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Title

Mast cell and eosinophil surface receptors as targets for anti-allergic therapy

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Abstract

Allergy is the host immune response towards harmless substances, called allergens. Allergic diseases comprise allergic asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, and food allergy. While some drugs counteract the symptoms and the inflammation arising from allergy, no completely effective and acceptable side effect free drug has been developed as yet. Moreover, severe asthma and atopic dermatitis are classified as unmet clinical needs. Mast cells and eosinophils are the main effector cells of the allergic response and thus, must be the first cells targeted to impede the allergic inflammation symptoms and evolution. The presence on mast cells and eosinophils of several surface receptors with either activating or inhibitory functions indicates the possibility of their pharmacological targeting. This review deals with some of the receptors expressed on mast cells and eosinophils and their ligand(s). Some receptors have already been exploited as drug targets and others can be feasibly utilized as novel targets for anti-allergic therapy.

Keywords

Activating receptors; allergy; anti-allergic therapy; eosinophils; inhibitory receptors; mast cells

Abbreviations

Ab	:	Antibody
AEU	:	Allergic Effector Unit
AHR	:	Airway Hyperresponsiveness
ATP	:	Adenosine 5'-triphosphate
BMMC	:	Bone Marrow derived Mast Cells
CB	:	Cannabinoid Receptor
CBMC	:	Cord Blood derived Mast Cells
CCR3	:	C-C Chemokine Receptor type 3
COPD	:	Chronic Obstructive Pulmonary Disease
CRH	:	Corticotropin-Releasing Hormone
CPTH2	:	Chemokine Receptor homologous molecule expressed on T Helper type 2
CS	:	Glucocorticosteroids
ECP	:	Eosinophil Cationic Protein
EP2, 3, 4	:	E-Prostanoid 2, 3, 4
EPO	:	Eosinophil Peroxidase
FPR	:	Formyl Peptide Receptor
GM-CSF	:	Granulocyte-Macrophage Colony-Stimulating Factor
GPCR	:	G-Protein Coupled Receptor
GPI	:	Glycosylphosphatidylinositol
HR	:	Histamine Receptor
Ig	:	Immunoglobulin
IL	:	Interleukin
ILC2	:	Innate Lymphoid Cell type-2
ITSM	:	Immunoreceptor Tyrosine-based Switch Motif

ITIM	:	Immunoreceptor Tyrosine-based Inhibitory Motif
ITAM	:	Immunoreceptor Tyrosine-based Activating Motif
LAIR	:	Leukocyte Associated Ig-like Receptor
LIR	:	Leukocyte Ig-like Receptor
mAb	:	monoclonal Antibody
MAFA	:	Mast Cell Function-Associated Antigen
MAPK	:	Mitogen Activated Protein Kinase
MBP	:	Major Basic Protein
MC _T	:	Tryptase Containing Mast Cells
MC _{TC}	:	Tryptase/Chymase containing Mast Cells
MHC	:	Major Histocompatibility Complex
MrgX	:	Mas-related gene X
PECAM	:	Platelet-Endothelial Cell Adhesion Molecule
PI3K	:	Phosphatidylinositol-3-Kinase
PGD ₂	:	Prostaglandin D ₂
PGE ₂	:	Prostaglandin E ₂
PIR	:	Paired Ig-like Receptor
S1P	:	Sphingosine-1-phosphate
sCD48	:	soluble CD48
SCF	:	Stem Cell Factor
SEB	:	<i>S. aureus</i> Enterotoxin B
SNARE	:	N-ethylmaleimide-sensitive factor Attachment protein Receptor
SYK	:	Spleen Tyrosine Kinase
Th2	:	T helper cell type 2
TNF- α	:	Tumor Necrosis Factor alpha

TSLP : Thymic Stromal Lymphopoietin

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1. Introduction

Allergic diseases that affect ~20% of the global population and are continually increasing include allergic asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis and food allergy. Even though their symptoms may be different, due to the different organs in which allergy develops, they are caused by similar cellular mechanisms. Atopy is defined as the genetic tendency or predisposition to develop allergic diseases to commonly harmless substances called allergens, by the production of allergen-specific immunoglobulin (Ig)-E antibodies (Abs). Allergy is therefore the host immune response of the atopic individual towards allergens driven by specific IgE bound principally to tissue resident mast cells. In the sensitization stage of allergy, the atopic individual exposed to an allergen produces specific IgE via T helper cell type 2 (Th2)-regulated mechanisms. These IgE sensitize tissue resident mast cells by binding to the high-affinity IgE receptors (FcεRI) expressed on their membrane. The allergic response that ensues upon subsequent exposure to the allergen is due to the allergen binding to the FcεRI bound IgE causing crosslinking of the receptors and finally mast cell activation and consequent mediator release. Activation of mast cells can take place in connective tissues and on mucosal surfaces of several body locations where these cells reside. This primary mast cell activation gives rise to the so-called early allergic inflammatory response, taking place within a few minutes after the encounter of a sensitized mast cell with an allergen. At this stage, mast cells typically degranulate and release a plethora of preformed mediators, produce and release lipid mediators and start the synthesis of several cytokines, growth and chemotactic factors. A few hours later, a late phase develops characterized by the infiltration of granulocytes, lymphocytes and monocytes/macrophages. The most notable inflammatory cells persisting side by side to the mast cells during all the stages of allergy and when the response becomes chronic are the eosinophils that have been long described as allergy biomarker cells (Katz, et al., 2014; N. C. Barnes, et al., 2016; Bayes

& Cowan, 2016; Metcalfe, et al., 2016). During the late phase, the infiltrated cells become activated by local/tissue factors and, as the mast cells in the early response, they now produce and release a number of pro-inflammatory mediators. Eventually, the allergic reaction becomes chronic either because of the persistent presence of the allergen(s) or because of an intrinsic failure of the patient to resolve it or, alternatively because it is insensitive to the current available therapeutics. If this happens, tissue damage and consequent organ failure will occur. Even though the main effector cells of allergy are the mast cells and the eosinophils, other cells are obviously necessary for the elicitation and propagation of the allergic response: resident innate lymphoid cells-2 (ILC-2) and infiltrating invariant natural killer T cells, basophils, B cells, macrophages and others (Minai-Fleminger & Levi-Schaffer, 2009; Stone, et al., 2010; Kumar, et al., 2013; Yu, et al., 2014). In addition, the crosstalk between inflammatory cells themselves as well as between inflammatory cells and structural cells, *via* released mediators and receptor/ligand interactions, can modulate the onset and the outcome of the allergic inflammation. One of these important cellular complex interactions, that we have described and termed the “Allergic Effector Unit” (AEU) (Figure 1), is the interplay between mast cells and eosinophils *via* both physical and soluble interactions (Minai-Fleminger, et al., 2010; Elishmereni, et al., 2011; Elishmereni, et al., 2013). The physical crosstalk is mediated by several receptor/ligand couples, the most prominent one being the CD48/2B4 (see in 4.1). The soluble interactions are constituted by released mediators and their receptors such as the ones mediated by tryptase/protease activated receptor 2 (PAR2) (Temkin, et al., 2002), tumor necrosis factor- α (TNF- α)/TNF- α R (Temkin, et al., 2003), eosinophil major basic protein (MBP)/CD29 (β 1 integrin) (Ben-Zimra, et al., 2013), stem cell factor (SCF)/c-Kit (Hartman, et al., 2001) and nerve growth factor (NGF)/TrkA (Solomon, et al., 1998; Levi-Schaffer, et al., 2002) (Figure 1). In this review, we will also highlight additional soluble pathways that might influence the pro-

inflammatory properties of the AEU. Finally, allergic diseases are often characterized by a rich concomitant microbiome component of bacterial (i.e. *S. aureus* and *H. influenzae* (Essilfie, et al., 2012)) or viral nature (i.e. rhinovirus and *Severe respiratory syncytial virus* (Schauer, et al., 2002)) that also shapes the development of the disease (J. H. Kim, et al., 2013; Gern, 2015).

