141} NFκB,^{19, 142, 143} ATF2,¹³⁵ and ELK1.¹³⁷ Both the Ras-Raf-MAP kinase pathway and the PI3K-regulated signaling network contribute to the activation of these factors. These signaling cascades are critical to the generation of, for example, cytokines and chemokines.¹⁶ In addition, both PKC and calcium, as regulated by the LAT/ PLCγ₁-calcium/ PKC axis, can contribute to transcriptional regulation, independently of MAP kinases and PI3K.¹⁶ It is clear however, that the signaling processes leading to transcriptional regulation can function in isolation from those required for degranulation.^{18, 19} For example, as discussed below, certain mast cell stimulants induce cytokine generation in the absence of a detectable degranulation response. Furthermore, the signal transduction events induced by these stimuli can interact with those initiated through FcεRI to markedly enhance cytokine production without enhancing degranulation.^{18, 19}

B. FcγRI and FcγRIII

In addition to the high affinity for IgE receptor, FcεRI, multiple other receptors for IgG are expressed on mast cells.^{45, 46} Such expression, however, may be dependent on the cytokine content of the surrounding milieu. Under the appropriate condition, mast cells express the FcγRI, FcγRIb and FcγRIII IgG receptors.^{45, 46, 68, 144} Both the FcγRI and FcγRIII consist of IgG-binding α subunits and the γ chain homodimer which is identical to the FcεRI γ subunits. The FcγRIα subunit binds IgG with high affinity ($K_A \sim 10^{-8} - 10^{-9}$ M) whereas the FcγRIIIα subunit binds IgG with relatively low affinity ($K_A \sim 10^{-7}$ M).⁶⁸ By virtue of the ITAM motifs contained within the γ chain cytosolic tails, FcγRI and FcγRIII have the capacity to activate mast cells in a similar manner to that elicited by the FcεRI.

Although multiple FcγRI transcripts have been recorded, only one full length protein (FcγRIα1) is expressed that binds IgG and that can elicit signaling.⁴⁵ Under resting conditions, the FcγRI is not expressed on rodent or human mast cells. However, in CD34⁺ peripheral blood-derived human mast cells, exposure to IFN-γ results in upregulation of FcγRI mRNA and the receptor is observed on the cell surface.^{45, 46, 144} Constitutive FcγRI expression is observed, however, in the LAD2 human mast cell line.¹⁴⁵ Furthermore, FcγRI is present in mast cells in psoriatic skin where IFN-γ levels are elevated,¹⁴⁶ implying that mast cell FcγRI expression is associated with specific disease states. The FcγRI thus expressed on human mast cells has been shown to be functional in that FcγRI aggregation resulted in degranulation and cytokine production in a similar manner to that observed following FcεRI aggregation.⁴⁶ The notable difference being the markedly higher production of TNFα observed following FcγRI aggregation compared to the relative lack of TNFα produced upon FcεRI aggregation.⁴⁶ The reason for this disparity is not entirely clear but may be due to differential requirements of FcεRI, and FcγR for PI3K in their activation,¹⁴⁷ and/or the influence of the β chain which is part of the FcεRI but not the FcγRI.

As would be expected with the FcεRI and FcγRI sharing common γ subunits, there appears to be little additive or synergistic enhancement of mast cell activation when both receptors are simultaneously, but independently, aggregated. Nevertheless signals produced upon FcγRI aggregation synergistically interact with those induced by the C3a GPCR to enhance mast cell degranulation.¹⁴⁸

The FcγRIII, although expressed in mouse BMMC following SCF treatment, does not appear to be expressed to the cell surface in human mast cells.⁴⁵ In the mouse however, as

with the Fc γ RI, it can induce degranulation, and generation of eicosanoids following aggregation.^{149–152} Furthermore, Fc γ RIII can induce mast cell adhesion to fibronectin.¹⁵³

In contrast to the Fc γ RI and Fc γ RIII, the Fc γ RII β receptor is a single chain receptor which is not associated with the common signaling γ chain homodimer. Therefore the Fc γ RII β does not possess the capacity to induce mast cell activation. However, due to the Immunoreceptor tyrosine-based inhibitory motif (ITIM) contained within the cytosolic tail, the Fc γ RIIb, when co-ligated with the Fc ϵ RI, it results in the down-regulation of antigen-induced degranulation.¹⁵⁴ The inhibitory properties of Fc γ RIIb is a consequence of recruitment of the Src homology 2 domain-containing inositol phosphatase (SHIP) following phosphorylation of the tyrosine residue in the Fc γ RIIb ITIM upon ligation and reversal of PI3K-mediated signaling.¹⁵⁴ This inhibitory function of the Fc γ RIIb, and other ITIM-containing inhibitory receptors expressed on mast cells, has led to the consideration of approaches to down-regulate mast cell activation through the engagement of these receptors. Studies demonstrating that a fusion protein, which coligates the Fc γ RI and Fc γ RIIb, produces inhibition of antigen-mediated human mast cell and basophil activation, provides proof of principle for this approach.¹⁵⁵

C. KIT

KIT is a member of the growth factor receptors with inherent tyrosine kinase activity family. It is a single chain receptor with 5 extracellular immunoglobulin-like domains and a split tyrosine kinase catalytic domain in the cytosolic tail. Also contained within the cytosolic tail are a number of tyrosine residues which are auto/transphosphorylation sites^{156–158} or may additionally be target substrates for Src family member tyrosine kinases.¹⁵⁹ KIT activation is essential for mast cell growth, differentiation and survival^{156, 157} and which can furthermore induce mast cell migration/homing through chemotaxis.¹⁵⁸ KIT catalytic activity and downstream signaling is initiated upon dimerization induced by binding of its specific ligand, stem cell factor (SCF).^{160, 161} Thus, mast cell numbers, homeostasis and function in resident tissues are to a large extent dictated by localized concentrations of SCF.¹⁶² SCF is presented in two major forms, a soluble form and a membrane-bound form, and is primarily expressed by fibroblasts but is also generated by mast cells and other tissues.^{163–166} There is some evidence that soluble and membrane bound forms of SCF may differentially influence KIT-mediated signaling in mast cells.^{157, 167} Whether this has functional consequences in a physiological setting however is unclear.

In addition to its effects on mast cell homeostasis and chemotaxis, under experimental conditions, SCF can substantially modulate mast cell degranulation and cytokine production.^{168–172} Nevertheless, the consensus of studies suggests that the signals generated by activated KIT alone are insufficient to induce degranulation but they can induce cytokine production in the absence of other stimulants (Figure 1).^{130, 172} The synergistic enhancement of antigen-mediated degranulation and cytokine production is seen in both mouse and human mast cells, and at least in the human mast cells, can be observed with concentrations of antigen which produce minimal degranulation in the absence of SCF.¹³⁰ Such synergy is not limited to antigen-dependent mediator release, however, as SCF has been shown to synergize with adenosine A_{2b} receptor agonists to synergistically enhance IL-8 production in the HMC-1 human mast cell line¹⁷³ and LPS (Toll-like receptor (TLR4) agonist) to synergistically enhance PGD₂ and cytokine production in BMMCs.¹⁷⁴ Furthermore, mast cell degranulation can be promoted by SCF in the presence of monomeric IgE, neither of which induces degranulation on their own.⁷⁶ Additionally, we have demonstrated that SCF and antigen, synergistically interact to markedly enhance mast cell chemotaxis.⁶⁹

The signaling pathways elicited by KIT share many common features with those induced by the FcεRI even though KIT lacks the ability to activate critical signals required for the ability to induce mast cell degranulation (Figure 2).¹⁷² Although KIT activates Src kinases, PLCγ₁, PI3K and the MAPK cascade,^{24, 130, 172} it does not appear to be able to recruit and activate Syk, phosphorylate LAT¹³⁰ or activate PKC¹⁷² at least to the same extent as that produced by the FcεRI. In addition, the calcium signal is much reduced and delayed compared to that observed upon FcεRI aggregation.^{130, 172} These absent or weak signals would account for the inability of KIT to induce a degranulation response. However, when these signals are supplied by aggregation of FcεRI, KIT then has the capacity to enhance degranulation and cytokine production through reinforcement or potentiation of FcεRI signals.

In mouse BMMCs²⁴ and especially in human mast cells,¹⁷² simultaneous addition of SCF and antigen induces a marked potentiation and prolongation of the calcium signal produced by antigen. This could be directly explained by a similar enhancement and extended duration of Btk and PLCγ₁ activations under these conditions.²⁴ Although a similar enhancement in PI3K activity was not observed,²⁴ both PI3K and Btk were determined to be essential for the synergistic enhancement of antigen-mediated degranulation and cytokine production by SCF as demonstrated by use of BMMCs expressing a catalytically inactive p110δ subunit of PI3K, PI3K inhibitors,¹²² and *btk*^{-/-} BMMCs.²⁴ Similar approaches have revealed that the PI3K/Btk/PLCγ₁ axis also regulates the enhanced cytoskeletal reorganization responsible for the synergistic enhancement of chemotaxis in response to antigen and SCF.⁶⁹ Whether this axis can sufficiently explain the enhanced cytokine release is less clear. However, synergy is observed in the activation of the transcription factors NFAT and NFκB which could account for the enhanced cytokine expression is markedly reduced in *btk*^{-/-} BMMCs²⁴. In addition, the calcium-dependent activation of PKC-β appears to be necessary for the synergistic production of IL-6 in response to SCF and antigen in BMMCs.¹⁷⁵

The amplification by SCF of the calcium signal and degranulation in antigen-stimulated human mast cells appears to require coordination through LAT2. Accordingly, siRNA-targeting of LAT2 inhibits such amplification.¹³⁰ We observed that KIT as well as Lyn and Syk, when activated via FcεRI, can phosphorylate LAT2 but at entirely different residues. Although the residue(s) phosphorylated by Syk were shown to be responsible for the indirect binding of PLCγ₁,¹²⁹ it remains to be determined how the residues phosphorylated by KIT enhance the recruitment of PLCγ₁ and the PI3K/Btk/PLCγ₁-mediated calcium signal.

