Molecular targets on mast cells and basophils for novel therapies

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Mast cells and basophils (MCs/Bs) play a crucial role in type I allergy, as well as in innate and adaptive immune responses. These cells mediate their actions through soluble mediators, some of which are targeted therapeutically by, for example, H1- and H2-antihistamines or cysteinyl leukotriene receptor antagonists. Recently, considerable progress has been made in developing new drugs that target additional MC/B mediators or receptors, such as serine proteinases, histamine 4-receptor, 5-lipoxygenase–activating protein, 15-lipoxygenase-1, prostaglandin D_2, and proinflammatory cytokines. Mediator production can be abrogated by the use of inhibitors directed against key intracellular enzymes, some of which have been used in clinical trials (eg, inhibitors of spleen tyrosine kinase, phosphatidylinositol 3-kinase, Bruton tyrosine kinase, and the protein tyrosine kinase KIT). Reduced MC/B function can also be achieved by enhancing Src homology 2 domain–containing inositol 5′ phosphatase 1 activity or by blocking sphingosine-1-phosphate. Therapeutic interventions in mast cell–associated diseases potentially include drugs that either block ion channels and adhesion molecules or antagonize antiapoptotic effects on B-cell lymphoma 2 family members. MCs/Bs express high-affinity IgE receptors, and blocking their interactions with IgE has been a prime goal in antiallergic therapy. Surface-activating receptors, such as CD48 and thymic stromal lymphopoietin receptors, as well as inhibitory receptors, such as CD300a, FcγRIIb, and endocannabinoid receptors, hold promising therapeutic possibilities based on preclinical studies. The inhibition of activating receptors might help prevent allergic reactions from developing, although most of the candidate drugs are not sufficiently cell specific. In this review recent advances in the development of novel therapeutics toward different molecules of MCs/Bs are presented. (J Allergy Clin Immunol 2014;134:530-44.)

Key words: *Mast cell, basophil, mediator, receptor, signaling protein, survival protein, drug, therapy*

Mast cells and basophils (MCs/Bs) have traditionally been associated with the induction of symptoms of type I type allergies, such as rhinitis, asthma, and urticaria, through the release of soluble proinflammatory mediators. However, this notion is an oversimplification given the growing evidence during the last 2 decades that both cell types can contribute to

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Supported by the COST Action BM1007 "Mast cells and Basophils: targets for innovative therapies." I.T.H. was supported, in part, by the Cancer Center of Eastern Finland and VTR funding of Kuopio University Hospital. F.L.-S.'s research is supported, in part, by grants from the Israel Science Foundation (grant 213/05); the MAARS (Microbes in Allergy and Autoimmunity Related to the Skin) EU 7th framework (grant no. HEALTH-F2-2011-261366); and the Aimwell Charitable Trust (London, United Kingdom). P.D. and I.P. were supported, in part, by project COST CZ LD12073 from Ministry of Education of the Czech Republic and grants 14-00703S, 14-09807S, and P302/12/G101 from the Czech Science foundation and by the Institute of Molecular Genetics ASCR (RVO 68378050). I.P. was supported in part by the Faculty of Science, Charles University, Prague. U.B is supported by the French National Research Agency (ANR-12-ISV3-0006-01), the Investissements d'Avenir programme ANR-11-IDEX-0005-02, Sorbonne Paris Cite, Laboratoire d'excellence INFLAMEX.

Disclosure of potential conflict of interest: I. T. Harvima has received travel support from the European Union COST action BM1007 and is employed by the University of Eastern Finland and Kuopio University Hospital. F. Levi-Schaffer has received research support from the Israel Science Foundation and the European Union FP7 Collaborative Project; has received travel support from the European Union COST action BM1007; has a patent for CD48 as a novel target for antiasthmatic and antiallergic therapy and as a marker for early prediction of allergy issued; has a patent for bispecific complexes for targeting cells involved in allergic-type reactions, compositions, and uses thereof issued; and has a patent on sialic acid–binding immunoglobulin-like lectin 7 and treatment of mast cell–related pathologies pending. P. Draber has received research support from the Ministry of Education of the Czech Republic, the Czech Science Foundation, and the Institute of Molecular Genetics ASCR and has received travel support from the European Union COST action BM1007. I. Polakovicova has received research support from the Ministry of Education of the Czech Republic, the Czech Science Foundation, and the Faculty of Science of Charles University and has received travel support from the European Union COST action BM1007. B. F. Gibbs has received travel support from the European Union COST action BM1007; is employed by the University of Kent; has received research support from Leverhulme Trust; and has received payment for lectures from the University of Virginia, Southampton, Kings College London, and ALK-Abelló. U. Blank has received research support from the French National Research Agency and the Investissements d'Avenir programme ANR-11-IDEX-0005-02, Sorbonne Paris Cite, Laboratoire d'excellence INFLAMEX and has received travel support from the European Union COST action BM1007. G. Nilsson has received research support from the Swedish Research Council and has received travel support from the European Union COST action BM1007. M. Maurer has received research support from Charit; has received travel support from the European Union COST action BM1007; has consultant arrangements from Almirall, Bayer, Biofrontera, FAES, Genentech, GlaxoSmithKline, Recordati, Novartis, Sanofi Aventis, Merck Sharp Dohme, Moxie, UCB, and Uriach; is employed by Charité–Universitätsmedizin Berlin; and has received research support from FAES, Genentech, Novartis, Merck Sharp Dohme, Moxie, UCB, and Uriach. S. Friedman declares no relevant conflicts of interest.

Received for publication December 20, 2013; revised February 24, 2014; accepted for publication March 7, 2014.

Available online April 24, 2014.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2014.03.007

Abbreviations used
BCL-2: B-cell lymphoma 2
BH: BCL-2 homology
Bs: Basophils
BTK: Bruton tyrosine kinase
CB: Endocannabinoid receptor
CRAC: Calcium release–activated calcium
cysLTR: Cysteinyl leukotriene receptor
DP: D-type prostanoid receptor
FLAP: 5-Lipoxygenase–activating protein
ITIM: Immunoreceptor tyrosine–based inhibitory motif
5-LO: 5-Lipoxygenase
15-LO-1: 15-Lipoxygenase-1
LT: Leukotriene
MC: Mast cell
MC/B: Mast cell and basophil
MMP: Matrix metalloproteinase
PGD_2: Prostaglandin D_2
PI3K: Phosphatidylinositol 3-kinase
SHIP-1: Src homology 2 domain-containing inositol 5′ phosphatase 1
Siglec: Sialic acid–binding immunoglobulin-like lectin
S1P: Sphingosine-1-phosphate
SPHK: Sphingosine kinase
SYK: Spleen tyrosine kinase
TRP: Transient receptor potential
TSLP: Thymic stromal lymphopoietin
TSLPR: Thymic stromal lymphopoietin receptor

inflammation, autoimmunity, chronic innate immune responses, and other conditions, as well as performing immunomodulatory roles.[1-3]

Two of the key soluble mediators released by MCs/Bs on activation by different stimuli are histamine and leukotrienes (LTs). Both are commonly targeted in clinical practice by various drugs, such as H1- and H2-antihistamines and LTC_4 synthesis inhibitors or receptor antagonists. Indeed, the treatment of different diseases or symptoms with these classes of drugs has generally been regarded as a success. However, there are numerous patients with MC/B-driven diseases who do not obtain sufficient relief of their symptoms, even after administration of high doses of the above drug classes. One of the reasons for this is that MCs/Bs release other preformed and *de novo*–synthesized mediators that also contribute to the pathogenesis of MC/B-mediated conditions.[1-3]