Given the predisposition to allergy with many genes implied, the gene-environment interactions influencing the history of the disease, the complexity of the allergic inflammation, and the individuality of the single patient, treatment is still a challenge. Until now, two main approaches have been applied. The first one is a prophylactic approach that is aimed to desensitize the patient to the relevant allergens (immunotherapy) and the second one relies on both symptomatic and anti-inflammatory drugs. While either one or both of these approaches are successful for a number of patients, they are not effective for all the patients. Importantly, atopic dermatitis and severe asthma are still defined as unmet clinical needs. Therefore, in the search for better therapeutics directed towards various mechanisms of the allergic inflammation, we believe that an important and promising approach is the targeting of the main effector cells of allergy, i.e. mast cell and/or eosinophil surface receptors. In this review, we will discuss mast cell and eosinophil surface receptors that have or might have potential for allergy treatment through activating or inhibitory functions.

2. Mast cells and eosinophils: The two key effector cells of allergy

2.1. The mast cells

Mast cells, characterized by prominent cytoplasmic granules, derive from $CD34^+$ hematopoietic stem cells. The human mast cell-committed progenitors, that are $CD34^+CD38^+CD13^+c\text{-Kit}^+Fc\epsilon RI^-Fc\gamma RII/III^+$ (Gauvreau & Denburg, 2015), migrate to tissues where they finally mature and reside. The main differentiation, maturation, survival, priming

and chemotactic factor for the human mast cells is SCF that acts by binding to the tyrosine kinase receptor c-Kit (CD117), expressed by both mast cell precursors and mature mast cells. Two main subclasses of mast cells exist, the one present in connective tissues such as the skin and the submucosal location (connective tissue type) and the one residing in mucosal surfaces such as the intestinal and lung mucosa (mucosal tissue type). Mast cells residing in the connective tissue are not likely to be dependent on T cell derived factors while the mucosal type appears to be finely regulated by T cell elements (Kitamura, et al., 1987). Importantly, these two subtypes differ in some biochemical characteristics as well. Mast cell cytoplasmic prominent granules contain several inflammatory mediators such as histamine, proteoglycans, neutral proteases and some cytokines (da Silva, et al., 2014). Specifically, human connective tissue mast cells contain the proteoglycan heparin and the proteases tryptase, chymase, cathepsin G and carboxypeptidases (hence termed tryptase/chymase containing mast cells (MC_{TC})) whereas mucosal tissue mast cells contain the proteoglycan chondroitin sulfate and the protease only tryptase (hence termed tryptase containing mast cells (MC_T)) (Irani, et al., 1986; Krishnaswamy, et al., 2006). Upon stimulation, mast cells degranulate, release the preformed mediators and produce newly formed ones such as membrane derived lipid mediators and an array of cytokines and chemokines. Notably, MC_{TC} produce and release mostly prostaglandin D₂ (PGD₂) in contrast to MC_T, which predominantly release leukotriene C₄. Regardless of their subtype, all mast cells display the high-affinity IgE receptor FcεRI and c-Kit but they greatly vary in the expression of several other receptors. For example, MC_{TC} but not MC_T express CD88 and C5aR (Oskeritzian, et al., 2005; Bradding & Arthur, 2016). Notably, MC_T and MC_{TC} show different profiles of sensitivity to mast cell stabilizers, suggesting that this mast cell heterogeneity is also relevant to therapy. In particular, disodium cromoglycate effectively inhibits peritoneal mast cell histamine release but fails in the case of mucosal mast cells (compound 48/80 and bee venom stimulation)

(Finn & Walsh, 2013). Other studies showed that nedocromil sodium successfully prevented histamine release from mast cells isolated from lung, tonsillar and adenoidal tissues whereas its effects were weaker in the case of intestinal mast cells and absent in the case of skin mast cells, but the reasons for such differences were not clear (Finn & Walsh, 2013).

Mast cell degranulation, either by piecemeal or anaphylactic mechanisms, is a finely regulated process. The first step is characterized by a selective release of granule contents without fusion between granule-granule or granule-plasma membrane whereas the second step, usually the most relevant in allergy, is similar to a burst of granule contents or even entire granules out of the mast cell with fusion processes mediated by soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs). These SNAREs are currently under intensive research since they might offer a suitable target to avoid mast cell degranulation in allergic diseases. In addition, mast cells release membrane-bound vesicles (exosomes) containing lipids, proteins, phospholipids, adhesion molecules, etc. through constitutive and regulated exocytosis (Villarroya-Beltri, et al., 2014), (discussed in (Moon, et al., 2014a)). Eicosanoids and lipid mediators, mostly but not exclusively derivatives of arachidonic acid (i.e., leukotriene C4, PGD₂, etc.), are *de novo* synthesized and immediately released from the activated mast cells upon phospholipase A2 and specific enzyme activity (Moon, et al., 2014a).

Mast cells play important roles in physiological functions by regulating innate and adaptive immune responses (Jang & Kim, 2015), tissue repair, vascular homeostasis, vasodilation, angiogenesis, and notably venom detoxification (Galli, et al., 2016). Current knowledge on their role in the pathophysiology of many diseases is mostly based on animal models. The extent to which those roles extend to human diseases awaits further research and testing, for example, with the therapeutic agents described in this review. Among this wide range of conditions (recently reviewed in (Krystal-Whittemore, et al., 2015; Arthur & Bradding,

2016)), it is worth mentioning: cardiovascular diseases; gastrointestinal disorders such as inflammatory bowel disease, Crohn's disease, ulcerative colitis, celiac disease, and irritable bowel syndrome (Boeckxstaens, 2015; Bischoff, 2016); many types of malignancies; and autoimmune diseases such as rheumatoid arthritis, scleroderma, and chronic graft-versus-host disease (Kolb, 2013; Reggiani, et al., 2015; C. Cho, et al., 2016; Rossini, et al., 2016; Suurmond, et al., 2016). Nevertheless, the best characterized pathological function of these cells has been in the field of allergy (Bradding & Arthur, 2016) in which mast cells are mostly acknowledged for their role in orchestrating the early IgE-mediated response (Strauss-Albee, et al., 2014) but also as active players in its late and chronic phases especially by interacting with the infiltrated eosinophils (Piliponsky, et al., 2002). The commonly used human mast cells in research are cord blood derived mast cells (CBMC), peripheral blood derived mast cells and mast cell lines (HMC-1 and LAD-2). Similarly, mouse bone marrow derived mast cells (BMMC) and rat peritoneal mast cells are the most commonly used rodent mast cells.