Whether the amplification noted with SCF occurs *in vivo*, especially in disease states, is an obvious question and one that has yet to be addressed. Given the role of SCF in homeostatic regulation of mast cells, it is to be expected that mast cells *in vivo* would be in constant contact with either the soluble or membrane-associated SCF. However, this chronic exposure has not always been considered in studies examining interactions between SCF and other mast cell stimulants. The studies described above have largely employed short term (30 minutes in the case of degranulation) exposure of SCF in cultures which have been starved for 4–16 h to down-regulate constitutive KIT activation. It is thus highly likely that the manifestations of chronic SCF exposure on mast cell activation would be markedly different from those observed and described to date. Nevertheless there are conflicting data as what may be the outcome for such exposure in an *in vivo* setting. The myeloproliferative disorder, systemic mastocytosis, is associated with an activating (D816V) mutation in KIT, and an increase incidence of anaphylaxis has been reported in individuals experiencing this disorder.¹⁷⁶ This would argue that KIT may indeed potentiate FcεRI-mediated mast cell degranulation *in vivo*. In contrast, it has been reported that repeated subcutaneous injections of SCF in mice reduces the incidence of fatal antigen-induced anaphylaxis which would

argue the contrary.¹⁷⁷ Further studies are therefore required to determine the precise influence that SCF plays on antigen-mediated mast cell responses both in health and disease states.

D. IL-1/TLR/ST2 Family of Receptors and Pathogen Recognition Receptors

1. Toll-Like Receptors (TLRs)—The discovery that the mammalian homologs of *Drosophila* TLRs are pathogen-recognizing receptors and that they are expressed on mast cells indicated that mast cells could directly participate in host defense. The primary response to TLR ligands is the production of inflammatory cytokines rather than degranulation (Figure 3A). The initial reports from 2001 to 2003 focused on TLR2 and TLR4^{178–183} but, since then, other functional TLRs have also been discovered on mast cells (reviewed in¹⁸⁴). Each of these receptors recognizes a distinct category of microbial products such as peptidoglycans (PGN) by TLR2, dsRNA by TLR3, lipopolysaccharides (LPS) by TLR4, and bacterial DNA and CpG-containing DNA by TLR9. Some TLRs rely on co-receptors that have no signaling capabilities by themselves. Examples include the interaction of TLR4 with CD14 which is essential for binding of lipopolysaccharide to a TLR4/CD14 complex and TLR2 with dectin-1 which acts as a co-receptor for the detection of fungal zymosan.¹⁸⁵

Expression of TLRs may vary among different subsets of mast cells and culture conditions.¹⁸⁴ For example, mast cells derived from human cord blood lack TLR4 under certain culture conditions but then express functional TLR4 on exposure to IFN- γ or IL-4.^{182, 183} The inducibility of TLRs and other pathogen-recognition receptors in mast cells is a topic, however, in need of a more systematic investigation.

TLRs belong to a superfamily of receptors consisting of two subgroups; one, the TLRs; and the other, receptors for IL-1, IL-18, and an orphan receptor ST2 which is now known to selectively recognize IL-33 (see next section). Both subgroups contain a common intracellular Toll/interleukin-1 receptor (TIR) domain but they differ in their extracellular ligand-binding domains; the TLRs possessing leucine-rich helical domains that recognize pathogen molecular motifs and the cytokine-receptor subgroup having Ig-like domains. Many of the TLRs, when bound by the appropriate ligands, interact with the adaptor protein, myeloid differentiation factor 88 (My88) and IL-1 receptor-associated kinases (IRAKs). Formation of this complex leads to recruitment of TNF receptor-associated factor 6 (TRAF6) and, in turn, TGF β -activated kinase1 (TAK1). TAK1 activates the nuclear factor κ B (NF κ B), JNK, and p38 mitogen-activated protein (MAP) kinase pathways (Figure 3B). The latter pathways are also activated via Fc ϵ RI but by different mechanisms. As discussed in the following section, TLR ligands, especially TLR2 and TLR4 ligands, interact synergistically with antigen to substantially enhance cytokine production with minimal effect on degranulation (Figure 3A).

2. ST2, the Receptor for IL-33—IL-33 is known to mediate Th2 immune responses and to activate mast cells.^{186–190} IL-33 accumulates in the affected tissues of patients with Crohn's disease, rheumatoid arthritis, atopic dermatitis, psoriasis, and anaphylactic reactions and is thought to play a role in these diseases which are associated with heightened mast cell activity.^{191–196} In animal models, IL-33 is reported to exacerbate autoantibody-induced arthritis with enhanced autoantibody-mediated mast cell degranulation in synovial tissues¹⁹⁷ and to be essential for the late phase inflammatory reaction during passive cutaneous anaphylaxis.¹⁹⁸

The IL-33 receptor, ST2 is expressed on mast cells and is a member of the Toll/interleukin-1 receptor (TIR) family of receptors¹⁹⁹ but acts in conjunction with the IL-1 receptor accessory protein (IL-1AcP).^{200–202} ST2, in common with IL-1/IL-18 receptors and TLRs,

contains a TIR domain which enables recruitment of MyD88 to the ST2/IL-1AcP receptor complex and, in turn, IRAK1, IRAK4, and subsequently TRAF6.^{203, 204} As with TLR2 and TLR4 ligands, the engagement of TRAF6 leads to the activation of TAK1, the MAP kinases and key transcription factors including NF- κ B through dissociation of the inhibitor of the NF- κ B complex (IKK) from this complex (Figure 3B).^{19, 186, 188} IL-33-mediated signaling¹⁸⁹ and cytokine production¹⁹ are MyD88-dependent as demonstrated in MyD88-deficient mouse BMMCs. Although some details of ST2-mediated signaling have not been unequivocally established in mast cells, they appear to share the same general features as those for other TIR family members including TLRs^{205–207} with key roles for the NF- κ B, p38 MAP kinase, and JNK pathways (Figure 3B).

IL-33 is reported to stimulate cytokine production, but not degranulation or eicosanoid production in mast cells^{187–190} and basophils,^{208–211} and it enhances Fc ϵ RI and G protein-coupled receptor mediated cytokine production in mast cells and basophils.^{188, 212} However, there are discrepancies in the literature in regard to IL-33 and degranulation. Our finding that IL-33 is unable to stimulate degranulation¹⁹ is consistent with the findings of other workers^{187–190} with the exception of Melendez and coworkers who reported that IL-33 induces an increase in $[Ca^{2+}]_i$ and degranulation in mast cells.¹⁹² We find, however, that RBL-2H3 cells, BMMC, and cultured human mast cells exhibit no such responses to IL-33 under the exact conditions described by these workers.¹⁹

IL-33¹⁹, like TLR2 and TLR4 ligands¹⁸, in combination with Ag can markedly enhance production of the inflammatory cytokines in mast cells even at low subthreshold concentrations. Synergy in signaling was apparent at the level of TAK1 and gene transcription. The synergistic pulse appears to propagate from TAK1 through the JNK/c-Jun and p38 MAP kinase/ATF-2 pathways as depicted in Figure 3B. IL-33 and the TLR ligands by themselves are unable to initiate signals that are essential for mobilizing Ca^{2+} and activation of NFAT. However, the activation of NFAT by Ag or thapsigargin provides a strong signal for enhancing cytokine production through co-operative interactions of NFAT with other transcription factors such as AP-1.¹⁹ The resulting amplification of cytokine production could lead to increased severity of mast cell-related diseases.

3. Nucleotide-binding Oligomerizing Domain (NOD)-like Receptors—The NOD-like receptors (NLRs) are of primary importance in responding to bacterial infections such as *Helicobacter pylori* and *Listeria monocytogenes* and are associated with Crohn's disease, asthma, and other inflammatory diseases (reviewed in²¹³). They are expressed largely in epithelial cells and antigen presenting cells (APCs) but have recently reported to exist in mast cells.²¹⁴ In contrast to TLRs, NLRs are cytosolic receptors but, like TLRs, they contain leucine-rich repeat domains that recognize microbial molecular motifs probably in the form of breakdown products rather than native microbial components because of the cytosolic location of NLRs. NLRs can be segregated into several subfamilies on the basis of their signaling domains which engage different signaling molecules to produce signaling patterns that differ from those produced through activation of TLRs.

The major categories of NLRs, namely the NOD, NALP, IPAF, and NAIP proteins, were identified as pathogen pattern recognition receptors (PPRs) when it was apparent that TLRs would not account for protection against all microbes. NOD1 and NOD2 recognize different subunits of PGN and their activation results in activation of NF κ B and JNK with production of inflammatory cytokines²¹⁵ As the downstream signaling pathways recruited by TLRs and NLRs and the spectrum of microbial products sensed by these two types of receptors differ, it was inferred that they acted independently of one another. Nevertheless, recent studies in dendritic cells and mast cells suggest that these two types of receptors can interact in a positive or negative manner.

In the case of human cord blood-derived mast cells, these cells express message for NOD2 and NALP3 both of which recognize the muramyl dipeptide fragment of PGN and its synthetic analog, murabutide.²¹⁴ Neither compound stimulated production of any of a wide range of cytokines tested whereas the TLR2 agonists, intact PGN from *Staphylococcus aureus* and the synthetic Pam3Cysteiny lipopeptide, stimulated production of IL-1 β , IL-6, IL-10, and CXCL8. However, muramyl dipeptide and murabutide potentiated the production of IL-6 by Pam3Cysteiny lipopeptide without affecting production of any of the other cytokines that are produced in response to the lipopeptide (Figure 3A). The selective potentiation of IL-6 production was attributed to a unique requirement for the cAMP response element-binding protein (CREB) in addition to NF κ B²¹⁶, both of which appear to be activated via TLR2.²¹⁴ Although IL-6 production by the TLR agonists, alone or in combination with TLR agonists, was suppressed in a dose dependent manner by an adenylyl cyclase inhibitor, the signaling interactions that lead to the potentiation were not defined. Neither TLR nor NLR ligands stimulated degranulation, although TLR ligands stimulated LTC₄ production which was unaffected by co-stimulation with NLR agonists. This one study adds to the expanding list of mast cell regulatory receptors and provides yet another example how mast cell responses can be selectively regulated by a wide range of endogenous and microbial factors.