Approaches to improve the treatment of MC/B-driven conditions include the development of inhibitors of additional MC/B mediators and their receptors and of inhibitors of MC/B-activating receptors and signal transduction pathways. Recently, MCs/Bs have been shown to express inhibitory receptors that, on activation, are able to downregulate the stimulatory signaling derived from activating receptors. For example, FcγRIIB, CD300, endocannabinoid receptor (CB) 1, CD72, and sialic acid–binding immunoglobulin-like lectins (Siglecs) have been described on mast cells (MCs) and might be promising targets for therapy.[4] In addition, MC/B activation can be blocked by inhibitors that act on signaling pathways transduced from plasma membrane receptors to cytoplasmic effectors. However, most of the signaling pathways used by MCs/Bs are not found exclusively in these cells.[5,6]

A therapy for disease should target only those cells and molecules that are specifically involved in the pathogenesis of that particular disease. However, in patients with allergy, as in those with many other diseases, several different cell types are involved in causing symptoms, and therefore a number of potential targets exist. The problem of selectivity and trying to hit multiple targets simultaneously increases potential side effects and adverse drug reactions. Despite this, in allergic patients the main *primum movens* are the MCs,[1] but growing evidence indicates an important role for Bs as well.[2]

During the last decade, considerable progress has been made targeting soluble mediators released from MCs/Bs. In addition, promising target molecules have been discovered among cell-surface receptors and intracellular signaling or survival molecules. Therefore in this review we focus on these mediators, receptors, and signaling molecules of MCs/Bs as targets for pharmacotherapy, especially those that are close to clinical application.

SOLUBLE MEDIATORS AS TARGETS

Proteinases

β-Tryptase, a tetrameric serine proteinase, is the major protein within the secretory granules of MCs. However, Bs can contain a small amount of β-tryptase.[1,7] The pathophysiologic role of β-tryptase is not clear, but the enzyme has been associated with the promotion of inflammation and matrix remodeling.[1,8] An essential new proteolytic target of β-tryptase is the proteinase-activated receptor 2, which is expressed by different inflammatory cells.[1,8] Several synthetic inhibitors have been produced since the 1990s,[9,10] such as APC-366 and dibasic APC-2059, which have been used in clinical trials. In a randomized, double-blind crossover study of 16 atopic asthmatic patients, inhaled APC-366 significantly inhibited allergen-induced late asthmatic responses.[11] In an open-label phase 2 pilot study, subcutaneously injected APC-2059 displayed efficacy in the treatment of ulcerative colitis.[12] Nafamostat mesilate, a drug used in the therapy of disseminated intravascular coagulation and pancreatitis, is a further candidate for inhibiting tryptase because of its inhibitory potency toward this proteinase, although it is not specific.[13] Nevertheless, despite positive expectations in the 1990s, specific tryptase inhibitors have thus far not appeared on the market. Future therapeutic approaches to inhibit tryptase might include designing molecules that are able to displace tryptase from heparin, leading to dissociation of the tryptase tetramer into monomers with low catalytic activity.[14]

Chymase is a chymotrypsin-like serine proteinase stored in high quantities in the secretory granules of the MC_{TC} (tryptase$^+$, chymase$^+$) type of MCs.[8] Unlike tryptase, chymase can be inactivated by endogenous protease inhibitors, and therefore chymase is under the control of protease inhibitors in inflamed tissue.[15,16] If left uncontrolled by inhibitors, chymase is a potent enzyme that causes matrix destruction[8,16] and inflammation, as well as producing angiotensin II from angiotensin I, suggesting a role in hypertension and cardiac failure.[8,17] Several potent chymase inhibitors have been synthesized and tested in a variety of animal and *ex vivo* models with proven physiologic effect.[17,18] However, clinical studies with chymase inhibitors are still lacking. The secretory granules of MC_{TC} cells also contain another chymotrypsin-like serine proteinase, cathepsin G,[8] and several existing chymase inhibitors also inhibit cathepsin G to some

extent.[17] Because chymase and cathepsin G share many similar biological functions, it might be therapeutically useful to develop inhibitors that inactivate both enzymes simultaneously, such as RWJ-355871, which has shown efficacy in rat, mouse, and sheep models of lung or paw inflammation.[19]

Human MCs can be a source of matrix metalloproteinases (MMPs), especially MMP-1 and MMP-9.[20,21] The clinical trials performed thus far with MMP inhibitors have been rather disappointing, especially in patients with cancer, because of their adverse effects, low specificity, or both.[22] However, targeting chymase in therapy might prevent the activation of the latent forms of MMP-1 and MMP-9.[23,24] Additionally, targeting tryptase might prevent the activation of prostromelysin to stromelysin (MMP-3) and subsequent activation of MMP-1.[25]

Histamine and histamine receptors

Histamine, a preformed mediator in MCs/Bs, has long been proven to be a critical factor in the cause and therefore treatment of allergy. Histamine has 4 distinct G protein–coupled receptors, histamine receptors 1-4 (H1-4R). H1R, discovered in 1937 by Bovet and Staub, is the major histamine receptor in allergies, whereas H4R was discovered some 12 years ago and has not been studied extensively as a therapeutic target.[26] H1-antihistamines are inverse agonists and are currently the most used antiallergic drugs, such as in patients with urticaria, atopic dermatitis, allergic rhinitis, and conjunctivitis, as well as in asthmatic patients.

In addition to its effects on vascular endothelial cells, T cells, and other cells, histamine also has autocrine effects on MCs through H1R and H4R. It has recently been shown that a combination of antihistamines targeting H1R and H4R has synergistic therapeutic effects in a mouse model of chronic dermatitis.[27] At high doses, H1-antihistamines can also reduce MC functions, acting as MC stabilizers.[28-30]

H2R agonists have been shown to mimic the inhibitory effects of histamine on MCs activated by compound 48/80, actions that were reversed by an H2R blocker.[31] The H2R-mediated inhibitory actions of histamine seem to be more prominent in Bs than in MCs,[32-34] where the receptor has been shown to be involved in early suppression of the release of all known major mediator classes during venom-specific allergen immunotherapy.[35]

H3R and H4R share high sequence homology, and some pharmacologic agonists and antagonists affect both receptors. In Bs H3R does not seem to affect function.[36,37] Although H4R expression has been shown on mature human MCs/Bs,[38,39] thus far, there is no clear evidence for a role of this receptor in controlling mediator release. Nevertheless, several experimental models suggest that H4R can modulate the function of MCs, Bs, or both.[39-41] H4R antagonists/inverse agonists are plausible new drugs for treating allergic diseases,[42] even though contradictory results in experimental models of atopic dermatitis have recently been published.[43] Systemic treatments are currently being tested in clinical trials (reviewed by Salcedo et al[44]), although the research has been progressing rather slowly. Future therapeutic applications might include combinations with H1-antihistamines, such as in the treatment of allergic inflammation.