Another cell type connected with Th2 responses that has frequently been associated with mast cells is the basophil. This elusive cell, that represents only 0.1% to 2% of peripheral blood leukocytes, expresses, like the mast cell, functional Fc ϵ RI, contains preformed histamine and following allergen activation releases it together with Th2 cytokines such as interleukin (IL)-4 and IL-13 (Stone, et al., 2010). Since basophils produce IL-4, they potentiate IgE-mediated degranulation and increase the expression of different chemokines including eotaxin-1 (CCL11) resulting in recruitment of eosinophils in allergic reactions (Otsuka, et al., 2016).

Mast cells display a vast array of activating receptors besides Fc ϵ RI and c-Kit. These include: the receptors for various chemokines (i.e. CXCR3, CXCL9, CXCL10, CXCL11, etc.), cytokines (i.e. thymic stromal lymphopoietin receptor (TSLPR), granulocyte-macrophage

colony-stimulating factor receptor (GM-CSFR), etc.), interleukins (i.e. IL-15R, IL-18R, IL-33R, etc.), amines (i.e. histamine receptor (HR)s, serotonin, etc.), cannabinoids (CB₁ and CB₂), pathogen-associated molecular pattern molecules (i.e. toll like receptors TLR2, TLR4, etc.) and several others, as well as of inhibitory receptors such as CD300a, Siglec-7 and Siglec-8 (Figure 2) (reviewed in (Migalovich-Sheikhet, et al., 2012)). The richness and variety of these receptors indicate that mast cells can contribute not only to allergy but also to several other diseases (in which the trigger is not the allergen) and also play a role in maintaining homeostasis.

Being the recognized “*primum movens*” by IgE-mediated activation, a reservoir of preformed pro-inflammatory mediators and a maker of several newly formed mediators, mast cells have long been a focus of anti-allergic therapy, mostly targeted by stabilizing drugs that have not been completely successful and recently by more promising anti-IgE Abs.

2.2. The eosinophils

Eosinophils are granulocytes that develop from the pluripotent CD34⁺ hematopoietic stem cells in the bone marrow. Eosinophil lineage-committed progenitors, CD34⁺CD38⁺IL-3R α ⁺CD45RA⁻IL-5R α ⁺ (Iwasaki, et al., 2005; Mori, et al., 2009), give rise to mature cells in the bone marrow under the control of the critical transcription factors GATA-1, PU.1 and C/EBP. Their development and proliferation is positively regulated by GM-CSF, IL-3 and IL-5 (Rosenberg, et al., 2013). Eosinophils can also develop from CD34⁺ progenitors in the lungs in the presence of IL-5 (Southam, et al., 2005). IL-5 is a key trigger for eosinophil expansion and release from the bone marrow and plays a crucial role in the entire life span of eosinophils from differentiation to maturation and survival. Eosinophils are the chemotactic cells “par excellence” migrating from the bone marrow to the peripheral blood and finally to the inflamed tissue. Hence, eosinophil chemotaxis has been an important target for anti-allergic drugs. Importantly, under homeostatic/physiologic conditions eosinophils reside in

the gastrointestinal tract, thymus, mammary gland and uterus. Eosinophils contain a characteristic bilobed nucleus, and different primary, secondary or specific small granules and lipid bodies in the cytoplasm. The primary granules are the sole deposit of Charcot-Leyden crystal protein in the body and their function is still unclear. The small granules contain most of the hydrolytic enzymes (acid phosphatase, arylsulfatase, etc.) having probably a “digestion/destruction” role together with secondary granules. These granules are characterized by a crystalline core compartment containing the cytotoxic preformed MBP, and a matrix compartment storing other cationic proteins, namely eosinophil peroxidase (EPO), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (Stone, et al., 2010). Together with these there are host hydrophobic proteins such as galectin-10 and a vast repertoire of preformed cytokines, chemokines, enzymes and growth factors comprising SCF, GM-CSF, nerve growth factor, TNF- α and others (reviewed in (Muniz, et al., 2012)). The cytoplasm also contains lipid bodies which are spherical organelles mainly housing arachidonic acid that eventually undergoes esterification into glycerophospholipids (reviewed in (Giembycz & Lindsay, 1999)).

Eosinophils, besides having detrimental effects in allergy and in other pathologies, are also well known for their protective role against pathogens. An elevation of the eosinophil count (eosinophilia) in both peripheral blood and tissue occurs typically in atopic asthma and other allergic disorders, helminthic infections, hypereosinophilic syndromes (Curtis & Ogbogu, 2016), ulcerative colitis, Crohn’s disease and many other diseases. Tissue eosinophilia is often accompanied by a conspicuous presence of mast cells in several of the aforementioned conditions, including mastocytosis in which mast cell tumor expansion is concomitant with an expanded eosinophil population (Kovalszki & Weller, 2014; Gangwar, et al., 2016). Once in the allergic inflamed tissues, eosinophils ‘communicate’ with several cells in the AEU, among them mast cells, reaching an activation state and amplifying the allergic response.

Eosinophil activation *via* different surface receptors results in the release of granule stored mediators, lipid mediators and cytokines through different mechanisms such as compound exocytosis, piecemeal degranulation and cytolysis (Spencer, et al., 2014).

Compound exocytosis is known to take place when eosinophils interact with parasites and implicates the fusion of granules with plasma membranes and extracellular release of the whole granule contents. Piecemeal degranulation involves mainly the granule contents that, once transferred to vesicles, dissociate from granules, fuse with the plasma membrane and are released at the cell surface of intact eosinophils. Behind all these events, there is a high coordination among a number of signaling mediators, GTPases, cytoskeletal components and specific SNARE proteins (reviewed in (MacKenzie, et al., 2014)) which mainly regulate eosinophil membrane-vesicle binding and fusion in piecemeal degranulation (Yang, et al., 2010). Last but not least, eosinophil cytolysis involves disruption of cell membrane integrity and deposition of entire membrane bound granules within tissues (Spencer, et al., 2014). While piecemeal degranulation is recognized as the prevalent mechanism, an increasing number of reports shows an association of eosinophil cytolysis events with eosinophilic disorders (reviewed in (Muniz, et al., 2012)).

Like mast cells, eosinophils display a vast array of activating receptors besides C-C chemokine receptor type 3 (CCR3) and IL-5R. They express on their surface activating receptors for various chemokines (i.e. CXCR3, CXCR4 CCR5, CCR6, etc.), cytokines (i.e. GM-CSFR), interleukins (i.e. IL-4R, IL-3R, IL-13R, ST2, etc.), amines (i.e. HRs), endocannabinoids (i.e. CB₁ and CB₂), pathogen-associated molecular pattern molecules (i.e. toll like receptors) and complementary systems (i.e. C3a and C5a etc.), and inhibitory receptors such as CD300a, Siglecs, FcγRIIb, and others (Figure 2). This variety of receptors indicates a versatile role of eosinophils not only in allergy but also in other diseases.