E. G Protein-coupled Receptors

1. Adenosine Receptors—Adenosine receptors (AR) are of four subtypes (A₁, A_{2A}, A_{2B}, and A₃) that couple to different G proteins. A₁R and A₃R act through G_i or G_o and, to a lesser extent, G_q to inhibit adenylate cyclase but additionally can activate PLC and downstream signals. In contrast, A_{2A}R and A_{2B}R couple to G_s thus activating adenylate cyclase although A_{2B}R, but they can also engage G_q to activate the PLC pathway. However, signaling properties may be modified by formation of AR homo- or hetero-dimers. Selective agonists and antagonists have been developed for all four subtypes which are either in clinical use or undergoing preclinical or clinical evaluation (reviewed in^{217–219}). In addition to this array of ligands, evaluation of the biological roles of adenosine, and thus suitability of ARs as therapeutic targets, is further aided by the development of single and double knockout mouse models for all AR subtypes as well as adenosine deaminase, an enzyme responsible for rapid inactivation of adenosine.²²⁰ Virtually all cells, including mast cells, express one or more AR subtypes and they are generally cytoprotective in tissues under stress, although adenosine has manifold effects on vascular, muscular, and immune systems depending on the AR subtype involved.²¹⁸ Intracellular adenosine levels increase as a result of metabolic stress or can be generated extracellularly as a result of the action of a plasma membrane 5'-nucleotidase on AMP in addition to export of intracellular adenosine through a bi-directional nucleoside transporter. Increases typically occur in tissues during ischemia, tissue injury, and inflammation associated with allergic and autoimmune disorders.²²⁰ In these conditions, adenosine is poised between being either anti- or pro-inflammatory.

The role of adenosine in allergic/autoimmune diseases, especially asthma and rheumatoid arthritis, has been of long-standing interest because of elevated production of adenosine in afflicted tissues and increased levels in related fluids such as bronchoalveolar lavage fluid in asthmatics (see reviews^{221–223}). Adenosine is believed to exacerbate the underlying disease as, for example in inflammatory lung disease. Indications of this, among many, are that diagnostic administration of AMP, as the source of adenosine, induces bronchoconstriction in asthmatics, but not normal subjects, and that genetically-induced adenosine-deficiency in mice elicits an inflammatory phenotype reminiscent of asthma, with elevated IgE, extensive mast cell degranulation, eosinophilia, and impaired airway dynamics (reviewed in²²⁴). Of relevance to this review, adenosine markedly influences antigen-induced mediator release from human and rodent mast cells *in vitro* and *in vivo*.

Human and rodent mast cells express A_{2A}, A_{2B} and A₃ receptors. The presumption is that selective stimulation of each type of receptor will elicit responses in accordance with the G protein to which the subtype can couple. Therefore, actions of adenosine itself may vary with concentration because of the different affinities of these receptors for adenosine. Early reports indicated that adenosine potentiates mediator release from human lung mast cells²²⁵ and mast cells in bronchoalveolar lavage fluid from allergen-challenged asthmatic patients.²²⁶ However, inhibitory and potentiatory effects of adenosine on IgE-dependent degranulation were also noted in mechanically-dispersed human lung mast cells.²²⁷ Subsequent studies revealed either synergistic or inhibitory effects of adenosine or its analogs on mediator release in cultured or mechanically dispersed human mast cells and the HMC-1 mast cell line. The heterogeneity of mast cells from different sources and previous lack of specific AR ligands were impediments to defining the exact roles of individual ARs. Nevertheless, the preponderance of evidence pointed to adenosine acting through high affinity A_{2A} receptors at physiologically low concentrations thus activating adenylate cyclase and dampening mast cell activation. At high, perhaps pathological, concentrations, adenosine was thought to activate the low affinity A_{2B}R which can couple PLC pathway via G_q (for more detailed discussion see²²¹).

Interpretation of studies in rodent systems has been equally vexing. Overall, studies indicate that adenosine can initiate or enhance mediator release from rodent primary and tumor mast cell lines (Figure 1).^{228–230} In one report, potentiation was attributed to A_{2B}R rather than A_{2A}R while other reports seemed to indicate that the A₃R is a prominent locus of adenosine action on mast cells.^{228, 231, 232} A preeminent role for the A₃R on mouse lung mast cells *in vitro* and *in vivo* was directly verified by use of selective AR ligands and A₃R-deficient mice.²³⁰ Collectively, these studies point to the A₃R as the predominant receptor although A_{2B}R may also contribute to the activation of rodent mast cells. It should be noted, however, that human lung mast cells do not appear to express significant amounts of A₃R whereas human eosinophils do so and may be a key site of action of adenosine in asthmatic subjects.²³³ In contrast, in the mouse, A₃Rs are expressed on lung mast cells and eosinophils and both cell types may be equally important in the contribution to pathogenesis of the asthmatic phenotype in mice.²³⁴ Studies such as these illustrate the pitfall in extrapolating results from one species to another or even from cell culture where the pattern of expression of AR subtypes are altered by exposure to the Th2 cytokines, IL-4 and IL-13,²³⁵ or glucocorticoids.^{229, 236, 237}

AR agonists by themselves are generally weak stimulants of mast cell degranulation but they can substantially upregulate expression of cytokines primarily IL-1 β , IL-3, IL-4, IL-8, and IL-13 in HMC-1 cells (Figure 1), which appeared to promote IgE production when co-cultured with B cells in an A_{2B}-dependent manner.²³⁸ Adenosine and related agonists elicit little, if any, degranulation of RBL-2H3 cells and mouse BMMCs which correlates with the relatively weak and transient calcium signal after such stimulation.^{228, 239} The most pronounced effect of adenosine is to enhance mast cell activation in conjunction with other stimulants including antigen, ionophore, and phorbol ester.^{229, 240}

2. Prostaglandin E₂ Receptors—Prostaglandin E₂ (PGE₂) is an eicosanoid, generated by multiple cell types including fibroblasts, macrophages, dendritic cells, epithelial cells and mast cells located in inflamed tissues.^{241–243} Thus, PGE₂ has the capacity to modulate the responses of mast cells in such tissues. Multiple GPCRs for PGE₂ are described and at least two of these receptor subtypes, the EP2 receptor and the EP3 receptor, are expressed in mast cells.^{244–246} The EP2 receptor is coupled to G_s which is linked to adenylate cyclase and which provides the capacity to down regulate antigen-mediated mast cell degranulation and cytokine production.^{245, 247} In contrast, the EP3 receptor, which in mast cells enhances mast cell-mediated responses (Figure 1) is linked to G_i, G_q and G_s. Nevertheless, responses

elicited by the EP3 receptor in mast cells are predominantly elicited by G_i as indicated by their reversal by the ADP-ribosylating agent pertussis toxin.²⁴⁸ Depending on the species and circumstance, both EP2 and EP3 can modulate mast cell responses. Therefore, the influence of PGE_2 on antigen-mediated responses in mast cells represents a balance between inhibitory signals produced by the EP2 receptor and activation signals produced by the EP3 receptor. The ability of PGE_2 to modulate mast cell activation is remarkably similar to that observed with SCF, in that, at least in mouse mast cells, PGE_2 alone fails to induce degranulation but markedly enhances antigen-mediated degranulation,^{244, 246, 248–250} cytokine production,^{244, 246, 248, 249} and chemotaxis.¹³³ However the ways in which the signals are integrated to produce these synergistic responses are distinctly different. This is likely a consequence of the different modes by which PGE_2 and KIT initiate their respective signaling cascades: G_i -GPCR vs tyrosine kinase activation. There is some disagreement, however, about how G_i -linked receptors may enhance antigen-mediated degranulation and cytokine production. By investigating the ability of adenosine to enhance antigen-mediated responses in PI3K γ knockout mice and mast cells derived from the bone marrow of these mice, the conclusion was made that GPGR-enhanced antigen-mediated degranulation required PI3K activation.²³⁹ However, in our subsequent studies,²⁴⁸ we determined that although PI3K certainly contributed to the Fc ϵ RI-mediated component of the response to co-stimulation of cells with antigen and PGE_2 , it was not the primary contributor to the synergistic interaction between these two stimulants. Instead, the synergy between the signaling processes, and hence degranulation, was determined to be a consequence of cross synergy between PLC γ_1 activated downstream of the Fc ϵ RI and PLC β activated downstream of the EP3 receptor resulting in a marked enhancement of the calcium signals (Figure 2).

Mast cells migrate into sites of inflammation and, based on the documented presence of PGE_2 and other mediators at these sites, we recently investigated whether GPCR agonists and SCF synergistically acted with antigen to induce enhanced mast cell chemotaxis.²⁵¹ In sensitized BMMCs, antigen, adenosine, PGE_2 and SCF, when added alone, all induced mast cell chemotaxis although the antigen response was noticeably lower than those produced by the other agents. Nevertheless, the chemotactic response was markedly augmented when antigen was added in combination with PGE_2 , adenosine or SCF. This synergy was found to be mediated by a PI3K-Btk dependent pathway leading to enhanced Rac-mediated F-actin rearrangement (Figure 4). This mechanism, at least for the PGE_2 , differed from that required for the synergistic enhancement of degranulation which was both PI3K and Btk independent.

In contrast to the synergistic responses elicited by PGE_2 and antigen in mouse mast cells, the synergistic effects in human mast cells are not apparent in all subjects. In this respect, the ability of PGE_2 to enhance antigen-mediated degranulation and cytokine production was observed to be highly donor dependent with synergy being observed in mast cells generated from the peripheral blood of only 50% of the donors examined.²⁴⁶ This was not attributable to differential expression of the inhibitory EP2 receptor, which is known to down-regulate antigen-mediated responses in human mast cells, or to differential expression of the EP3 receptor. Nor was the ability of the EP2 receptor to generate cAMP or the EP3 receptor to activate critical signaling processes impaired in the respective PGE_2 -responding and non-responding cells. However, in the nonresponding cells, PGE_2 lacked the ability to enhance the antigen-mediated membrane translocation of PLC γ_1 and subsequent calcium response for reasons that are still unclear. Human mast cells also differ from rodent mast cells in other respects. We have yet to observe chemotaxis of cultured human mast cells in response to PGE_2 or indeed adenosine and antigen, either added alone or concurrently. Whether such differences occur *in vivo* has not been determined.