De novo–synthesized lipid mediators

LTC_4 is synthesized *de novo* in MCs/Bs from arachidonic acid through the consecutive action of 5-lipoxygenase (5-LO) and LTC_4 synthase, followed by conversion to LTD_4 and LTE_4.[45,46] LTC_4 and LTD_4 are potent bronchoconstrictors and play an important role in asthma through binding to cysteinyl leukotriene receptor (cysLTR) 1 and 2. Several specific cysLTR1 antagonists have been developed and are in clinical use, including zafirlukast, pranlukast, and montelukast.[45,46] Even though the stable product LTE_4 does not bind to traditional cysLTRs, it might cause clinical reactions in asthmatic patients by possibly binding to the purinergic $P2Y_{12}$ receptor and/or to another, yet uncharacterized LTE_4 receptor.[45,46]

The current cysLTR1 antagonists do not antagonize cysLTR2, the LTE_4 receptors, and/or the effects of LTB_4, with the latter binding to its receptors BLT1 and BLT2,[45,46] which might explain their variability in efficacy. However, this problem can be overcome by using an inhibitor of 5-LO, such as zileuton, which was introduced in the 1990s and has been used for the prevention and chronic treatment of asthma in the United Kingdom and United States.[45,46] A recent randomized head-to-head trial on chronic persistent asthma comparing the zileuton extended-release tablet with the montelukast tablet suggests that the zileuton extended-release tablet (2400 mg/d) is well tolerated and probably more efficacious than montelukast (10 mg/d).[47] Another strategy is to target the 5-lipoxygenase–activating protein (FLAP), a protein that facilitates the transfer of arachidonic acid to 5-LO.[45] In fact, several FLAP inhibitors have been developed and tested in clinical trials, although they have not yet reached the market.[45] In a recent study investigating the efficacy, safety, and pharmacodynamics of the new and potent FLAP inhibitor GSK2190915 in patients with mild asthma, results show that the drug is well tolerated and effective in inhibiting both the early and late responses to inhaled allergen.[48]

MCs in human skin and lung tissue express 15-lipoxygenase-1 (15-LO-1), an enzyme that produces substantial amounts of the arachidonic acid metabolite 15-ketoeicosatetraenoic acid, as well as smaller amounts of 15-hydroxyeicosatetraenoic acid, in IL-4–stimulated cord blood–derived human MCs.[49] This enzyme might play a role in chronic inflammation, atherosclerosis, diabetes, and carcinogenesis. Several potent inhibitors of the enzyme, such as PD146176, have been developed and shown to have efficacy in animal models.[50,51]

Prostaglandin D_2 (PGD_2) is another soluble lipid mediator produced *de novo* predominantly by MCs and in small amounts also by Bs.[52-55] The characterization of PGD_2 receptors, namely D-type prostanoid receptor (DP) 1 and 2 (also known as CRTH2) and the thromboxane receptor, has uncovered novel roles for PGD_2 in allergic inflammation given their expressions on endothelial and airway smooth muscle cells, as well as on eosinophils, T_H2 cells, and Bs.[53,54,56] PGD_2 induces bronchoconstriction through thromboxane receptors on airway smooth muscle cells, vasodilatation through DP1 receptors on endothelial cells, and activation of immune cells through DP2. These findings have promoted intense research on developing specific antagonists for these receptors, as well as dual DP1-DP2 antagonists, some of which have proceeded to clinical trials.[53,54,56] For example, the DP2 antagonist OC000459 has shown promising clinical effects in phase 2 studies in patients with rhinoconjunctivitis, asthma, and eosinophilic esophagitis.[57-59] In contrast, the dual DP1-DP2 antagonist AMG 853 was not effective at improving the symptoms of patients with moderate-to-severe asthma as an add-on to inhaled corticosteroid therapy.[60] Likewise, the results of a phase 2 clinical trial with the DP1 antagonist

laropiprant (MK-0524) in patients with asthma and allergic rhinitis were disappointing.[61] Another possibility is to specifically inhibit the formation of PGD_2 by designing an inhibitor of hematopoietic prostaglandin D synthase, as shown in experimental models of allergic rhinitis in guinea pigs,[62,63] although clinical trials are currently lacking. However, PGD_2 can display both proinflammatory and anti-inflammatory functions or even a protective role in infections,[53,54] attributes that need to be clarified in future studies.

Cytokines and chemokines

Both MCs and Bs synthesize and release a variety of cytokines and chemokines.[1,2,64] Even though these proinflammatory factors are not exclusively produced by these cells, drugs can be designed to specifically target different cytokines or chemokines secreted from MCs/Bs. TNF-α is one of the most relevant proinflammatory cytokines produced by MCs/Bs on activation,[1,65,66] and biological drugs (eg, infliximab, adalimumab, and etanercept) that target TNF-α are well established in the therapy of patients with psoriasis, rheumatoid arthritis, and other chronic inflammatory conditions. IL-6 is another proinflammatory cytokine that is produced by MCs/Bs and numerous other cell types.[64,67] Blocking the interaction between IL-6 and its receptor has been under clinical investigation, although most phase 2 and 3 clinical trials have been conducted with tocilizumab, a biological drug targeting the IL-6 receptor.[68] During recent years, the "T_H17" cytokine IL-17 has received considerable attention because of its key role in different inflammatory and autoimmune diseases. Recently, MCs were found to be the predominant cell type producing IL-17 in patients with inflammatory skin and joint diseases.[69,70] IL-17–targeted therapies are currently being investigated in phase 3 trials with secukinumab (a fully humanized anti–IL-17A $IgG_{1\kappa}$ mAb), ixekizumab (a humanized, hinge-modified anti–IL-17A IgG_4 mAb), and brodalumab (a fully humanized anti–IL-17RA receptor IgG_2 mAb) in patients with psoriasis, psoriatic arthritis, uveitis, and/or rheumatoid arthritis.[71] CXCL8/IL-8 is a chemokine that attracts neutrophils and is produced by different cell types, including MCs[72] and Bs (Gibbs et al, unpublished observations). Because of its plausible role in patients with diseases characterized by neutrophil accumulation, such as psoriasis and palmoplantar pustulosis, fully humanized anti–IL-8 mAbs have been produced and tested in clinical drug trials with efficacy.[73,74] MCs/Bs are also thought to play a key immunomodulatory role by releasing IL-4 and IL-13, which promote T_H2-associated allergies and certain autoimmune diseases.[2,75,76] IL-4 is a particularly important cytokine in this regard, and clinical trials are currently in progress to test the efficacy of neutralizing mAbs against this cytokine.[77] Even though the ability of isolated human MCs to generate these cytokines in relevant levels is not clear,[2,75] human Bs are important early sources of both IL-4 and IL-13.[78]

MCs/Bs are also known to release the angiogenic cytokine vascular endothelial growth factor A,[79] which is thought to be involved in tissue remodeling associated with chronic allergic inflammation (especially in asthma), as well as in tumor progression. This cytokine is usually generated by various leukocytes under hypoxic conditions that result in the stabilization of hypoxia-inducible factor 1α.[80-82] However, it remains to be determined whether anti–vascular endothelial growth factor approaches can actually reverse the pathology associated with chronic allergic inflammation.

NOVEL THERAPEUTICS THAT TARGET INTRACELLULAR SIGNALING AND SURVIVAL PATHWAYS

Activation of MCs/Bs can be blocked by inhibitors that act on signaling pathways transduced from plasma membrane receptors to cytoplasmic effectors. Most of the signaling pathways used by MCs/Bs are not found exclusively in these cells, and therefore it is a demanding task to find drugs specifically inhibiting the activation of MCs/Bs. Here we will focus on several cytoplasmic signaling proteins that have been targeted with pharmacologic inhibitors to suppress antigen-induced degranulation. Specifically, we will deal with spleen tyrosine kinase (SYK), phosphatidylinositol 3-kinases (PI3Ks), Src homology 2 domain-containing inositol 5′ phosphatase 1 (SHIP-1), Bruton tyrosine kinase (BTK), the protein tyrosine kinase KIT, and sphingosine kinases (SPHKs).