In addition to the classical portrait of eosinophils as main tissue destroying cells, novel evidence pictures these cells as players in organ development, glucose and lipid homeostasis and tumor immunity (Gouon-Evans, et al., 2000; Berlin, et al., 2006). In particular, recent studies support the concept of a ‘pro-resolution’ role in inflammation of eosinophils (Rhee, et al., 2011). Eosinophils produce pro-resolving lipid mediators such as protectin D1 (Yamada, et al., 2011) and resolvin E3 (Isobe, et al., 2012), promoting elimination of apoptotic neutrophils and impeding polymorphonuclear cell infiltration in the inflamed tissue, respectively. Moreover eosinophils stimulate macrophages switching to a M2 phenotype, characterized by increased phagocytic functions and synthesis of resolving mediators (reviewed in (Barnig & Levy, 2015)). In line with these observations, the biosynthesis of protectin D1 by eosinophils, as well as airway lipoxin A4 has been found to be dysregulated in severe asthma patients (Planaguma, et al., 2008; Miyata, et al., 2013), suggesting that therapeutic treatment of allergic inflammation could be pursued with these lipid mimetics. The eosinophil, being able to perpetuate but also to resolve the allergic reaction, is an example of a bifunctional cell. Therefore, pharmacological targeting should take this into consideration.

3. Therapeutic approaches for allergy: where we stand now

Glucocorticosteroids (CS) are the most effective drugs for downregulating inflammation and, in consequence, allergic inflammation. However, CS have several and sometimes severe side effects, especially when given over a long period of time and at high doses. Furthermore CS resistance is a major problem in treating asthmatic patients (Thomson, 2016).

Anti-histamines, targeting the H1 receptor (anti-H1R), are well known to ease some of the symptoms of allergy as do β 2 adrenoceptor agonists in asthma but, despite their wide use, they are not the ultimate solution either for managing the symptoms or for the treatment of allergy/asthma. Therefore, alternative and/or additional therapeutic approaches have been

pursued. A better alternative to the aforementioned drugs to treat the majority of allergic patients has not yet been found.

As mast cells, when activated by IgE-dependent mechanisms, are the first cause of the allergic reaction, they are unequivocally the critical cells to be downregulated for a successful treatment of allergy. This is so even though, upstream to mast cells, other cellular mechanisms can be appropriate therapeutic targets and are currently under investigation. Furthermore, since usually the eosinophils are associated with most of the pro-inflammatory cellular features of allergy and their presence in the blood en route to the tissues is an easier location to be targeted than tissues, these cells are a suitable “second best” objective for the treatment of allergic diseases.

Few attempts have been made over the years to directly inhibit mast cells and/or eosinophils. They have mainly focused on mast cell activation and eosinophil recruitment and differentiation/survival mechanisms. Regarding the possibility to block activation of mast cells, chromones such as cromolyn sodium and nedocromil have been developed and used although their precise mechanism of action is still debated (i.e. tachykinin antagonism, release of annexin I, signaling via the G-protein coupled receptor (GPCR) 35). More recently, other compounds such as iodoxamide, bufrolin and the flavonoid quercetin have been proposed as mast cell stabilizers (Yang, et al., 2010; MacKenzie, et al., 2014) (reviewed in (Weng, et al., 2012; T. Zhang, et al., 2016)). Most recently, anti-IgE monoclonal Abs (mAbs) for blocking mast cell activation, and anti-IL5 mAbs for inhibiting eosinophil differentiation, survival and activation have been investigated (see below). Additional strategies have focused on targeting mast cell activation signaling molecules using specific inhibitors of spleen tyrosine kinase (SYK), phosphatidylinositol-3-kinase (PI3K), SHIP-1, Bruton's tyrosine kinase, KIT, sphingosine kinase, and others (T. Zhang, et al., 2016). Moreover, researchers have attempted to target the eosinophil proliferation and survival signaling

pathways using peptide inhibitors against the tyrosine kinase Lyn (Adachi, et al., 1999) and using neutralizing Abs directed to the vesicular SNARE associated membrane protein-7 to block the degranulation process (Logan, et al., 2006).

Other studies have been carried out to counteract mast cell or eosinophil released mediators such as tryptase, histamine, PGD₂, leukotrienes and TNF- α with antagonists, Abs, synthetic inhibitors or signal transduction inhibitors (T. Zhang, et al., 2016). Relatively few therapeutically useful options targeting mast cell and eosinophil membrane receptors exist or have been attempted.

4. Surface receptors on mast cells and eosinophils as targets for anti-allergic therapy

Besides their key activating receptors such as Fc ϵ RI and c-Kit for mast cells and IL-5 and CCR3 for eosinophils, these two cells express a plethora of different surface receptors, some of which are shared with other cells, with specificity for several ligands. Importantly, some of the receptors activate their pathophysiological functions while some others limit their excessive activation and/or keep them in homeostasis. Moreover, few of the receptors are displayed both by mast cells and eosinophils, and therefore are optimal targets for allergic inflammation treatment. It is important to note that even though some of the receptors are expressed by cells other than mast cells and eosinophils, their presence on additional effector or target cells involved in Th2 responses renders them a valid therapeutic aim. Therefore, mast cell and eosinophil activating and/or inhibitory receptors and their signaling pathways can be targeted to downmodulate their function in allergy and its outcome.

Generally, if activation is harmful, blocking the activating receptors will be the objective that can be achieved by antagonists or neutralizing mAbs; *vice versa*, if inhibition is useful, activation of inhibitory receptors, that causes downregulation of cell activation, is also likely to be targeted by specific ligands/agonists or activating mAbs.

Of the tools to target the activating and inhibitory receptors that we will discuss in this review, some have already been developed into drugs, some are in preclinical or clinical trials and some are just reasonable objectives for anti-allergic therapeutic purposes. For the ease of the reader, the mast cell and eosinophil receptors examined in this review are broadly characterized by their main functional role, i.e. an activating or inhibitory one (Figure 2) and by their ligand. We will first describe the most crucial and best defined ones that belong to the activating type that are already a drug target and then continue with others, both activating and inhibitory, currently under clinical or preclinical trials or still in basic science research.

4.1. Activating surface receptors

Targeting activating receptors is one of the first approaches that has been taken for the development of drugs. The activation cascade generated by the receptor-ligand interactions can be inhibited by blocking the receptor itself or by blocking the binding region of the ligand *via* antagonists or neutralizing/blocking Abs. In some cases, the surface receptors are also present in soluble form that frequently act as decoy receptors. Another therapeutic possibility to prevent receptor-mediated activation is to block signal transduction molecules intracellularly. We will discuss targeting the central activating receptors by reviewing the receptor and/or the ligand blocking procedures.