3. Sphingosine 1-Phosphate Receptors—Sphingosine 1-phosphate (S1P) is a potent lipid-derived mediator formed by the phosphorylation of sphingosine as a result of activation of sphingosine kinases (SphK) 1 and 2.²⁵² SphK1 and 2 are both activated in mast cells^{253, 254} by a Fyn-regulated pathway upon FcεRI aggregation.²⁵⁴ However, the respective roles of the individual SPKs in mast cell function is still a matter of debate.²⁵⁵ Nevertheless, It is probable that S1P is generated and released from mast cells as a consequence of FcεRI-dependent SPK activation.^{253, 256} Although S1P may function as an intracellular signaling molecule in mast cells,^{257, 258} S1P also appears to regulate mast cell activation through binding to cell surface GPCRs.^{253, 256}

Five GP-coupled S1P receptors are described (S1P₁₋₅), however mast cells only appear to express two of these receptors S1P₁ and S1P₂.^{256, 259} S1P₁ and S1P₂ receptors have quite diverse roles in mast cell function. Studies from gene-deletion and/or knock out approaches in mouse BMMCs, RBL 2H3 cells and human mast cells have suggested that whereas the S1P₁ receptor induces mast cell chemotaxis,²⁵³ the S1P₂ receptor induces mast cell degranulation, and the release of chemokine and cytokines.²⁵³ The respective sensitivities of these responses to pertussis toxin suggest that S1P₁-induced chemotaxis may be mediated via G_i whereas S1P₂-dependent mediator release may be mediated via G_q or G₁₂.²⁶⁰ Higher concentrations of S1P are required to elicit mediator release than those required for the chemotaxis response and these higher concentrations also down-regulate the chemotaxis response.²⁵³ From this it was inferred that localized S1P concentration gradients *in vivo* would initially promote mast cell migration to tissues where S1P concentrations are high. Once there, the high S1P concentrations would inhibit further mast cell chemotaxis but would promote degranulation.²⁵³

The precise role of the S1P₂ receptor in mast cell activation is still not entirely clear. Although data from S1P₂-deficient BMMCs suggests that S1P released from FcεRI-activated mast cells acts through S1P₂ to induce degranulation,²⁵³ direct addition of S1P to both BMMCs and RBL 2H3 cells has a limited effect on degranulation.^{253, 254} However, other reports suggest that S1P added together with antigen produces at least an additive degranulation response in BMMCs.²⁶⁰ Furthermore, in human mast cells it has been reported that S1P does induce substantial degranulation²⁶⁰ and that degranulation, as well as cytokine production in these cells, could be inhibited by the addition of an S1P₂ antagonist or by siRNA knock down of S1P₂ expression.²⁵⁵ Antigen-mediated passive systemic anaphylaxis reactions are reported to be similarly reduced in mice injected with an SP² antagonist and in SP2-knockout mice when compared to wild type controls.²⁶¹

The above reports suggest a role for S1P in the regulation of mast cell-driven reactions in a physiological setting. Nevertheless, the contribution of S1P to disease states remains to be established. There are certainly reports of elevated localized levels of S1P in asthma. However, the S1P may originate from multiple sources in addition to mast cells.²⁶² Evidence has suggested that whereas S1P released from mast cells is largely responsible for mast cell chemotaxis via S1P₁, S1P from other sources may be responsible for promotion of degranulation mediated by S1P₂.²⁶² S1P can also act on other tissues that contribute to the anaphylactic response. Indeed, recent reports suggest that S1P may actually promote recovery from anaphylactic reactions by acting on the vasculature.²⁶³ Further studies are thus necessary to define the role of S1P in mast cell-driven disorders especially in the human disease.

4. C3A and Chemokine Receptors—In addition to PGE₂ and S1P, agonists of other GPCRs are reported to possess potent mast cell chemotactic properties. These agents include serotonin (5-hydroxytryptamine, 5-HT), the anaphylatoxin peptide (C3a), fractalkine (CX₃CL1), MIP-1α (CCL2), eotaxin (CCL11), MCP-1 (CCL3) and RANTES (CCL5) (as

reviewed in²⁶⁴). Although 5-HT,²⁶⁵ CX₃CL1,²⁶⁶ CCL11,²⁶⁷ and CCL2²⁶⁸ do not appear to influence degranulation, C3a,^{269–271} CCL3,²³⁹ and CCL5²³⁹ can regulate mast cell degranulation and cytokine production. C3a elicits its specific cellular responses via the G_i-linked C3a receptor and, in both human and rodent mast cells, C3a induces both degranulation and cytokine production and can act in an additive manner with antigen to further enhance degranulation.^{68, 148} Similarly, CCL3,²³⁹ probably via the CCR1 receptor, and CCL5, probably via the CCR1, CCR3, or CCR5 receptors, are reported to potentiate antigen-mediated mast cell degranulation.²⁶⁴ As is true for adenosine, this potentiation appears to require activation of PI3K γ .²³⁹

5. Neuropeptide Receptors—There is evidence for biological interactions between neurons and mast cells. Mast cells are found in close proximity to neurons and can be activated by neuropeptides.²⁷² The best studied of these neuropeptides is substance P but vasoactive intestinal peptide (VIP), neuropeptide Y, and the calcitonin gene-related peptide (CGRP) have also been shown to activate at least some types of mast cells.²⁷³ To what extent these peptides activate the G α_1 subunit of the trimeric G α protein directly²⁷⁴ or indirectly through GPCRs is not entirely clear. The activation of G α_1 , whether direct or indirect, is indicated by the suppression mast cell activation by pertussis toxin in the instances where this has been tested.

Substance P is released from nerve terminals of sensory nerves in the CNS and peripheral tissues and is associated with inflammation and pain (neurogenic inflammation) in response to infection and injury. The endogenous receptor for substance P, the GPCR neurokinin-1 receptor (NK1R), is expressed in human CD34⁺-derived cultured mast cells and LAD2 cells²⁷⁵ and is thought to be expressed in rat peritoneal mast cells on the basis of studies with NK1R ligands.^{276–278} Human mast cells and mast cell lines, and rat peritoneal mast cells, degranulate^{276, 279, 280} as well as produce cytokines^{275, 281} in response to substance P. However, studies with chemically modified versions of substance P suggest that activation of rat peritoneal mast cells was not dependent on NK1R but was an inherent property of the polybasic N-terminal domain of substance P,²⁷⁷ possibly permitting direct activation of G proteins.²⁷⁴ Similar studies suggest that substance P can also act independently of NK1R in human mast cell lines while acting in part through NK1R.²⁷⁵ As with other polybasic mast cell-secretagogues that are thought to directly activate G_i proteins²⁷⁴ (see also Section 7 below), the secretory activity of substance P is suppressed in pertussis toxin-treated cells.²⁸⁰ Nevertheless, mast cells appear to express functional NK1Rs in certain circumstances. Peritoneal mast cells from a strain of Wistar rats are reported to secrete histamine when exposed to nanomolar concentrations of substance P and this response is blocked by a NK1R antagonist.²⁷⁸ NK1Rs are inducible in BMMCs by co-culture with SCF and IL-4 and, in this circumstance, respond to physiologically relevant concentrations of substance P with secretion of histamine which is inhibited a NK1R antagonist.²⁸²

Other histamine-releasing neuropeptides include VIP which can activate isolated human skin mast cells²⁸³ as well as human CD34⁺-derived and LAD2²⁷⁵ mast cell lines, neuropeptide Y which activates rat peritoneal mast cells,²⁸⁴ and CGRP in human skin mast cells²⁸³ as well as mouse BMMC²⁸⁴. In the latter study, degranulation of BMMC *in vitro* in response to CGRP, substance P or compound 48/80 (see also section 7 below) was associated with a transient increase in [Ca²⁺]_i and, in the presence of CGRP-containing neurons, activation of these neurons. Bidirectional communication between mast cells and CGRP-containing neurons was proposed on the basis of these and previous findings of increases in densities of mucosal-type mast cells and primary CGRP-containing afferent nerve fibers, often in close apposition, in the ileum of schistosomiasis-infected mice²⁸⁵ and references cited therein). Bidirectional interactions have also been noted in co-cultures

between RBL-2H3 cells and neurons²⁸⁶ via substance P and NK1R²⁸⁷ as indicated by increases in $[Ca^{2+}]_i$ in both cell types.

The notion of a functional relationship between mast cells and neuropeptides is further supported by reports of elevations of VIP, substance P and somatostatin in patients with urticaria pigmentosa and systemic mastocytosis^{288–290} and a correlation between plasma levels of substance P, VIP, CGRP, and somatostatin and mast cell load and mast cell expression of NK1R in patients with cutaneous and systemic mastocytosis.²⁹¹ Apart from neuropeptides themselves contributing to the multiple symptoms associated with mastocytosis, the neuropeptides may promote mast cell recruitment and mast cell-driven inflammation and thus have impact at multiple levels.

Neuropeptides such as substance P, VIP, and CGRP exhibit variable degrees of antimicrobial activity towards a disparate range of microorganisms²⁹² a topic that is discussed in more detail in the next section. In some instances, the antimicrobial activities were enhanced by heparin which might fit a scenario whereby release of neuropeptides induces release of mediators, including heparin, and thereby cause inflammation while suppressing further microbial infiltration. Such a scenario, however, remains theoretical and requires experimental validation.