SYK

The cytosolic nonreceptor protein tyrosine kinase SYK is recruited to FcεRI after tyrosine phosphorylation of its γ chain immunoreceptor tyrosine–based activation motifs by the Src family kinase LYN. SYK is involved in the tyrosine phosphorylation of numerous substrates, degranulation, and production and secretion of LTC_4 and cytokines after FcεRI triggering.[83] Targeting SYK is desirable because of its role in several diseases, including asthma, allergic rhinitis, and rheumatoid arthritis.[84] There are several SYK inhibitors that have been tested in clinical trials. Fostamatinib (also called R-788) is a prodrug of the active compound tamatinib (R-406).[85] Fostamatinib passed the phase 2 clinical trial for treatment of patients with rheumatoid arthritis.[86] However, the phase 3 clinical trials investigating fostamatinib as an oral treatment for rheumatoid arthritis have recently been terminated. Another SYK inhibitor, PRT062607 (P505-15), seems to be more selective for SYK, safer, and better tolerated than other compounds in development. PRT062607 reduced inflammation in a dose-dependent manner in several preclinical *in vivo* models,[87] but a phase 2 clinical trial for the treatment of rheumatoid arthritis has been withdrawn. R343, an inhaled SYK inhibitor, was tested as a potential therapeutic drug for patients with allergic asthma but also failed in a recently completed phase 2 clinical study. Another SYK inhibitor unsuccessfully tested in a phase 2 study is the compound R112, which was used to treat allergic rhinitis.[88,89]

PI3Ks

PI3Ks are enzymes involved in catalysis of ATP-dependent phosphorylation of phosphoinositides and generation of the lipid-based second messenger phosphatidylinositol 3,4,5-trisphosphate (PI[3,4,5]P3) from phosphatidylinositol 4,5-bisphosphate (PI[4,5]P2).[90] This enzymatic step is crucial for the development of inflammatory responses.[91] Several compounds inhibiting the class I PI3K isoforms γ and δ have been identified as possible targets in patients with inflammatory diseases. One of them, IC87114, is a highly selective inhibitor of PI3Kδ with potential for treatment of rheumatoid arthritis and allergic asthma.[92,93]

CAL-101 (GS1101), a chemical derivative of IC87114, has increased potency and inhibits the δ isoform of PI3K with 40- to 300-fold higher selectivity than other class I PI3K isoforms.[94] Oral inhibitors of the P13Kδ isoform, CAL-101 and CAL-263, completed phase 1 clinical trials for the treatment of allergic rhinitis.[95,96] Currently, a potent oral inhibitor of both isoforms of PI3K, δ and γ, IPI-145, is in phase 2 clinical trials for the treatment of allergic asthma and rheumatoid arthritis.[97]

SHIP-1

Activation of MCs/Bs can be also inhibited by activation of enzymes involved in termination of the signaling pathways. One such enzyme is the lipid phosphatase SHIP-1, which dephosphorylates the inositol ring of PI(3,4,5)P3 to yield phosphatidylinositol 3,4-bisphosphate (PI[3,4]P2). Reduction of PI(3,4,5)P3 levels leads to inhibition of calcium influx, followed by changes in gene transcription and downregulated production of cytokines.[98] It has been shown that SHIP-1–deficient mice exhibit progressive inflammation[99] and that enhanced activity of SHIP-1 suppresses MC activation.[100] In accordance with these findings, the small molecule AQX-1125, which has been shown to increase the catalytic activity of human SHIP-1, inhibited activation of MCs and chemotaxis of leukocytes. Furthermore, AQX-1125 decreased passive cutaneous anaphylaxis, LPS-mediated pulmonary neutrophilic infiltration, and ovalbumin-mediated airway inflammation.[101,102] This highly active and selective small-molecule allosteric activator of SHIP1 demonstrated a favorable safety profile and anti-inflammatory activity in phase 2 clinical studies for the treatment of mild and moderate asthma and is now being investigated in a phase 2 clinical trial for the treatment of chronic obstructive pulmonary disease.

BTK

An important target downstream of SYK is the Tec family tyrosine kinase BTK, which has been shown to play important roles in antigen-activated MCs/Bs.[103] BTK is selectively inhibited by ibrutinib (PCI-32765), which binds covalently to the noncatalytic Cys-481 residue in the active site of BTK and thereby inhibits its phosphorylation on Tyr-223. Structural alignments revealed that only 10 kinases have a Cys at this position, contributing to significant selectivity of the drug.[104] Ibrutinib has been shown to block MC degranulation[105] and inhibit IgE-mediated activation of human Bs[106] and appears to have therapeutic potential for arthritis treatment.[107] AVL-292/CC-292 is a novel, orally available, irreversible inhibitor of BTK with clinical potential for treatment of patients with rheumatoid arthritis and some other autoimmune diseases.[108] AVL-292/CC-292 is in clinical development and has successfully completed 2 phase 1a clinical studies.[109]

KIT

KIT is an MC surface receptor with tyrosine kinase activity. Binding of stem cell factor, a KIT ligand, to its receptor leads to MC activation, proliferation, differentiation, and survival. There are several small inhibitors of KIT that have been considered for treatment of asthma, anaphylaxis, or systemic mastocytosis. Patients with mastocytosis often carry a gain-of-function mutation of KIT (D816V), and most KIT inhibitors cannot sufficiently block the mutated KIT.[110] Imatinib and nilotinib are 2 compounds with inhibitory effects on the KIT-mediated MC response, but they are not suitable for the treatment of patients with mastocytosis carrying mutated KIT (D816V).[111,112] Imatinib has been reported to be efficient in the treatment of arthritis and mastocytosis,[110,113-115] whereas nilotinib has recently been shown to have an antiallergic effect on MC-mediated anaphylaxis.[116] Dasatinib is a drug that inhibits not only KIT but also several other tyrosine kinases, including BTK. Dasatinib has been shown to inhibit FcεRI-induced histamine release in Bs and allergen-induced release of histamine in sensitized subjects.[117] Masitinib is a potent tyrosine kinase inhibitor that seems to be promising for the treatment of asthma and systemic or cutaneous mastocytosis.[118,119] Its combined inhibition of KIT and LYN/FYN kinases makes it particularly efficient in controlling MC activity. Clinical phase 2 studies focused on mastocytosis or corticosteroid-dependent asthma have shown sustainable improvement and acceptable tolerability for long-term treatment.[118,119] Midostaurin inhibits several tyrosine kinases, including KIT, and *in vitro* studies have shown its efficacy also against the D816V mutation. First results from a phase 2 clinical trial showed efficacy in patients with this mutation.[120] However, none of the above-mentioned inhibitors is specific for KIT; they also inhibit platelet-derived growth factor receptors and some other proteins with tyrosine kinase activity. Imatinib, nilotinib, and dasatinib also inhibit the protein tyrosine kinase BCR/ABL and are therefore used mainly in the treatment of chronic myeloid leukemia.[110]

SPHKs

Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid mediator produced and secreted by activated MCs and plays an important role in allergic reactions within the respiratory system.[121] S1P levels have been found to be increased in the airways of asthmatic patients but not healthy control subjects after antigen challenge.[122] There are 2 kinases responsible for the production of S1P, SPHK1, and SPHK2. SPHK1, but not SPHK2, has been shown to play a critical role in antigen-induced degranulation.[123] Targeting S1P through inhibition of SPHKs, use of S1P-neutralizing antibodies, or administration of S1P receptor antagonists are possible strategies to treat allergic disorders, anaphylactic reactions, or asthma. Several specific S1P receptor agonists and antagonists have recently been described.[124] FTY720 (fingolimod) is phosphorylated by SPHK2 to function as an agonist for S1P receptors.[125] FTY720 promotes endocytosis and degradation of S1P receptors, thereby resulting in functional antagonistic effects. It has been shown to be highly effective in reducing the severity of autoimmune diseases in several animal models and has recently been approved as an oral treatment for relapsing forms of multiple sclerosis.[126,127]