FcεRI: the high-affinity IgE receptor as a key modulator of mast cell activation

FcεRI, the high-affinity receptor for IgE, belongs to the Ig superfamily, and is expressed primarily on human mast cells and basophils as a tetramer composed of three subunits ($\alpha\beta\gamma_2$) (Figure 2). The α -subunit is responsible for IgE binding, the β -subunit regulates receptor expression and signaling, and the γ -subunit, which forms a homodimer through disulfide-linkage, is mainly responsible for signal transduction (Blank, et al., 1989; Donnadieu, et al.,

2000; Kraft & Kinet, 2007). Moreover, a soluble form of the Fc ϵ RI also circulates in human serum free or bound to IgE (Dehlink, et al., 2011). Fc ϵ RI has been reported also to be expressed in the absence of the β -chain as a trimer ($\alpha\gamma_2$) (Kraft & Kinet, 2007) on eosinophils (Rajakulasingam, et al., 1998) and many other immune cells (antigen presenting cells and neutrophils (Gounni, et al., 2001), platelets (Joseph, et al., 1997), monocytes (Maurer, et al., 1994), Langerhans cells (Bieber, et al., 1992; Haas, et al., 1992), dendritic cells (Maurer, et al., 1996)), airway smooth muscle cells (Gounni, et al., 2005) and even on some nerve cells (van der Kleij, et al., 2010)).

Once activated, the complete tetramer ($\alpha\beta\gamma_2$) becomes a key regulator of immediate allergic responses. The allergen crosslinking of the IgE bound to the α -subunit of the Fc ϵ RI activates the Lyn kinase that phosphorylates the immunoreceptor tyrosine based activating motifs (ITAM) located on both β and γ chains of Fc ϵ RI. Phosphorylated ITAM of the γ chain facilitates the binding of SYK, which becomes activated by phosphorylation by Lyn or possibly through auto-phosphorylation. These processes enhance the activating signaling cascade (T. Zhang, et al., 2016). Further, following SYK binding, activation of mitogen-activated protein kinases (MAPK), protein kinase C and phospholipase C γ takes place by intermediate phosphorylated events. This results in the rise of cyclic adenosine monophosphate (cAMP) that mediates the phosphorylation of mast cell granule membrane proteins and alters their permeability. This in turn leads to the fusion of granule and plasma membrane followed by release of granule content (Turner & Kinet, 1999; T. Zhang, et al., 2016).

IgE binds to the Fc ϵ RI at a very high affinity ($K_d \sim 10^{-9}$ – 10^{-10} M) (Garman, et al., 2000; Wan, et al., 2002) and the dissociation half-life for IgE bound to Fc ϵ RI is very slow ($k_{off} \sim 10^{-7}$ s $^{-1}$), in the order of weeks. This high-affinity binding and exceptionally slow rate of IgE dissociation from Fc ϵ RI is responsible for persistent sensitization of mast cells and their

readiness to allergen challenge (Wan, et al., 2002). The interaction between the FcεRI and the IgE is a key component of the allergic response, and it is almost impossible to dissociate the bound IgE from FcεRI; therefore, blocking this interaction in the first place is the most effective approach to prevent this classical manner of mast cell activation.

Regarding the eosinophils, in the past some groups have reported that FcεRI on eosinophils plays a role in immune responses towards parasite infections and that IgE-dependent activation of these cells is able to induce their degranulation (Tomassini, et al., 1991; Gounni, et al., 1994; Kayaba, et al., 2001). Nevertheless, this issue is controversial, due to the fact that recent studies did not detect IgE-associated activation of eosinophils (Monteseirin, et al., 2007; Stone, et al., 2010; Elishmereni, et al., 2013).

FcεRI can be targeted for therapeutic purposes by preventing the binding of IgE and by interfering/inhibiting the FcεRI-generated signaling. Both strategies are currently used (Arthur & Bradding, 2016). Preventing the FcεRI–IgE interaction is achieved by blocking the FcεRI or the Fc portion of the IgE. Anti-IgE mAbs are a few of the effective approaches that have been taken in anti-allergic therapy in recent years (Ozdemir, 2015; N. Landolina & Levi-Schaffer, 2016). Anti-IgE mAbs block and reduce the free IgE molecules in the serum of patients and downregulate FcεRI expression on mast cells and basophils, thus minimizing the overall probability of FcεRI–IgE interaction. Omalizumab, a humanized anti-IgE mAb has been approved for therapy of moderate to severe persistent allergic asthma and chronic idiopathic urticaria (Kaplan, et al., 2008; Genentech, 2014; K. C. Wu & Jabbar-Lopez, 2015). Moreover, it is also being investigated for allergic rhinitis, chronic obstructive pulmonary disease (COPD) (Bozkurt, et al., 2014; Ciprandi, et al., 2015; Tat & Cilli, 2016; Vennera Mdel, et al., 2016), atopic dermatitis (Zink, et al., 2016), nasal polyposis (Bachert, et al., 2015) and food allergy (Schneider, et al., 2013).

Two novel mAbs (h4B12 and quilizumab) have been recently developed to target the IgE producing B-cells to control IgE production (Brightbill, et al., 2010; J. B. Chen, et al., 2010). mAb h4B12 has been in a clinical trial involving patients with atopic dermatitis (National Taiwan University Hospital, 2013) but, although the study has been completed, no results have been posted. Quilizumab is in phase 2b for patients with moderate to severe allergic asthma (H. M. Chu, et al., 2014) and most recently in refractory chronic spontaneous urticaria (Genentech Inc, 2016) with no results as yet (Table 1). Interestingly, both mAbs bind to the same epitope (C ϵ mX) on IgE-B cells but in different conformations and mediate IgE-expressing B cell apoptosis and Ab-dependent cellular cytotoxicity (Brightbill, et al., 2010; J. B. Chen, et al., 2010; H. M. Chu, et al., 2014). Liour et al. reported that anti-C ϵ mX mAb binds and lyses IgE-expressing B cells and prevents the allergen-induced proliferation of IgE producing plasma cells (Liour, et al., 2016). Moreover, anti-C ϵ mX mAb does not bind to free IgE, but can modulate IgE pathways regardless of the serum IgE levels, which might also be an important therapeutic/prophylactic approach (Liour, et al., 2016).

Another approach to interrupt the Fc ϵ RI–IgE interaction is to use small peptides mimicking the sequence and structure of the Fc portion of the IgE which binds to the Fc ϵ RI α -chain (Burt & Stanworth, 1987; Offermann, et al., 2012) or mimicking the extracellular region of Fc ϵ RI α -chain which binds to IgE (Sandomenico, et al., 2009; Zhou, et al., 2013). This strategy seems promising as it effectively blocks the Fc ϵ RI–IgE interaction and has been shown to protect animals in experimental studies (Sandomenico, et al., 2009; L. D. Smith, et al., 2013; Zhou, et al., 2013).