6. Antimicrobial Peptide Receptors—Antimicrobial peptides evolved as part of an innate host-defense mechanism in primitive invertebrate species and have retained this function throughout evolution. The major categories include short amphipathic α -helical peptides (e.g., maganins and cathelicidins such as LL-37), cationic-rich peptides (e.g., indolicidins and histatins), anionic (e.g., dermicidins), and cysteine-stabilized β -pleated sheets consisting of anionic with cationic peptides (e.g., α - and β -defensins). These peptides are expressed largely in epithelial cells but also in keratinocytes, dendritic cells and in immune cells such as neutrophils, intestinal Paneth cells, NK cells, and B cells. Human and murine mast cells express cathelicidins²⁹³ which appear to protect against skin infection.²⁹⁴ Mast cells are also reported to form extracellular DNA-chromatin webs, with cathelicidin LL-37 attached, that trap and kill microbes.²⁹⁵ In addition to their direct microbicidal activity, because of their ability to form membrane pores, they induce cytolysis, and in some instances suppress essential microbial intracellular cellular functions (reviewed in²⁹⁶), the antimicrobial peptides also act indirectly by augmenting innate and adaptive immune responses by regulating function of the host's immune cells. An important component of these actions is the induction of inflammatory reactions by activating mast cells and thus recruitment of other immune cells²⁷³ as described elsewhere in this article.

Many of the antimicrobial peptides are thought to act through GPCRs because their actions on host immune cells are blocked on treatment with pertussis toxin but the identity of these receptors in mast cells is largely unknown.²⁷³ However, it is postulated from studies with signaling inhibitors that the human α and β defensins stimulate mast cell chemotaxis through separate GPCRs with each family acting through a common GPCR which is subject to PKC-independent homologous desensitization.^{297, 298} In addition to chemotaxis, the defensins and cathelicidin LL-37 induce degranulation as well as production of PGD_2 ,^{299–302} PGE_2 , and LTC_4 .³⁰³ These peptides also stimulate production of Th1, Th2, puritogenic, and inflammatory cytokines including IL-2, IL-4, IL-5, IL1 β , TNF γ ,³⁰² IL-6, IL-31, and GM-CSF.³⁰³ The β -defensins and LL-37 induce phosphorylation of the MAP kinases p38 and ERK.^{301, 304} As with the identity of receptors, little else is known about the signaling processes involved except from studies with inhibitors that point to dependence on G_i /PLC, PI3-kinase, and PKC pathways for the actions of β -defensins and LL-37.^{300, 301, 303, 305, 306} The antimicrobial neuropeptide, catestatin, was shown recently to

activate mast cells in a similar manner as β -defensins and LL-37 to induce chemotaxis and degranulation as well as production of eicosanoids and inflammatory cytokines.³⁰⁷

7. Other Activators with Undefined Receptors and Mechanisms of Activation

—A diverse group of cationic compounds, sometimes referred to as “mast cell secretagogues”, were known to cause degranulation of mast cells long before the discovery of IgE-mediated activation of mast cells. Classic examples include the polymeric compound 48/80, the polyamines spermine and spermidine, various kinins and cationic peptide hormones, hymenoptera venom constituents such as mastoparan, mellitin, and mast cell degranulating peptide.^{274, 308} They all induced degranulation within seconds in only some categories of mast cells (e.g. serosal but not mucosal mast cells in rodents) and act through pertussis toxin-sensitive heterotrimeric G_i proteins. In addition to degranulation, compound 48/80 in common with substance P and VIP peptides induces production of IL-3 IL-8, $TNF\alpha$, and GM-CSF but not IL-4, $IFN\gamma$, and eotaxin in the human LAD2 mast cell line.²⁷⁵ Interestingly compound 48/80 and these peptides also induced substantial production of several chemokines and thus differed from IgE-mediated stimulation which did not.

It was originally proposed that the “secretagogues have the ability to penetrate the plasma membrane, via either α -helices of peptides or aromatic rings of compound 48/80, and directly activate G_i proteins in a receptor independent manner.³⁰⁸ Such a mechanism, however, would not be applicable to all known basic “secretagogues” and the concept has been since extended to include additional mechanisms for their membrane translocation and access to G_i such as low affinity non-selective membrane receptors or transporters on serosal mast cells.³⁰⁹ Also, some, but by no means all, basic peptides have since been shown to act through their own GPCRs³⁰⁹ and recently the action of compound 48/80 was reported to be dependent on the presence of neuronal GPCRs known as Mas-related genes (Mrgs), specifically MrgX1 and MrgX2.²⁷¹ More studies are clearly needed to clarify mechanisms whether they involve direct activation of G_i proteins, GPCRs, or both.

Of clinical concern is that certain categories of cationic drugs also possess “secretagogue” activity and can directly activate human mast cells *in vitro* and *in vivo*. These include opiates, neuromuscular blocking agents (e.g. tubocurarine), antimicrobial agents (e.g. pentamidine and noemycin), local anesthetics (e.g. lidocaine), and antimalarials (e.g. quinidine).³¹⁰ Allergic- or anaphylactic-like (often referred to as “anaphylactoid”) symptoms are manifested within hours or minutes on first exposure to the drug, presumably through non-immunological mechanisms. Although relatively rare, such reactions can be mild or life threatening depending on route of administration.

Current information on the signaling systems activated by compound 48/80 and other classic “secretagogues” is incomplete and somewhat incoherent. A seminal observation was that compound 48/80 induced rapid stimulation of a pertussis toxin sensitive membrane GTPase activity (identified as N_i and later renamed G_i), transient production of inositol polyphosphates, and Ca^{2+} -influx in rat peritoneal mast cells.³¹¹ This influx coincides with release of histamine, arachidonic acid,^{311, 312} and PGD_2 .³¹³ Subsequent studies indicated direct interaction of compound 48/80 with the COOH-terminal end of the α -subunit of G_{i3} at the plasma membrane³¹⁴ and initiation of additional signals via PKC and PI3K.³¹⁵ The latter signals appeared to play no role in degranulation but were essential for production of arachidonic acid.³¹⁵ The proposed model was that 48/80 activates G_{i3} , which suffices to induce degranulation, and a PKC/PI3K/tyrosine pathway that leads to activation of activation of PLA_2 with the associated production of arachidonic acid metabolites such as PGD_2 . The activation of PKC and PI3K is also evident in 48/80-stimulated NIH3T3 cells except that in this model PI3K is thought to be primary effector with downstream activation of PKC α as well as PKB and calcium mobilization.³¹⁶ In addition, compound 48/80³¹⁷ and

mastoparan³¹⁸ can activate PLD, either directly or via G₁₃ (or G₁₂), which theoretically could result in activation of conventional PKC isoforms in conjunction with elevated cytosolic Ca²⁺ levels.³¹⁹ Apart from the question of whether compound 48/80 activates multiple independent pathways or not, it is important to note that compound 48/80 and similarly acting “secretagogues” act on other cell types (e.g. NIH3T3 cells). Therefore, their actions *in vivo* do not necessarily implicate mast cells exclusively.

IV. INHIBITORY RECEPTORS

In addition to the specific mast cell receptors that upregulate antigen-induced responses, such responses can be down-regulated by a variety of other receptors expressed on the surface of mast cells.^{20, 21, 68} These include the FcγRIIb IgG receptor,¹⁵⁴ Sialic acid-binding, Ig-like lectins (Siglecs),³²⁰ Mast cell function-associated antigen (MAFA),³²¹ Platelet endothelial cell adhesion molecule (PECAM-1),³²² Gp49B1,³²³ paired Ig-like receptor-B (PIR-B),³²⁴ CD200 receptor,³²⁵ CD300a,³²⁶ and CD72.³²⁷ Although these receptors are quite diverse in nature, with the exception of CD200 receptor, they all contain at least one, and up to four, immunoreceptor tyrosine-based inhibitory motifs (ITIM).²¹ ITIMs are consensus motifs (I/V/L/SxYxxL/V, where x is any amino acid) that are targets for Src kinases activated upon receptor ligation.²¹ Following phosphorylation of the tyrosine residues contained in these sequences, they recruit inhibitory phosphatases and other signaling proteins which can then impact responses elicited by both FcεRI and KIT. Indeed a fusion protein colligating both the FcγRIIb and FcεRI has proven efficacious in preventing activation of human mast cells and basophils.¹⁵⁵ Both the tyrosine phosphatases, SHP1 and 2, and the inositol phosphatase SHIP are recruited to the phosphorylated ITAM.^{21, 68} However, there appears to be a degree of selectivity in the recruitment of these phosphatases to specific receptors. For example, the FcγRIIb recruits SHIP whereas other ITIM-containing inhibitory receptors such as Siglecs, Gp49B1, LAIR-1 and PECAM-1 primarily recruit SHPs. By virtue of their ability to dephosphorylate tyrosine residues of signaling proteins, SHP1 and 2 terminate signaling processes regulated by tyrosine kinases including Lyn, Fyn, Btk and Syk. SHIP on the other hand dephosphorylates inositol 3, 4, 5-trisphosphate at the D5 position thereby terminating signaling processes regulated by PI3K.¹²⁴ These molecules, therefore, effectively reverse both of the major pathways regulating mast cell activation downstream from FcεRI and KIT.

Until recently, the natural ligands for many of these inhibitory receptors were unknown. However, recent studies have determined that some of these ligands are widely distributed in blood and tissues, for example IgG/immune complexes for the FcγRIIb and MHC-1 molecules for PIR-B.²¹ This may provide a clue as to why so many inhibitory receptors have evolved to downregulate the activation of mast cells and other cell types. Mast cell degranulation must be highly regulated to prevent inappropriate consequences for the host organism. This would be especially true during migration of precursors and immature mast cells from the bone marrow and during the maturation process before the mature mast cells take up residence in their target tissues. Engagement of the inhibitory receptors during the early steps of mast cell development and migration through encounters with commonly expressed molecules would thus ensure mast cells are maintained in an inactivated but primed state until required for immune defense in the appropriate tissues. Disruption of these inhibitory processes through inactivating mutations would likely have the potential to significantly impact disease.^{21, 271}

V. PHENOTYPIC PLASTICITY AND ACCOMPANYING CHANGES IN RECEPTOR EXPRESSION

Mast cells exhibit phenotypic variability depending upon the type of tissue in which they reside.¹³ In rodents, mast cells have been broadly categorized into connective tissue-type (also known as serosal) and mucosal-type mast cells on the basis of their distinctive histochemical staining characteristics which reflect differences in the glycosaminoglycan component of the proteoglycan core of mast cell granules. The granules of serosal mast cells exhibit metachromatic staining with toluidine blue (i.e. a shift from navy blue to purple) and stain red with safranin due to the presence of heparin, a highly sulfated glycosaminoglycan. In contrast, mucosal mast cell granules contain a less highly sulfated chondroitin E as the predominant core component and stain blue after sequential staining with alcian blue and safranin.^{328–330} Serosal mast cells are found largely in skin, connective tissue, and tissue spaces such as the peritoneum and for this reason were referred to as connective tissue mast cells. Mucosal mast cells, as implied, are found in mucosal tissue of intestine and airways.