Ion channels

Calcium ions are essential for MC/B activation and degranulation. Calcium release–activated calcium (CRAC) channels are important for the influx of extracellular Ca^{2+} into the cytoplasm and have been considered potential targets for the treatment of diseases caused by activation of MCs/Bs. Experiments with MCs derived from mice deficient in Orai1 or stromal interaction molecule 1, the proteins forming the CRAC channel pores, or functioning as Ca^{2+} sensors in the endoplasmic reticulum and interacting with Orai1, respectively, showed an important role of

CRAC channels in degranulation, cytokine secretion, and LT production *in vitro*. These structures are also involved as positive regulators of IgE-mediated immediate-phase anaphylactic responses *in vivo*.[128,129] Several compounds blocking CRAC channels have been described, including 2-aminophenylborane and SFK96365. The channels can be also blocked by low concentrations of trivalent cations Gd^{3+}[130] or by Synta compound 66, which do not interfere with potassium channels or ATPase pumps.[131] However, these compounds are not specific for MCs.[132] To solve this problem, it has been suggested that CRAC channels can be inhibited more specifically by combining low concentrations of CRAC channel inhibitors and an LT receptor antagonist.[133] Further studies showed that the 3,5-bis(trifluoromethyl) pyrazole derivate BTP2 (YM-58483) blocks CRAC channels, facilitates the activity of the nonselective transient receptor potential (TRP) M4 channel,[134] and inhibits the activity of TRPC3 and TRPC5.[135] BTP2 exhibited inhibitory effects in allergy asthma models in rats and guinea pigs.[136] Membrane potential and calcium signaling in MCs and other cells is also regulated by the calcium-activated potassium channel KCa3.1. A potent blocker of the human KCa3.1 channel ICA-17043 (senicapoc, PF-05416266) showed good pharmacokinetic properties and was well tolerated in human subjects. However, clinical phase 2 trials did not show any improvement after administration of ICA-17043 in asthmatic patients.[137]

Regulation of survival/apoptosis

MCs express proteins of the B-cell lymphoma 2 (BCL-2) family, which are involved in regulation of cell apoptosis. The family consists of proteins with proapoptotic and antiapoptotic functions, and balance between these proteins determines cellular fate through protein-protein interactions.[138] The proapoptotic effector proteins, including BAX and BAK, are crucial for the induction of permeabilization of the outer mitochondrial membrane and irreversible onset of apoptotic cell death. The antiapoptotic proteins (BCL-2, BCL-XL, BFL-1/A1, MCL-1, and BCL-W among others) inhibit apoptosis through direct interactions with effector proteins.[139] Members of the BCL-2 family share 1 or more of the 4 characteristic domains of homology named BCL-2 homology (BH) domains. BH3-only proteins, such as BIM, PUMA, BAD, and NOXA, are capable of inducing apoptosis by binding to and neutralizing the antiapoptotic proteins. Activation of human MCs through FcεRI leads to upregulation of the antiapoptotic BCL-2 family members MCL-1 and BFL-1.[140] Further studies showed that BFL-1 is a major effector in activation-induced human MC survival.[141] In recent years, several small molecular compounds mimicking the BH3 domain have been developed in the frame of anticancer research. These included ABT-737, TW-37, and ABT-263 (navitoclax).[142-145] Experiments in mice showed that intraperitoneal administration of ABT-737 resulted in selective abolishment of MCs in the peritoneum. Furthermore, *ex vivo* treatment of human skin biopsy specimens with ABT-737 demonstrated increased MC apoptosis.[146] Recent experiments with the novel BH3 mimetic obatoclax (GX015-070) showed that this drug induces growth arrest in primary human MCs and MC lines and exerts synergistic antineoplastic effects on MCs when combined with other targeted drugs, such as dasatinib.[147] The combined data suggest that BH3-only mimetic compounds are good candidate drugs for treatment of MC-associated diseases, such as mastocytosis, allergy, asthma, and chronic inflammatory diseases.

SURFACE RECEPTORS AS TARGETS

Targeting surface inhibitory and activating receptors on different cell types is a valid means of therapeutic intervention. In allergic patients considerable efforts are being made to control the activity of effector cells through their functional receptors. Blocking FcεRI is already being used as a treatment and is the basis of many ongoing studies. However, there are also several less developed yet promising new candidate receptors as targets for treatment of MC/B-mediated diseases.

Inhibitory receptors

Among the inhibitory receptors, we decided to focus on 3 receptors that have been shown to be expressed on MCs/Bs with promising preclinical results: CD300a, FcγRIIB, and Siglec-8. CD300a contains 4 immunoreceptor tyrosine–based inhibitory motifs (ITIMs) in its cytoplasmic tail and belongs to the immunoglobulin superfamily. Although CD300a is not expressed only on MCs,[148] eosinophils,[149] and Bs,[150,151] selective targeting of this receptor has been shown to be feasible for treatment of allergies and other diseases mediated by MCs/Bs.[152]

FcγRIIB is one of the most studied IgG receptors, which was found to be expressed on MCs (except from human skin[153]) and Bs both of human and mouse origin[154] and shown to negatively regulate the activation of these cells through ITIM-mediated signaling after allergen binding to IgE.[155,156]

Siglec-8 is the most characterized receptor among the Siglecs that are expressed on MCs and inhibits their activation through ITIMs located in its intracellular domain. Siglec-8 is a promising candidate for treating allergy because it was shown to be functional not only on human MCs but also on eosinophils and Bs.[157-159]

We also briefly introduce the cannabinoid receptors, which in recent years were shown to play a role in the regulation of the immune system in general and of MCs in particular. Although the mechanism for this regulation is not fully understood, growing evidence suggests that these receptors probably inhibit MC activation.[160]

CD300a receptor

The inhibitory function of CD300a was demonstrated in several cell types, including human cord blood–derived mast cells, in which coaggregation with IgE-bound FcεRI led to the inhibition of IgE-induced β-hexosaminidase, tryptase, and IL-4 release, as well as a reduction in stem cell factor–mediated survival.[148] In addition, a bispecific anti-KIT/anti-CD300a antibody abolishes KIT-mediated cord blood–derived mast cell differentiation, survival, and IgE-dependent activation, as well as inhibiting mediator release in the malignant human MC line (HMC-1), where KIT is constitutively activated.[148] The CD300a murine orthologue Lmir-1 was also shown to be an inhibitory receptor in murine bone marrow–derived MCs, and the bispecific anti-IgE/anti-CD300a antibody was demonstrated to abrogate allergic peritonitis, passive cutaneous anaphylaxis, and acute asthma models in mice.[152] Another bispecific antibody fragment linking CD300a to CCR3 (which is specific for human MCs and eosinophils) was shown to affect eosinophil signaling and function *in vivo*, reducing the levels of proinflammatory mediators in bronchoalveolar lavage fluid and MC mediator release. It also reversed lung inflammation in a murine model of chronic

established asthma.[161] CD300a-deficient mice showed improved bacterial clearance in the peritoneal cavity and longer survival, which supports a role for CD300a in regulating MC-mediated inflammatory responses to microbial infections.[162]

Human Bs also express CD300a in the peripheral blood of both healthy and allergic subjects. The basal expression of CD300a from patients with birch pollen allergy is significantly lower than that in healthy control subjects.[150] Bs preincubated with anti-human CD300a/c mAbs displayed reduced IgE-mediated CD63 expression, indicating decreased activation.[150] Moreover, CD300a was shown to be rapidly upregulated after IgE-dependent triggering, indicating that Bs might express intracellular pools of this receptor, as was found in eosinophils,[163] and cross-linking this receptor suppressed anaphylactic degranulation in these cells.[150]

It was recently described that phosphatidylethanolamine and phosphatidylserine act as ligands for CD300a on dead cells,[164] which is interesting for its potential role in the removal of apoptotic cells[162] and might be highly relevant in the resolution phase of allergic inflammation.

