Current perspectives

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;■■■:■■■-■■■.)

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

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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

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 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 cross-over 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