Human mast cells were initially characterized according to differences in the expression of tryptase and chymase in mast cell granules. One type, called MC_T, contains tryptase only and is the predominant subtype in respiratory and intestinal mucosa often in association with T cells. Another, MC_{TC}, contain both tryptase and chymase in addition to other proteases such as carboxypeptidase A and cathepsin G and is predominant in skin, synovium, conjunctiva, lymph nodes, myocardium as well as submucosa of stomach and intestine. A third type, MC_C, expresses chymase and is found in mucosal tissue of stomach, small intestine, and colon. MC_{TC} is, in some respects, the counterpart of the serosal mast cell in rodents whereas MC_T most closely resembles rodent mucosal mast cells.

It is thought that mast cell heterogeneity in different tissues arises from differences in the tissue microenvironment given that mast cell maturation occurs within peripheral tissues.¹³ In addition, it is unlikely that mast cells are irreversibly cast into distinct subtypes as described above but retain phenotypic flexibility to respond to physiologic/pathologic events and the accompanying alterations in the milieu of cytokines and other conditioning factors. Phenotypic changes can be teased in culture as, for example, co-culture of tissue-derived mast cells^{331–333} or RBL-2H3 cells³³⁴ with fibroblasts or by use of different culture supplements³³⁵ as well as in tissues by *Trichinella spiralis* infection³³⁶. The distinctive features and locations of the mast cell subtypes suggest functional specialization, a concept that is further supported by differences among mast cells from different tissues in the pattern of cytokines produced and in their sensitivity to secretagogues such as compound 48/80 and morphine.³³⁷

As should be evident from this review, a variety of receptors positively or negatively influence FcεRI-induced mast cell activation. Expression of these regulatory receptors varies from one species to another³³⁸ but remarkably little is known about the differences in expression of receptors among mast cell subtypes in a given species although there are indications that this may be so. Early studies had indicated that rodent serosal, but not mucosal, mast cells responded to the G protein stimulant, compound 48/80.³³⁹ Similar differences in responses to this compound had been noted between mast cells from human skin and those from lung, colon, tonsils and adenoids³⁴⁰ and between MC_{TC} and MC_T cells from human skin and lung.³⁴¹ The latter study also indicated that both types of cells responded to FcεRI ligation but only MC_{TC} express C5aR (CD88) and respond to C5a. Expression of the neurokinin receptor 1 (NKR1) and responsiveness to its agonist, substance P, occur after co-culture of murine BMMC with SCF and IL-4²⁸² in which these cells acquire the characteristics of connective tissue-type cells.³³⁵ Clearly these studies indicate that growth factors or culture conditions normally associated with expression of particular

subtypes of mast cells can induce expression of receptors not normally expressed on mast cells

Mast cells and basophils are derived from pluripotent hematopoietic stem cells but their developmental pathways probably differ³⁴² although there are remaining issues.³⁴³ Human mast cells are thought to originate from CD34⁺ stem cells in bone marrow, circulate in the blood as progenitors, and acquire their mature phenotype within tissues as a result of exposure to tissue factors such as, SCF, IL-3, IL-4, IL-9, nerve growth factor (NGF), and likely others.³⁴⁴ SCF is produced mainly by stromal cells where it is expressed on the cell surface or released in soluble form.³⁴⁵ The SCF receptor, Kit (CD117), is expressed on hematopoietic stem cells and is retained on mast cells throughout their development and differentiation but is down-regulated during differentiation of basophils and other bone marrow-derived cells. In contrast to mast cells, basophils reach their mature state in bone marrow before release into blood.

The early observations of two histochemically distinct populations of mast cells in rodents^{328, 329} and that one subset, the mucosal mast cell, was resistant to compound 48/80³⁴⁶ led to the concept of mast cell “heterogeneity”. This concept was reinforced by significant differences in expression of proteoglycans and proteases in serosal and mucosal mast cells.^{347, 348} Nevertheless, these two subsets exhibit “plasticity”. When BMMC from normal mice are injected into mast cell-deficient mice, the cells retain their mucosal cell characteristics at tissue sites that normally bear this phenotype while adopting a serosal mast cell phenotype at sites that contain such cells³⁴⁹. A similar change in phenotype occurs on co-culture of BMMC with fibroblasts.³³³ IL-3 and SCF were found to be two factors regulating differentiation to, respectively, either the mucosal (i.e. chondroitin sulfate E positive)³⁵⁰ or serosal (i.e. heparin positive)³⁵¹ mast cell phenotypes. Subsequent studies also imply that mast cells are conditioned by their cytokine environment under normal or pathological situations¹⁶². The “heterogeneity” and “plasticity” of mast cells likely contribute to their multifunctional capability in immunological and pathological settings.

VI. BIOLOGICAL ROLES OF MAST CELLS IN HEALTH AND DISEASE

Evidence has been presented in the preceding sections that the multifunctional adaptability of mast cells is conferred by the flexibility in receptor expression, and that their interactions, might allow selective release of mediators in given situations. The following sections examine such flexibility in the immunological and non-immunological conditions that have been attributed to mast cells. Some of the consequences of mediator release from mast cells, regardless of stimuli, are illustrated in Figure 5.

A. Hypersensitivity Reactions and Autoimmune Diseases

The mechanisms and consequences of mast cell activation in IgE-dependent allergic reactions, classified as type I or immediate hypersensitivity reactions, are described in detail in the previous sections. They include allergic asthma, rhinitis, conjunctivitis, atopic dermatitis, food allergies, and anaphylactic reactions. As these disorders have been extensively reviewed,^{13, 338, 352–354} they need no further discussion here. The detrimental effects of mast cell activation, however, extend to other types of hypersensitivity reactions that include various autoimmune diseases.³⁵⁵ The most widely studied are bullous pemphigoid, rheumatoid arthritis (type II hypersensitivity), rheumatoid arthritis (categorized as a type III hypersensitivity by some or type IV by others), and multiple sclerosis (type IV or delayed hypersensitivity).³⁵⁵

The participation of mast cells in bullous pemphigoid was suspected from reports of high concentrations of IgE, degranulated mast cells and mast cell-derived chemoattractants in the

subepidermal skin blisters of patients with bullous pemphigoid. These lesions contain high levels of histamine, eosinophils, and IgE class autoantibodies³⁵⁶ which elicit lesions reminiscent of bullous pemphigoid when injected into human skin grafted on athymic mice.³⁵⁷ These lesions likely result from formation of IgE and IgG autoantibodies against two skin hemidesmosomal proteins, BP180 and BP230. The disease can be closely mimicked in normal but not mast cell-deficient neonatal mice by intradermal injection of IgG antibodies against murine BP180 or BP230.³⁵⁸ Using this and genetic models, the mast cell C5a receptor and MCP-4 protease have been implicated in mast cell activation and subsequent tissue damage (See³⁵⁹ and citations therein).

The synovial joints are the primary, but not only, sites affected in rheumatoid arthritis. The underlying etiologic factors involved are uncertain although rheumatoid factor, an autoantibody the Fc portion of IgG, and anti-citullinated cyclic peptide antibodies are characteristic of this disease in many but not all patients. Uncertainty extends to animal models as no two are alike and none exactly reproduces human disease.³⁶⁰ The involvement of mast cells, among many ongoing processes, is indicated by their increased numbers, some in a degranulated state, in synovial tissues and the appearance of mast cell-derived mediators in synovial fluid and tissue.³⁶¹ Mast cell-deficient mice fail to develop the disease when injected with serum from arthritic K/BxN mice,^{362, 363} one of the several mouse models of this disease. Reconstitution studies in genetically modified mice have demonstrated that mast cell Fc γ RIII and mast cell-derived IL-1 are essential for progression of disease.^{363, 364} Mast cells have also been implicated in collagen as well as various forms of antibody-induced arthritis in mice^{355, 365} in which activation of mast cells by IL-33 through the IL-33 receptor (ST2) is said to play a critical role.¹⁹⁷ IL-33, which is expressed in synovial membranes from patients with rheumatoid arthritis, markedly enhances production of TNF α and IL-1 β in cultured synovial fibroblasts from these patients. It is proposed that IL-33, along with IgG, stimulates synovial mast cells to generate additional cytokines thereby amplifying the inflammatory response. Experimentally induced Arthus reaction, like rheumatoid arthritis, is dependent on formation of antigen-antibody complexes. The inflammatory reaction is dependent on activation of mast cells through Fc γ RIII and is not apparent in mast cell-deficient mice.³⁶⁶

Interest in the role of mast cells in multiple sclerosis (MS) and its experimental counterpart, experimental allergic encephalomyelitis (EAE) in mice³⁵⁵ arose from early reports of correlations between progression of disease (inflammatory demyelination) and localization of mast cells in a degranulated state in human lesions³⁶⁷ in addition to the presence of mast cell proteases in cerebrospinal fluid.³⁶⁸ EAE is induced by immunization of genetically susceptible mice with myelin peptides although the causative agent in humans is unknown. Along with Th1, Th9, and Th17 cells, mast cells have been implicated in EAE, in part because of the effects of various pharmacologic agents.³⁶⁹ More direct evidence is the diminished severity of EAE in mast cell-deficient mice, unless deficiency is rectified by adoptive transfer of wt BMMC,³⁷⁰ by mechanisms that likely require activation of mast cells via Fc γ receptors,³⁷¹ production of TNF α , and mast cell-associated neutrophil infiltration.³⁷² Other autoimmune disorders thought to be mast cell related, based largely on correlative evidence, include type 1 diabetes, Guillain-Barré syndrome, scleroderma, ulcerative colitis, Crohn's disease, Sjögren's syndrome, Graves' eye disease, and chronic idiopathic urticaria.^{355, 365} One large family of chronic urticarial diseases, cryopyrin-associated periodic syndrome (or CAPS), has been linked recently to constitutive production of IL-1 β by skin mast cells which bear an active NOD-like receptor (NLRP3) caused by an activating missense gene mutation common to CAPS patients.³⁷³ The production of IL-1 β results in the characteristic vascular leakage and neutrophil infiltration in CAPS urticarial lesions.