Further strategies to use Fc ϵ RI for therapeutic purposes are the targeting of the Fc ϵ RI signaling cascade with protein kinase inhibitors (recently described in (Blank, et al., 2016)). Since many signal transduction proteins are common among different receptors and on different cells, this approach is by no means a specific one and therefore, might give rise to a

plethora of side effects. Another strategy can be to co-crosslink FcεRI with inhibitory receptors such as CD300a to generate an inhibitory signal. Our laboratory has demonstrated that crosslinking of IgE bound to FcεRI with CD300a using a bispecific Ab could effectively downregulate mast cell IgE-mediated activation (Bachelet, et al., 2006).

c-Kit: the SCF receptor as a main regulator of mast cell development and function

c-Kit (CD117), also referred to as SCF receptor, was identified in 1987 (Yarden, et al., 1987). It is a type III receptor tyrosine kinase with a large extracellular portion containing five Ig-like domains, a transmembrane domain, and a long cytoplasmic tyrosine kinase tail (Reber, et al., 2006). SCF binds to c-Kit with very high affinity ($K_d \sim 200$ pM) leading to receptor dimerization and phosphorylation of tyrosine residues by inducing the tyrosine kinase activity of c-Kit (Jensen, et al., 2007). c-Kit is expressed on hematopoietic cells and on different non-hematopoietic cells (i.e. melanocytes, interstitial cells of Cajal) and on some tumors (Miettinen & Lasota, 2005). Among these cell types, the expression of c-Kit on human basophils is controversial. Even though the presence of c-Kit on mature basophils has been reported to be weak (reviewed in (Arock, et al., 2002)), SCF has been shown to modulate peripheral blood basophil chemotaxis, integrin upregulation, and survival through its functional receptor (Heinemann, et al., 2005). Interestingly, also human peripheral blood eosinophils were reported to express c-Kit (Q. Yuan, et al., 1997) (Figure 2) that upon SCF binding induces the generation of eosinophils from bone marrow progenitors in the presence of GM-CSF and their degranulation (Metcalf, et al., 2002; Oliveira, et al., 2002; Ray, et al., 2010). c-Kit can exist as a soluble form due to proteolytic cleavage from the surface of hematopoietic cells, mast cells and endothelial cells. Four different isoforms of c-Kit have been reported in humans due to alternative splicing events (Reber, et al., 2006).

c-Kit is the main receptor expressed throughout the life span of mast cells, from the stage of mast cell progenitors to their differentiation and maturation (Figure 2). Mast cell development and survival are dependent on the c-Kit-mediated activation of PI3K and its downstream target protein Kinase B. PI3K is crucial for SCF-mediated mast cell chemotaxis and adhesion, and SCF induced allergen-mediated mast cell degranulation and cytokine production (reviewed in (Jensen, et al., 2007)). Moreover, we have shown that SCF is also produced by eosinophils that can bind to c-Kit, addressing even more the importance of this receptor in the frame of the AEU (Hartman, et al., 2001).

Due to its central task in mast cell biology and its importance in eosinophil biology as well, targeting c-Kit for therapeutic purposes in allergic inflammation is feasible. c-Kit mediated activation of mast cells can be prevented either by blocking the SCF or the c-Kit receptor itself. Studies done in experimental animal models have demonstrated that anti-SCF neutralizing mAbs inhibit, by reducing SCF levels, the allergic airway response in cockroach allergen-challenged mice (Berlin, et al., 2004). In another study, intranasal administration of SCF antisense oligonucleotides has been reported to suppress airway inflammation and IL-4 production in a murine model of asthma (Finotto, et al., 2001). Recently, systemic administration of small interference RNA to inhibit the expression of the c-Kit in a murine asthma model has been shown to reduce the infiltration of eosinophils and lymphocytes into the lung and in bronchoalveolar lavage fluid and to decrease Th2 cytokine production (W. Wu, et al., 2012).

Strategies to inhibit c-Kit are under development especially for mastocytosis, in which mast cell c-Kit is mutated and constitutively auto-phosphorylated. Synthetic tyrosine kinase inhibitors such as imatinib mesylate, nilotinib, dasatinib, AMN107, EXEL-0862, hypothemycin, PKC412, OSI-930, and SU11248 that inhibit c-Kit activation by blocking its tyrosine kinase catalytic activity have been designed and some of them (imatinib, nilotinib,

dasatinib) are currently in clinical use. Imatinib inhibits the phosphorylation of c-Kit but not of any kinases that are critical for FcεRI-mediated responses (Jensen, et al., 2007). Imatinib also inhibits SCF-mediated effects of CBMC such as survival, chemotaxis, and adhesion (Takeuchi, et al., 2003). Finally studies in asthma patients with airway inflammation and airway remodeling associated with chronic allergen challenge (Berlin, et al., 2006; Rhee, et al., 2011) and with hypereosinophilic disorders (Ustun, et al., 2011) have shown that attenuating c-Kit activation by imatinib is an effective strategy.

Our group has shown that crosslinking of the inhibitory receptor CD300a with c-Kit by bispecific Abs downregulates human mast cell differentiation from cord blood precursors, as well as CBMC survival and activation. Moreover, the bispecific Ab blocks spontaneous tryptase release from HMC-1 and allergic inflammation in a murine model of cutaneous anaphylaxis (Bachelet, et al., 2008). In allergic inflammation, this bispecific Ab targeting c-Kit and CD300a would at the same time prevent c-Kit mediated mast cell differentiation and survival and hence the expansion and activation of mature mast cells. In addition, the Ab might block c-Kit positive eosinophils that also express CD300a. Specific c-Kit tyrosine kinase inhibitors might be useful in otherwise untreatable allergic patients such as those with severe steroid resistant asthma (Adcock & Caramori, 2004; Ramanujam, et al., 2009; Rhee, et al., 2014).

IL-5 receptor: the key receptor in eosinophil biology

The IL-5 receptor (IL-5R) is a heterodimeric membrane receptor complex characterized by a transmembrane binding domain, consisting of 'α' and 'β' subunits. The 'α' subunit is mostly present on the eosinophil surface (Figure 2) and importantly also on mast cells (Dahl, et al., 2004), while the 'β', which is shared with IL-3 and GM-CSF receptors, is more broadly expressed. IL-5R also has a soluble isoform (Tavernier, et al., 1992; Devos, et al., 1993).

Both the heterodimeric membrane IL-5R complex and the soluble form bind IL-5 with equally high affinity (Tavernier, et al., 1992; Devos, et al., 1993), which is consistent with this cytokine being crucial for eosinophil differentiation, adhesion to endothelial cells, maturation, activation and survival (reviewed in (N. A. Landolina & Levi-Schaffer, 2014)).

High levels of IL-5 are detected in bronchial biopsies, serum and bronchoalveolar lavage of asthmatic patients who are also characterized by upregulation of both membrane IL-5R and its soluble form (Yasruel, et al., 1997). Administration of recombinant human IL-5 to the airways of asthmatic patients has been reported to cause sputum eosinophilia, bronchial hyperreactivity and ECP release, indicating the importance of this cytokine and its receptor in asthma. Moreover, IL-5/IL-5R might be one of the crucial players in the vicious cycle between mast cells and eosinophils. We have indeed found that in the AEU, IL-5 is one of the cytokines responsible for prolonged eosinophil survival (Elishmereni, et al., 2011). Most notably, the presence of both IL-5 mRNA and protein in mast cells located in allergen-challenged bronchial biopsies of asthmatic patients strengthens the possibility that activated mast cells in allergic reactions synthesize higher amounts of IL-5 resulting in enhanced recruitment and survival of eosinophils (reviewed in (Kouro & Takatsu, 2009)).