It is clear that the inhibitory receptor CD300a, as expressed by MCs/Bs and eosinophils, might display therapeutic antiallergic potential, particularly when targeted through bispecific antibodies to the cells of interest.

IgG receptors

It has long been known that MCs/Bs not only express IgE but also IgG receptors, which consist of both excitatory and inhibitory receptor types. In mice allergen-IgG immune complexes cause systemic anaphylaxis and are dependent on Bs activation, as well as the release of platelet-activating factor from these cells.[165] However, in human subjects Bs cannot be activated through IgG receptors[166,167] unlike their MC counterparts, which have been shown to express FcγRI, which is induced by IFN-γ.[168] Cassard et al[154] recently demonstrated that the differential responses of mouse and human Bs to IgG-mediated triggering is because of the more robust responses of FcγRIIIA on mouse Bs than FcγRIIA, which is expressed on human Bs.

A human IgG-IgE Fc fusion protein (GE2), which co–cross-linked FcεRI with FcγRII receptors, inhibited histamine release from human Bs and lung tissue fragments, as well as reducing tissue reactivity to allergen stimulation in several *in vivo* models.[169-171] Recently, several studies have been carried out to enhance FcγRIIB affinity by designing fusion proteins that inhibit activation in a more specific and efficient way, regardless of the degree of activation. One recent study showed that coengagement of FcεRI with FcγRIIB, using a dual-targeting tandem IgE–IgG Fc domain biologic with 100-fold enhanced affinity compared with native IgG_1 Fc, resulted in marked suppression of MC degranulation.[155] Another fusion protein (Fcγ-Der f2) was shown to prevent and treat allergic inflammation in a murine model of dust mite–induced asthma, suggesting that chimeric human Fcγ allergen proteins can be used as an immunotherapy tool.[172]

Siglec-8

Siglec-8 can undergo alternative splicing to yield a "short form" and a "long form" containing 2 tyrosine cytoplasmic motifs.[173,174] In various human blood samples Siglec-8 was shown to be expressed at normal levels on Bs from patients with chronic eosinophilic and chronic myelogenous leukemia, on normal murine bone marrow MCs, and on MCs from patients with indolent systemic mastocytosis.[175] Siglec-8 is expressed by several MC lines, such as LAD2, LUVA, and HMC1.2.[175,176] In human MCs generated from $CD34^+$ precursors, Siglec-8 engagement did not induce apoptosis[177] compared with its apoptotic function on eosinophils.[178,179] However, preincubation with Siglec-8 mAb significantly inhibited FcεRI-dependent histamine and PGD_2 release from purified MCs and the FcεRI-dependent Ca^{2+} flux and release of β-hexosaminidase of MCs. It remains to be seen whether the synthetic Siglec-8 ligand polymeric 6′-sulfated sialyl Lewis X, as reported by Hudson et al,[180] would be more effective at causing MC/B apoptosis than Siglec-8 mAb. Siglec-8–mediated inhibition of MC degranulation and its apoptotic effects on eosinophils should be considered in concert when developing new therapies for MC- and eosinophil-related disorders, such as asthma (the Siglec-8 apoptotic function on human eosinophils was recently broadly reviewed by Farid et al).[181]

Siglec-F, which is the orthologue for Siglec-8 in mice, is expressed on a wider range of cells than Siglec-8,[182-184] although not on mouse MCs, and its function on these cells is not clear. Stimulation with IL-4 or IL-13 caused an increase in Siglec-F-Fc binding to airway epithelium *in vivo* and *in vitro*.[185,186] Engagement of Siglec-8 with antibodies or glycan ligands used as a cell-directed therapy can specifically inhibit or deplete MCs, eosinophils, and Bs and provide specific targets for treatment in MC-related diseases.

CBs

Two G protein–coupled CBs, CB1 and CB2, have been discovered thus far, which are targeted by 2 endogenous ligands and many more natural and synthetic exogenous compounds that can bind and activate them in either a specific or nonspecific manner. Endocannabinoids are being used already as therapeutic targets in the treatment of anxiety, obesity, movement disorders, and glaucoma,[187] and growing evidence supports their role in health and diseases of the immune system as well.

CB2 was shown to be expressed on cells of the immune system 2 decades ago, and recent studies support an important regulatory role of both CB2 and CB1 regarding allergy and MC-driven diseases, although the latter is found predominantly on cells from the central nervous system.[188] CB1 is expressed constitutively on T lymphocytes, which can be upregulated by cannabinoid stimulation through IL-4 and is involved in promoting a T_H2 phenotype.[189,190]

Regarding specific studies involving MCs and allergy, CB1 was shown to be expressed on human mucosal MCs (from serum-free nasal polyp organ culture model)[191] and on the connective tissue sheath MCs of human hair follicles.[192] In the latter it was demonstrated that blocking this receptor increased both MC degranulation and cell numbers without affecting MC proliferation *in situ*.[192] CB1 and CB2 were shown to be coexpressed and function through different pathways in the MC line RBL2H3.[193]

In rats there are controversial data. One group found that degranulation of resident MCs induced by substance P was fully abrogated by the endocannabinoid agonists anandamide and palmitoylethanolamide in the ear pinna.[194] Peritoneal MCs were shown to express both CB2 mRNA and protein,[195] although other groups were not able to confirm these observations.[160]

In addition, a selective CB2 agonist was shown to reduce MC-dependent edema in response to compound 48/80 in the mouse ear pinnae, and cannabidiol was shown to inhibit collagen-induced arthritis in mice.[196]

In guinea pigs the endogenous ligand 2-arachidonoylglycerol was shown to significantly reduce the release of histamine from MCs, an effect that was then reversed by a selective CB2 antagonist but not by an antagonist for CB1.[197]

To date, most of the data obtained in human studies indicate an inhibitory effect of endocannabinoids on MC function both directly through CB2 and indirectly through CB1. However, research in the field of allergy and endocannabinoids is still evolving, and along with some controversial animal studies, it is clear that further investigations are needed to reveal the underlying mechanisms of CB involvement in the treatment of allergic conditions.

ACTIVATING RECEPTORS AS TARGETS FOR NOVEL THERAPIES

FcεRI is the quintessential activating receptor expressed on MCs/Bs, and it plays a crucial role in the initiation of allergic reactions and chronic allergic inflammation, such as in asthmatic patients, by launching the rapid release of preformed and *de novo*–synthesized mediators. Therefore targeting this receptor provides an effective way for treating allergy and allergic inflammation. However, inhibition of other activating surface receptors is another way to target the proallergic and anti-inflammatory functions of MCs/Bs in the treatment of allergic diseases. Here we introduce activating receptors for which promising results have been shown both *in vitro* and *in vivo* for regulating MCs/Bs in allergy-driven conditions.