B. Innate Immunity

As discussed in previous sections, the widespread distribution of mast cells in skin and mucosal surfaces, and their ability to detect a broad variety of pathogens, places mast cells in a prime position for detection of invading organisms. The first evidence to support this hypothesis came from studies of models of intestinal helminth infection in which mast cells appear to accumulate and to degranulate at sites of parasite infestation, whereas mast cell-deficient *W/W^v* mice had diminished capacity for worm expulsion.^{374, 375} Subsequent studies have revealed that mast cells protect against diverse types of parasitic infections in animal models, including malarial parasitaemia, by a variety of mechanisms that involve recruitment and proliferation of mast cells, recruitment of other key immune cells which include eosinophils, release of SCF, IL-3, IL-4, mast cell proteases, and expulsion of parasites (reviewed in⁴).

Mast cells have also been shown to play a critical protective role, at least in animal models, against systemic or localized bacterial infections at sites as varied as peritoneum following caecal ligation,^{376, 377} lung,^{376, 378} bladder,³⁷⁹ intestine,³⁸⁰ and skin^{379, 381} by facilitating clearance of enterobacteria from these tissues^{376, 378, 379} or by limiting skin lesions caused by *Pseudomonas aeruginosa*.³⁸¹ In some of these studies, protection is dependent on mast cell production of TNF α ,^{376, 377, 379} IL-6,³⁷⁸ and leukotrienes³⁸² as well as recruitment of neutrophils³⁷⁶ or dendritic cells.³⁷⁹ Data on viral infection is limited although it is known that mast cell numbers increase during pulmonary viral infections in rats and humans^{383, 384} and that cultured mast cells can be activated by viral challenge^{385, 386} or viral products.^{386, 387} One immunological consequence of viral challenge (with Newcastle disease virus), which is impaired in mast cell-deficient mice, is the recruitment of CD8⁺ T cells.³⁸⁶ Fungi are also known to exacerbate airway inflammatory disease by IgE-dependent and -independent mechanisms. The ubiquitous *Aspergillus fumigatus*, for example, is reported to induce degranulation of RBL-2H3 cells in an IgE-independent manner³⁸⁸ in addition to its well established propensity to cause IgE-dependent allergic disease in humans. Fungal spores of another common fungus, *Trichoderma viride*, potentiate IgE-dependent histamine release from human cells obtained by bronchial lavage.³⁸⁹ Yeast zymosan is an activator of mast cells, resulting in release of IL-6,³⁹⁰ GM-CSF, IL-1 β , and leukotrienes but not degranulation¹⁸¹, as well as mast cell-mediated peritoneal inflammation in mice.^{391, 392} The release of GM-CSF, IL-1 β , and leukotrienes in the absence of degranulation in human cord blood-derived mast cells¹⁸¹ illustrates the capacity of these cells to respond selectively to a particular stimulant.

C. Adaptive Immune Responses: Acquired Immunity and Immune Tolerance

Apart from acting as first responders to microbial agents, mast cells can recruit other immune cells within lymph nodes to set the stage for adaptive immune responses.³⁹³ Early reports indicated that induction of contact dermatitis in a mouse model leads to migration of mast cells to regional lymph nodes³⁹⁴ and in such locations, mast cells produce MIP-1 α to promote recruitment of T cells.^{394, 395} Mast cells were later shown to play a critical role in lymph node hypertrophy and the engagement of T cells with APCs upon bacterial infection,³⁹⁶ *Leishmania major* parasite infection,³⁹⁷ contact dermatitis,^{398, 399} and IgE-dependent cutaneous anaphylaxis.⁴⁰⁰ Mast cell-derived TNF α seemed to play a predominant role in lymph node hypertrophy during bacterial infection,³⁹⁶ contact dermatitis,³⁹⁹ and IgE crosslinking,⁴⁰¹ but only a partial role in the responses to the bacterial component, PGN.⁴⁰¹ Other mast cell mediators implicated in cell recruitment include MIP-1 α ,^{394, 395} IL-1⁴⁰², and histamine.⁴⁰⁰ Mast cells also express ligands that activate co-stimulatory molecules on T cells. For example, OX40L, has been identified on mast cells as enhancing T cell activation following antigen stimulation⁴⁰³. More details need to be elucidated but it is apparent that mast cells promote migration of peripheral lymphocytes,³⁹⁶ Langerhans

cells,⁴⁰⁰ and dendritic cells⁴⁰⁴ to regional lymph nodes thereby promoting interaction of APCs with T helper cells as a prelude to T cell/B cell collaboration⁴⁰⁵ or cytotoxic T cell (CTL) activation⁴⁰⁶ (Figure 5). The CTL connection was established by topical application of a TLR7 ligand (imiquimod) as adjuvant along with a MHC class 1 restricted cytotoxic T lymphocyte peptide in mice.⁴⁰² Mast cell-derived IL-1 and TNF α mediated different phases of the response, namely, inflammation, migration of Langerhans cells, and lymph node hypertrophy. These responses were much diminished in mast cell-deficient mice but were restored by pre-immunization with peptide-loaded dendritic cells.

Evidence for the participation of mast cells immune suppression comes from studies of the regulatory T cell (T_{reg})-dependent allograft tolerance model in mice. In this model CD4⁺ Th1 and Th2 cells enable rejection of allogeneic tissue grafts whereas T_{reg} cells suppress rejection. The possibility of interaction between T_{reg} cells and mast cells was initially indicated by the finding that expression of specific markers of both cell types were increased in syngeneic skin grafts or tolerated allogeneic grafts.⁴⁰⁷ Production of IL-9 by T_{reg} cells was thought to promote recruitment and activity of mast cells in tolerant tissue. It was reported later that inoculation of mast cell-deficient mice, which do not tolerate allogeneic grafts, with BMMCs from normal mice restored tolerance in an IL-9-dependent manner.⁴⁰⁸ There is also evidence for direct interaction of T_{reg} cells with mast cells through the OX40-OX40L connection.⁴⁰⁹ This interaction suppresses Fc ϵ RI-mediated mast cell activation *in vitro* and dampens the allergic response *in vivo* to suggest that mast cells have a pro-growth role in immune tolerance. These results could have therapeutic value once the mast cell factors involved and their roles have been identified.

D. Angiogenesis, Wound healing, and Tumor Growth

An angiogenic role for mast cells was suspected because of their proximity to blood and lymphatic vessels and their accumulation in tissues associated with angiogenesis such as hemangiomas, polyps, and tumors. Moreover, mast cells are now known to release various angiogenic factors including fibroblast growth factor-2 (FGF2), vascular endothelial growth factor (VEGF), TGF β , IL-8, histamine, heparin, and angiopoietin 1.^{11, 410, 411} Past evidence relied on the use of pharmacologic agents to block effects of mast cell mediators as well as the mast cell stabilizing compounds cromolyn and salbutamol. More direct evidence has come from studies involving reconstitution of mast cells in mast cell-deficient mice as, for example, the demonstration of mast cell-dependent angiogenesis in arthritic lesions in the K/BxN mouse model⁴¹² and Myc-driven cancer of pancreatic β cells in mice.⁴¹³ Membrane tissues such as the chick chorioallantoic membrane and rat mesentery have been used also as models to identify histamine,⁴¹⁴ VEGF-A,⁴¹⁵ and FGF2⁴¹⁶ as mast cell products capable of inducing angiogenesis in addition to the activation of mast cells themselves.^{414, 417} As noted in recent reviews, interest has focused on angiogenesis during tissue repair^{11, 13} and tumor development.^{6, 11, 418} Several mast cell mediators have been linked to angiogenesis in these models but a remaining challenge is dissecting their specific roles in the various phases of angiogenesis.

Mast cells are also thought to regulate tissue remodeling during wound healing,^{9, 11} tumor progression,⁴¹⁹ and autoimmune arthritis.⁴²⁰ Apart from the original proposal that histamine was an essential mediator in wound healing and rapid tissue growth some 50 years ago,⁴²¹ it has been proposed that mast cells regulate all phases of healing from the initial inflammatory response to tissue remodeling and re-epithelialization.⁹ Mast cells accumulate along edges of healing wounds, scar tissue, keloids, and hypertrophic scars, and can produce fibroblast as well as keratinocyte growth factors in addition to matrix remodeling factors.^{9, 11, 422} Mast cell tryptase and chymase specifically stimulate α -1 collagen production by dermal fibroblasts and production of angiogenic factors by the extracellular matrix and thus implicated in tissue remodeling in squamous carcinomas.⁴²³ Studies of the

role of mast cells in skin-incision healing models in both animals and humans have resulted in inconsistent conclusions. Mast cell reconstitution studies in W/W^v mice suggested that skin wound closure was dependent on mast cells in one study⁴²⁴ but not in another where collagen remodeling appeared to be defective during the final phase of wound healing.⁴²⁵ In a scald-injury model, extravasation and fibrous proliferation was impaired in W/W^v mice during wound healing although eventual wound closure and re-epithelialization was not.⁴²⁶ Apart from the previously noted caveats in the use of W/W^v mice,⁴²⁷ a further handicap in the interpretation of such studies is the complexity of the healing process and the participation of other cells during the healing process. Although it is thought that mast cells play a role, perhaps substantial, in angiogenesis during tissue remodeling,¹¹ the individual roles of other participating cells and their interactions with mast cells need further clarification.