Targeting IL-5/IL-5R (E. R. Walsh, et al., 2010; Fulkerson & Rothenberg, 2013; Legrand & Klion, 2015; Eng & DeFelice, 2016; George & Brightling, 2016) is mostly done by mAbs directed against the cytokine (Rothenberg, 2016), such as with mepolizumab (Nucala, IgG1 κ) and reslizumab (Cinqair, IgG4 κ), which are in use for the treatment of severe eosinophilic asthma (Cardet & Israel, 2015; G. M. Walsh, 2015; Fainardi, et al., 2016) and have recently been taken into phase 3 clinical studies for COPD (GlaxoSmithKline, 2016) (Table 1). A mAb drug directed against the IL-5R, benralizumab (IgG1), is currently under evaluation for the same pathology. Both mepolizumab and reslizumab prevent the binding of IL-5 to its receptor, improve lung function, decrease exacerbations and ameliorate asthma symptoms

and quality of life with a good safety profile (Menzella, et al., 2015; Bjermer, et al., 2016). Benralizumab, which has been shown to cause a reduction in both asthma exacerbation rates and baseline blood eosinophil counts in patients with uncontrolled eosinophilic asthma (Castro, et al., 2014), is in phase 3 trials in combination with medium-dose inhaled CS plus long-acting β 2-adrenoceptor agonist in patients with uncontrolled asthma showing no severe side effects (AstraZeneca, 2015). Moreover, benralizumab is currently in a phase 3 study involving COPD patients with no results posted as yet (AstraZeneca & MedImmune LLC, 2016). Its transition to regulatory review is expected by the end of 2016 (Reichert, 2016). The specific targeting of IL-5 has recently achieved success, and it is anticipated that the same positive results will be found for IL-5R targeting eosinophilic asthma as well as COPD. Although IL-5 is the key cytokine in eosinophil biology, IL-3 and GM-CSF are also important factors. Indeed, eosinophil survival has been targeted by the mAb KB003 directed against GM-CSF. This mAb has completed a phase 2 study involving subjects with inadequately controlled asthma (KaloBios Pharmaceuticals, 2015) reporting an improvement of lung functions (although not in the overall population), adverse event $\geq 5\%$ but no effects on asthma control or exacerbation rates (Molfino, et al., 2016). Further studies involving KB003 are required in order to provide the proper dose and the best asthma phenotype candidate.

IL-4 and IL-13 sharing receptor: to catch two pigeons with one fava bean

The receptors for the Th2 expressed cytokines IL-4 and IL-13 are complex systems. They are classified into the IL-4 type I receptor (composed of the IL-4R α chain paired with the γ chain, binding only IL-4), the IL-4 type II receptor (composed of the IL-4R α paired with the membrane bound IL-13R α 1, binding both IL-4 and IL-13) and the membrane bound IL-13R α 2 receptor (binding IL-13 with high affinity) (reviewed in (Ranasinghe, et al., 2014)).

Among these distinct receptor systems, membrane bound IL-13R α 2 signaling is not well characterized whereas soluble forms of IL-4R chains and IL-13R α 2 have been recently described in humans and mice, respectively (reviewed in (McCormick & Heller, 2015)). IL-4 and IL-13 are short α -helix bundle glycoproteins, sharing about 25% sequence similarity, which are produced by IL-13R α 1 expressing mast cells and other cells (Kaur, et al., 2006; McLeod, et al., 2015).

Eosinophils have been shown to constitutively produce IL-4 (Nakajima, et al., 1996) and express IL-4 type I receptor (Dubois, et al., 1998) (Figure 2), while IL-13 generation and release have been demonstrated with CD28 stimulated eosinophils (Woerly, et al., 2002) and eosinophilic inflammatory responses (Schmid-Grendelmeier, et al., 2002). Thus, IL-4, IL-13 and their receptors are a complex system linking mast cells and eosinophils.

Both IL-4 and IL-13 regulate the human mast cell phenotype, decrease HMC-1 proliferation rate and increase and reduce the expression of the intercellular adhesion molecule 1 (ICAM-1) and c-Kit, respectively (Nilsson & Nilsson, 1995). Contrarily, other studies, performed in mature human mast cells, showed that, in synergy with SCF, IL-4 promotes mast cell proliferation and shifts IgE-dependent cytokine production toward an increased release of Th2 cytokines including IL-13 and a decreased IL-6 expression, these effects being blocked by the MEK inhibitor PD98059 (Lorentz, et al., 2005).

IL-13 promotes Ig class switch toward IgE in B cells and eosinophil survival. It also regulates eosinophil homing, recruitment and activation in the airways, thus covering all possible aspects of a useful candidate to target in the development of allergic asthma (reviewed in (Davoine & Lacy, 2014)). Moreover, because of the IL-4 and IL-13 binding to their shared receptor, these interleukins act as important players in the pathogenesis of allergic asthma, allergic hypersensitivity and viral infections (reviewed in (Ul-Haq, et al., 2016)). Accordingly, elevated levels of IL-4 and IL-13 have been found in the skin of atopic

dermatitis patients (reviewed in (Brandt & Sivaprasad, 2011)). A polymorphism in the IL-4R α motif (Y500F) does not show any significant difference between mice susceptible to IgE-mediated, food-induced experimental anaphylaxis or wildtype mice, except for accelerated disease progression together with a faster anaphylactic response in mice carrying the polymorphism, suggesting a critical role for IL-4R α in the negative regulation of IgE-mediated anaphylactic reactions (Sledd, et al., 2015). Recent research has also shown that respiratory chlamydia infection, a common cause of pneumonia in early life, decreases levels of IL-13R α 2 in the lung mucosae, thereby elevating the constitutive expression levels of IL-13, aggravating infections and promoting hyperresponsiveness and allergic airway disease (Starkey, et al., 2013). Sputum cells of asthmatic patients have increased IL-4 and IL-13 mRNA levels, and this significantly correlates with the eosinophil count, indicating the importance of these cytokines and their shared receptor in asthma (Truyen, et al., 2006).

In recent years, research has moved forward to prevent the interaction of IL-4 and IL-13 with their receptors by using various types of inhibitors (IL-4 mutant analogs, anti-IL-4 or IL-13 mAbs) and to develop a few small inhibitor molecules targeting the high affinity IL-4R α . Furthermore, novel classes of inhibitors (fusion of cytokine protein with a toxin or suicidal gene) are now being investigated for cancer therapy (Ul-Haq, et al., 2016).