CD48 is a CD2-like molecule expressed on the surfaces of hematopoietic cells, including MCs/Bs (reviewed by Elishmereni and Levi-Schaffer[198]). This 40-kDa glycosyl-phosphatidyl inositol–anchored protein also has a soluble form that is generated by cleavage on cell activation. Stimulated CD48 associates to the kinase LCK and leads to tyrosine phosphorylation.[198]

The thymic stromal lymphopoietin receptor (TSLPR) is involved in promoting T_H2-type immune responses, such as the release of proallergic and inflammatory cytokines from MCs (reviewed by Migalovich-Sheikhet et al[4]), and supporting T_H2 cytokine responses of murine Bs during helminth infection.[199]

CD48

CD48, which is expressed on human MCs, was shown to bind to both gram-negative and gram-positive bacteria, leading to the release of prestored mediators and proinflammatory cytokines, including TNF-α.[200-204] The physical interaction of CD48 expressed on MCs with the human high-affinity ligand 2B4 on eosinophils plays an important role in allergic inflammation by facilitating the formation of an allergic effector unit between the 2 cells.[205] CD48-2B4 binding induces the degranulation of MCs and increases eosinophil survival and activation.[205] Interestingly, Bs and eosinophils both express 2B4, but it is unknown whether the functions of Bs are affected by CD48-2B4. CD48 is overexpressed in murine asthma models, where it serves as a signature gene in this condition.[206] Treatment with a neutralizing CD48-specific antibody was shown to markedly inhibit lung inflammation in these models.[207]

TSLPR

Thymic stromal lymphopoietin (TSLP), the ligand for TSLPR, is an IL-7–like cytokine that was shown to be expressed on a variety of hematopoietic cell lineages, including MCs/Bs, B cells, T cells, eosinophils, and dendritic cells.[208-211] TSLP plays a significant role in the initiation of T_H2 responses.[212] It is highly expressed at the interfaces of the body and the environment and can directly activate human MCs.[208] TSLPR has a low affinity to TSLP, but together with IL-7Ra, it triggers signaling.[213] TSLPR and IL-7Ra chain expressions were demonstrated on MC progenitors and different cell lines.[208,214,215]

There is an increased expression of TSLP in the inflamed tissues of patients with allergic rhinitis, atopic dermatitis, and asthma,[212,216] in whom MCs play an important role in TSLP production.[215] MC activation by TSLP reportedly increased the production of chemokines and cytokines by MCs but did not affect MC survival or proliferation.[217] Therefore TSLPR might be a promising candidate for antiallergic intervention. Indeed, Zhang et al[218] recently reported that soluble TSLPR immunoglobulin prevents airway inflammation by modulating dendritic cell function, and therefore this might be a viable strategy for treating asthma.

FcεRI

Activation of FcεRI on MCs/Bs by allergens results in the explosive release of mediators that are preformed in cytoplasmic granules. This is rapidly followed by the synthesis and release of newly synthesized mediators from cellular lipid components and, after the activation of specific genes, various cytokines, chemokines, and growth factors. Increasing evidence also shows an important role for FcεRI in tissue responses associated with chronic allergic inflammation and asthma.[219] Hence interfering with the activity of this receptor has been a prime goal for many years in the treatment of allergies.

FcεRI is a tetrameric structure composed of an IgE-binding α subunit and a single 4-transmembrane–containing β chain, as well as a disulfide-linked dimer of γ chains.[220] Both β and γ subunits are implicated in signal transduction.[221] The interaction of IgE with its receptor has been characterized extensively, and the tridimensional structure of this interaction was solved at the turn of this century.[222] The IgE monomer binds to FcεRI with 1:1 stoichiometry. The interaction is characterized by a slow dissociation rate ($k_{off} < 10^{-5}\ s^{-1}$), accounting, to a large extent, for the high affinity of the interaction.[223] As a consequence, any treatment interfering with IgE binding will not be effective immediately but requires considerable time, as has been observed in a rat model.[224]

Although under development,[225] thus far, no low-molecular-weight compound exists that can interfere with IgE binding. Likewise, inhibitors of signal transduction, although effective, do not show a high degree of specificity (see above). The only specific inhibitor in clinical use is the humanized mAb omalizumab (Xolair), which blocks the interaction of IgE with FcεRI by targeting IgE at a site that overlaps with receptor binding and thus by itself does not have any activating effect itself. This antibody has been approved for the treatment of moderate and severe asthma with proven efficacy and safety.[226] The major effect of treatment is the reduction of plasma IgE levels, as well as FcεRI expressions on MCs/Bs. Other effects, such as downregulation of IgE class-switching in B cells, might also contribute to its

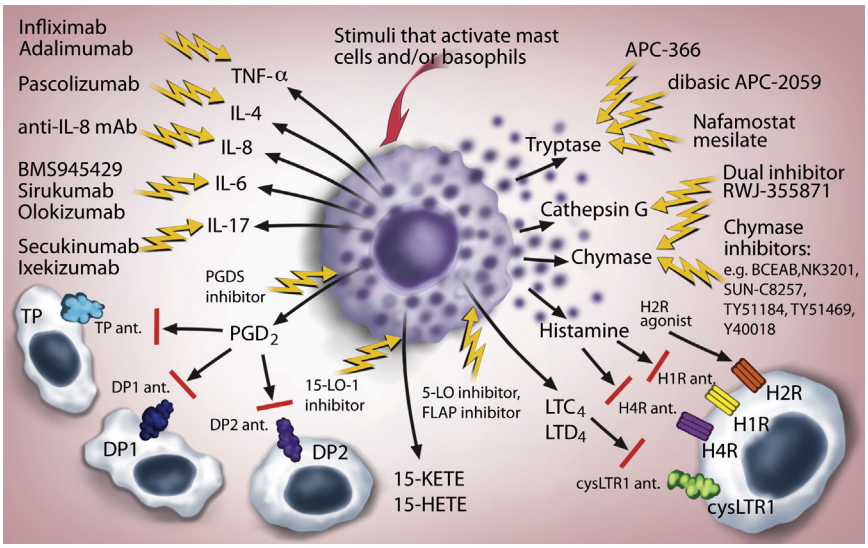

FIG 1. Soluble mediators of MCs, Bs, or both as targets for novel therapy. The effects of mediators stored in the secretory granules or produced *de novo* on cell activation can be prevented by drugs targeting tryptase, chymase, and/or cathepsin G by drugs targeting 5-LO, FLAP, 15-LO-1 or prostaglandin D synthase *(PGDS)*; by mAbs targeting proinflammatory cytokines; or by specific receptor antagonists. *TP*, Thromboxane receptor.