Equally complex is the role of mast cells in tumor formation and progression. Ehrlich first noted the abundance of mast cells in carcinomas where mast cells accumulate at the periphery rather than the interior of the tumor nodules⁴²⁸ Current studies reveal both positive and negative relationships between mast cell activity and tumor progression (see reviews^{5, 11, 13, 429, 430}). Indicative of protumorigenic relationships are reports of abundant numbers of mast cells in proximity of blood vessels surrounding certain tumors and an apparent correlation with tumor-associated angiogenesis and adverse course of disease in patients.^{431–433} Positive relationships are also indicated in studies with mast cell-deficient mice. For example, neoplastic progression of squamous carcinoma⁴²³ and pancreatic islet tumors⁴¹³ are substantially reduced in mast cell-deficient W/W^v and W^{sh}/W^{sh} mice, respectively. W/W^v mice are also less susceptible to development of chemically-induced intestinal epithelial tumors⁴³⁴ and metastases from subcutaneously administered murine B16 melanoma cells.⁴³⁵ A protumorigenic role is also implied in mouse studies of thyroid⁴³⁶ and colonic⁴³⁷ carcinomas. In the latter study, the evidence was buttressed by ablation of hematopoietic cells in a chimeric mouse model of polyposis, a predisposition to colon cancer. Reconstitution of bone marrow cells from W^{sh}/W^{sh} but not wt mice resulted in remission of existing polyps suggesting that mast cells were essential for polyps formation and by inference the environment conducive to malignancy. In these studies, tumor-induced angiogenesis and tumor penetration into the extracellular matrix appear to be dependent on release of cytokines, chemokines, and proteases from mast cells.^{415, 423, 436}

One topic of particular interest is the involvement of mast cells in the inflammation associated with malignancy. Depending on the type of tumor, inflammation may exist before malignant changes or be induced by the malignant process itself but in either case inflammation may be conducive to tumor growth.⁴³⁸ Tumors can arise at sites of chronic inflammation and certain chronic inflammatory diseases are associated with increase susceptibility to cancer. The onset of malignancy itself may lead to recruitment of inflammatory cells including mast cells. The production of growth-promoting, chemotactic, and angiogenic factors by mast cells may then facilitate progression of tumors.^{5, 413, 439, 440}

In contrast to the above reports, several clinical reports note favorable correlations between patient survival and numbers of tumor-associated mast cells in patients with breast⁴⁴¹ and prostate⁴⁴² cancers and B-cell lymphomas.⁴⁴³ Similarly, mast cells appeared to play a protective role in an intestinal adenoma mouse model.⁴⁴⁴ When these mice were bred with W^{sh}/W^{sh} mice, mast cell deficiency resulted in a marked reduction of tumor cell apoptosis without affecting tumor cell proliferation. An added twist to the story was the recent report⁴⁴⁵ that the reported tumorigenic activity of mast cells in the B16 melanoma mouse model⁴³⁵ was reversed after stimulation of mast cells by injection of a TLR2 agonist (Pam_3CSK_4). Moreover, the tumor suppressive action of Pam_3CSK_4 was not observed in W^{sh}/W^{sh} mice but was apparent after provision of BMDCs from wild type but not TLR2-

deficient mice.⁴⁴⁵ Co-culture of BMMCs and melanoma cells indicated enhanced production of cytokines and chemokines by TL2-activated mast cells without provoking degranulation. Production of CCL3 and IL-6 were apparently critical factors in recruitment of NK and T cells as well as tumor growth.

The general impression from the reports so far is that the role of mast cells varies according to the type of tumor and phase of malignant growth. As noted in recent reviews,^{5, 429, 446} research is handicapped by the correlative nature of clinical research, the diversity of experimental models, and the complexity of tumor biology. Even so, the cumulative evidence points to a regulatory role for mast cells in tumor growth and could be a potential target for adjuvant therapy⁴²⁹ in some but not all types of cancers.⁴⁰⁰

VII. CONCLUDING COMMENTS

Although mast cells are well recognized initiators of acute allergic reactions associated with urticaria, rhinitis, atopy, anaphylaxis, and in combination with other immunological cells chronic allergic inflammation, it is now apparent that they also contribute to the body's innate and adaptive defense mechanisms against invading micro-organisms. Central to these defense mechanisms, is the ability of mast cells to generate and release a wide array of bioactive molecules that produces a concerted attack on pathogens and which promote recruitment of other critical immune cells. However, it is these same mediators that can adversely affect surrounding tissues in the host resulting in autoimmune disease as well as allergic disorders. As discussed here, other less well established roles, adverse and beneficial, include immune suppression, tumor generation and progression, and wound healing. Therefore, complete assessment of the biologic role of mast cell remains elusive but much progress has been made in recent years. We have noted, as have others, that activation of mast cells is not necessarily global but, depending on the type of stimulus or combination of stimuli, can be more attuned for a given pathophysiologic situation. Some recent examples of selective release of mediators have been described that, as more examples emerge, point to possible refinement of therapy for particular disease types. An example is the NOD-like receptor-dependent release of IL-1 β from mast cells and ensuing histamine-independent rash in CAPS. This disease is effectively treated with IL-1 receptor antagonists instead of antihistamines.³⁷³ This topic, in our view, is worthy of additional research.

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Figure 1.

Activation of mast cells following FcεRI aggregation and the ability of KIT and GPCRs to modify these responses. Ligands are depicted in brown text, receptors in large blue text, and modes of initiating signal transmission in green text. The diagram depicts the release of the various classes of inflammatory mediators and induction of chemotaxis by FcεRI- and KIT-mediated signaling (small blue text), or the ability of KIT (Section **III C**) and GPCRs (Section **III E**) to enhance the FcεRI-mediated responses (bold red arrows).

Figure 2.

Integration of the signals induced by KIT and the prototypical mast cell GPCR, the PGE₂-EP3 receptor, with those elicited by the FcεRI for the synergistic enhancement of mast cell degranulation. For clarity, other signals that may be required for KIT, EP3, and FcεRI-mediated mast cell responses but which have not been directly linked to the synergy have not been included. Further details about these additional signals can be found in Sections **III C** and **III E** and references.^{16, 65, 66}

Aggregation of the FcεRI results in the activation of the Src kinases Lyn and Fyn and the recruitment of the ZAP 70 tyrosine kinase family member Syk to the receptor complex and its subsequent activation. This, in turn, results in the activation of PLCγ, tethered to the transmembrane adaptor molecule LAT, and the activation of PI3K tethered to the cytosolic adaptor molecule Gab2 as a result of its phosphorylation by Fyn. PLCγ induces hydrolysis of PIP₂ to yield IP₃ and DAG thereby respectively releasing calcium from intracellular stores and promoting PKC activation. The depletion of the intracellular calcium stores leads to enhanced calcium sequestration by store operated calcium entry (SOCE). PI3K induces the phosphorylation of PIP₂ to yield PIP₃, thereby providing a docking site for the PH-domain of the Tec Kinase Btk, the activation of which further enhances the PLCγ-induced calcium signal which also appears to require the indirect binding of PLCγ₁ to the LAT-related transmembrane adaptor molecule LAT2 (NTAL/LAB). The capacity of KIT to enhance FcεRI-mediated degranulation is dependent on the ability of LAT2 and BTK to

regulate an amplification loop for PLC γ_1 -dependent calcium mobilization and PKC activation, key signals for mast cell degranulation. In contrast to the SCF/KIT-mediated enhancement of Fc ϵ RI-mediated degranulation, PGE $_2$ /EP3 alternatively utilizes a mechanism involving the cross-synergistic activation of PLC γ_1 and PLC β with a resulting augmentation of the necessary calcium signal.

3A

3B

Figure 3.

Interaction of pathogen recognition and ST2 receptor systems with FcεRI leads to substantial enhancement of production of cytokines and chemokines. Panel A. Mast cells express receptors for IL-33 (ST2), various Toll-like receptors (TLRs) of which three are shown, and NOD-like receptors (NLRs) (see Section IIID). All these receptors act through the MyD88 to strongly activate the NFκB pathway. As discussed in Section IIID, the NFκB pathway is only weakly activated by low concentrations of antigen that barely stimulate degranulation but can still stimulate the NFAT pathway which ligands for ST2, TLRs, and NLRs do not. Both NFκB and NFAT are key regulators of cytokine gene transcription.

Consequently cytokine production is amplified. As shown in more detail in panel **B**, additional amplification occurs at the level of the kinase TAK1 to enhance activation of the p38 and JNK MAP kinases and their downstream targets ATF2 and the AP1 component, c-Jun. A third level of amplification occurs through co-operative interaction between AP1 and NFAT.^{18, 19} The calcineurin inhibitor, cyclosporine A, effectively blocks the NFAT pathway as well as cytokine production. The intermediate signaling steps between FcεRI and TAK1 is not determined and is indicated by the dashed line.

Figure 4.

Integration of the signals induced by KIT, and the prototypical mast cell GPCR, PGE_2 -EP3 receptor, with those elicited by the FcεRI for the synergistic enhancement of mast cell chemotaxis. The initial steps in the signaling process are described in the legend to Figure 2. The subsequent activation PI3K/Btk axis in addition to increasing calcium release through the enhancement of PLCγ activation, allows potentiation of Rac activation with resulting elevated reorganization of the actin cytoskeleton. These responses lead to enhanced mast cell migration through chemotaxis.

Figure 5. Mast cell mediators and pathways in inflammatory and immune responses to allergenic and pathogenic stimuli. Secretion of granules leads to release of histamine and mast-cell specific proteases (Section **IIA**). Histamine acts through its various receptors to induce smooth muscle contraction or relaxation, enhanced permeability across vascular endothelial cells, and itching or pain by activating sensory neurons. These actions account for many, but not all, of the cardinal symptoms of acute allergic reactions. The proteases degrade endogenous and pathogenic proteins and thus contribute to innate immune responses (Section **VIB**) as well as tissue remodeling (Section **VID**). The lipid mediators are rapidly synthesized and include the arachidonyl-derived prostaglandins and leukotrienes (Section **IIB**). These compounds also contribute to allergic symptoms such as bronchial constriction, increased vascular permeability, and recruitment of granulocytes and macrophages to facilitate innate and adaptive immune responses. The subsequent production of a wide range of cytokines and chemokines (Section **IIC**) promotes not only the classic delayed reaction to allergenic stimuli but also to processes essential for adaptive immune responses (Th1 and Th2) and possibly immunosuppression (Section **VIC**) as shown. The figure is an updated version of Figure 4 from a previous publication.¹²