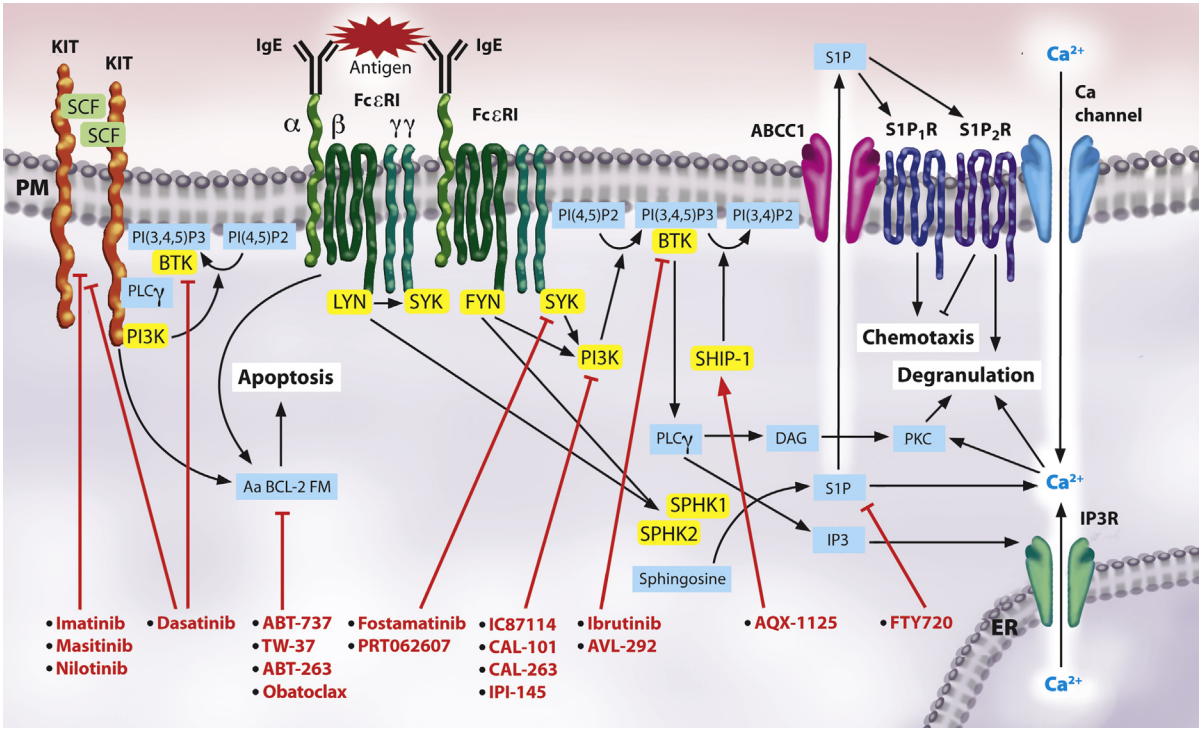

FIG 2. Intracellular signaling pathways of MCs, Bs, or both as targets for novel therapy. Antigen-aggregated IgE-FcεRI complexes or stem cell factor (SCF)–activated KIT initiate signaling pathways leading to degranulation, chemotaxis, and/or apoptosis depending on the signaling pathway triggered. Some of the proteins and other effectors executing these processes (in *yellow* and *blue boxes*) can be inhibited or potentiated by various drugs (in *red*), as described in the text. *Aa BCL-2 FM*, Antiapoptotic BCL-2 family members; *ER*, endoplasmic reticulum; *IP3*, inositol triphosphate; *IP3R*, inositol triphosphate receptor; *PKC*, protein kinase C; *PLC*, phospholipase C; *PM*, plasma membrane.

efficacy.[227] A recent phase 3 clinical trial has been completed, showing efficacy in patients with moderate-to-severe chronic idiopathic urticaria.[228] It has also been shown to be beneficial in food allergies,[229] atopic dermatitis,[230] and persistent allergic rhinitis,[231] as well as in some patients with idiopathic anaphylaxis and MC disorders.[232] However, the high treatment costs limit its

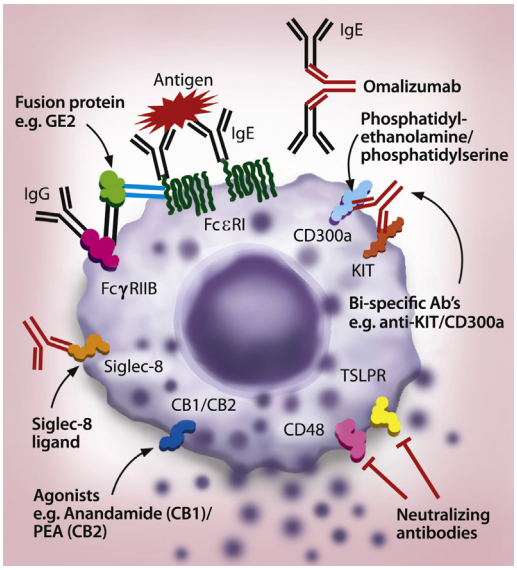

FIG 3. Novel surface receptors that alter IgE-dependent mediator release in MCs, Bs, or both. Stimulation of inhibitory receptors, such as CB1, CD300a, FcγRIIB, and Siglec-8, or blockade of surface activating receptors, such as CD48 and TSLPR, could potentially serve as targets for future allergy therapy. *PEA*, Palmitoylethanolamide.

use.[219] Much of the future will depend on the successful development of small molecular compounds that could further reduce treatment costs at a similar efficacy.

CONCLUSIONS

MCs/Bs generate a highly diverse number of mediators that perform crucial roles in the induction of symptoms and the pathogenesis of many diseases, primarily allergic and other inflammatory conditions. Indeed, it is increasingly apparent that MCs/Bs are capable of generating far more mediator types than previously appreciated. In addition to traditional antihistamines and LTC_4 blockers, there has been significant progress in the design of new candidate drugs that target MC/B mediators to a varying extent and specificity (Fig 1 and see Table E1 in this article's Online Repository at www.jacionline.org). These include inhibitors of serine proteinases, H4-antihistamines, FLAP inhibitors, inhibitors of 15-LO-1 and PGD synthase, and PGD_2 receptor antagonists. Furthermore, new biological agents directed against cytokines released by MCs/Bs might significantly reduce their ability to support inflammatory responses, as well as underlying T_H2 immunity.

Numerous inhibitors have been developed against individual components of signaling pathways that are involved in the activation and degranulation of MCs/Bs (Fig 2 and see Table E2 in this article's Online Repository at www.jacionline.org). These inhibitors are very useful in the treatment of various diseases, including allergy and asthma, and their usefulness could be further increased when used in combination with other drugs, gene-targeting techniques, or both. However, enzymes involved in the activation of MCs/Bs are not exclusively expressed in these cells, and therefore local rather than systemic applications could be preferable in many cases. Importantly, MCs/Bs are involved not only in undesirable hypersensitivity reactions but also in innate and acquired immunity; this should be taken into account when drugs that limit their functions are used for therapeutic purposes. It can be anticipated that the best therapeutic results will be obtained with multicomponent drugs that inhibit certain proinflammatory pathways and at the same time enhance the activity of enzymes involved in the termination of signaling pathways.

MCs/Bs express FcεRI, which is the traditional receptor responsible for the release of most of the proinflammatory mediators from these cells and is the prime target in therapeutics (Fig 3 and see Table E3 in this article's Online Repository at www.jacionline.org). However, there is growing evidence that MCs/Bs also express a variety of surface receptors that can either potentiate or limit the effects of FcεRI through several mechanisms (Fig 3). Surface-activating receptors, such as CD48 and TSLPR, and inhibitory receptors, such as CD300a, FcγRIIb, Siglec-8, and the CBs, provide promising possibilities in therapeutics. The direct or indirect blockade of FcεRI-mediated signaling might help prevent allergic reactions from developing and is a promising approach for treating allergies and other MC/B-driven diseases.

Finally, MCs interact with several cell types, including eosinophils, fibroblasts, airway smooth muscle cells, and neuronal cells. Under certain conditions, these interactions lead to increased MC survival, proliferation, activation, and secretion of proinflammatory mediators.[233,234] For example, interactions between human lung MCs and human airway smooth muscle cells and lung fibroblasts are mediated, in part, through cell adhesion molecule 1.[235-237] Recent studies in mice showed that the increased expression of cell adhesion molecule 1 causes enhanced nerve-MC interactions in a hapten-induced atopic dermatitis model.[238] MCs also express various receptors for chemoattractants that direct their migration into target tissues.[239] Thus cell adhesion molecules and chemoattractant receptors are potential therapeutic targets in diseases caused by aberrant localization of MCs in target tissues, their interactions with other cell types, or both.

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