As evidenced by allergen challenge studies, the anti-IL-13 mAbs IMA-638 and IMA-026 do not affect blood or sputum eosinophils or airway hyperresponsiveness (AHR) in patients with mild atopic stable asthma (reviewed in (N. A. Landolina & Levi-Schaffer, 2014)). mAbs directed against IL-13 include lebrikizumab (IgG4) and tralokinumab (IgG4), both binding to soluble IL-13 and thus preventing the activation of the shared receptor. While the former mAb has been shown to improve both asthma exacerbations and lung function in moderate to severe asthmatic patients (Hanania, et al., 2015), more studies are required to prove the efficacy of the latter (Brightling, et al., 2015). Both mAbs are currently in phase 2

(Hoffmann-La Roche, 2016b) and phase 3 (AstraZeneca, 2016) trials for the treatment of asthma respectively, and recently completed phase 2 trials for persistent moderate to severe atopic dermatitis (Hoffmann-La Roche, 2016c; MedImmune LLC, 2016) with no results posted as yet. Lebrikizumab is also in a phase 2 safety evaluation clinical trial for COPD (Hoffmann-La Roche, 2016a). The anti-IL-4R α mAb dupilumab (IgG) has been shown to improve clinical responses in adults with moderate to severe atopic dermatitis in a dose-dependent manner, accompanied by a good safety profile (Thaci, et al., 2016). It is currently in phase 3 for severe steroid dependent asthma (Sanofi, 2016) and phase 3 studies for moderate to severe atopic dermatitis have already been completed with no results are yet (Regeneron Pharmaceuticals & Sanofi, 2016).

Lebrikizumab and dupilumab are among the ‘Abs to watch’ since their development is currently promising (Reichert, 2016) for both the therapy of asthma and atopic dermatitis. Nevertheless pascolizumab, an IgG1 mAb targeting IL-4, although showing good potential in preclinical studies, appears not to have progressed beyond phase 2 studies for symptomatic steroid naïve asthma (Facet Biotech, 2012) (Table 1).

CCR3: the driver of eosinophil trafficking

CCR3, a GPCR, is the high affinity receptor for the CC chemokines eotaxin-1/CCL-11, eotaxin-2/CCL24 and eotaxin-3/CCL-26, among the eleven natural CCR3 ligands (Gong & Wilhelm, 2009). CCR3 is highly expressed on eosinophils (Figure 2) and is the primary receptor mediating differentiation, chemotaxis and degranulation of these cells (Lamkhioed, et al., 2003; Ahmadi, et al., 2016). In the context of allergy, CCR3 is also expressed on mast cells, basophils and Th2 lymphocytes (Neighbour, et al., 2014) rendering it an attractive target. Expression of CCR3 is upregulated in asthma and correlates with disease severity, eotaxin levels and AHR (Gong & Wilhelm, 2009; Neighbour, et al., 2014). It is widely accepted that CCR3 and eotaxins play a critical role also in allergic rhinitis and contact

dermatitis that are characterized by eosinophil migration into affected tissues (Ma, et al., 2002; Amerio, et al., 2003; Teran, et al., 2006; Paplinska, et al., 2007; Saito, et al., 2016). For example, in allergic rhinitis eotaxin challenge in the nasal mucosa after allergen priming causes a strong eosinophil influx (Gorski, et al., 2002). Based on all these observations, considerable research has been carried out in the past decade to block CCR3 or eotaxins in order to stop eosinophil mobilization and infiltration (reviewed in (N. A. Landolina & Levi-Schaffer, 2014)) with trials now ongoing in asthmatic patients. Preclinical studies have shown that in an allergic airway mouse model, anti-CCR3 mAbs abrogated eosinophil recruitment to the lungs, AHR and decreased mucus hypersecretion (Justice, et al., 2003). Similarly, Ki19003, a CCR3 antagonist, prevented the infiltration of eosinophils into the airways and allergen-induced subepithelial and peribronchial fibrosis (Komai, et al., 2010). So far, numerous novel CCR3 antagonists have been developed and their efficacy and usefulness in downregulating eosinophil recruitment into inflamed tissues have been investigated *in vitro*, *in vivo* in animal models and in clinical studies in patients with asthma, allergic rhinitis and other eosinophil mediated allergic diseases (Erin, et al., 2002; Amerio, et al., 2003; Gangur, et al., 2003; Elsner, et al., 2004; Pruitt, et al., 2007; Gong & Wilhelm, 2009; Neighbour, et al., 2014). Recently, in a murine model of IgE-mediated allergic conjunctivitis in CCR3 knockout mice, it was shown that CCR3 receptor regulates both eosinophilia and hyperresponsiveness, (Fukuda, et al., 2012). Interestingly, Provost et al. (2013) have reported that eotaxin-3 is more effective to induce the migration of eosinophils of asthmatics than eotaxin-1 and eotaxin-2 (Provost, et al., 2013). These authors found that eotaxin-3 triggered a second phase of eosinophil migration between 12 and 18 h. The CCR3 antagonists SB 328437 and SB 297006 inhibited eosinophil migration, while the CCR3 selective antagonist GW766944, which has been evaluated in phase 2 studies in patients with mild to moderate asthma, failed to show efficacy (GlaxoSmithKline, 2012; Neighbour, et al.,

2014) (Table 1). An anti-CCR3 mAb completely blocked the effect of all eotaxins on eosinophils of healthy subjects and the effect of eotaxin-2 on the eosinophils of asthmatic patients. Interestingly, CCR3 blockade did not affect the eotaxin-3 induced second migration phase of eosinophils in asthmatics. It was therefore concluded that eotaxin-3 is a more effective chemoattractant than eotaxin-1 and eotaxin-2 for eosinophils of asthmatics (Provost, et al., 2013). In another recent study, eotaxin-3 was also more effective in bactericidal activity against the airway pathogens *Streptococcus pneumoniae*, *S. aureus*, *nontypeable Haemophilus influenzae*, and *Pseudomonas aeruginosa*. These findings indicate that the eotaxins could contribute to host defense against common airway pathogens and that their activities are modulated by mast cell proteases (Gela, et al., 2015). Additional clinical trials with TPI ASM8, a drug product containing two modified phosphorothioate antisense oligonucleotides downregulating the common β -chain of IL-3, IL-5, GM-CSF receptors and human CCR3, have been reported (Gauvreau, et al., 2008). This construct has been shown to limit the allergen-mediated increase in target gene mRNA and airway responses in asthmatic patients.

Although CCR3 is expressed on mast cells, there are controversial data regarding its role on mast cells in allergy. Collington et al. (2010) reported that on murine BMMC, CCR3 may not mediate mast cell migration towards LTB₄ or SCF since BMMC obtained from CCR3 knockout and wildtype mice were similar in their chemotaxis (Collington, et al., 2010). However, in another study of CCR3 knockout mice, allergen-mediated hypersensitivity reactions as well as IgE-mediated mast cell degranulation were significantly inhibited (Miyazaki, et al., 2009). Taken together, the CCR3 and eotaxin network is a potential therapeutic target for allergies. However, the hunt for the best method to exploit this therapeutic avenue is still ongoing (Ahmadi, et al., 2016).

Histamine receptors: H4R continues the HR saga

The discovery and characterization of histamine, its receptors (H1R, H2R, H3R, and the recently found H4R) and blocking drugs is one of the great milestones in the history of medicine. This breakthrough was marked by two Nobel Prize awards in the field of histamine research, *Daniel Bovet*, in 1957, for the discovery of an H1R antagonist (Bovet, 1957) and *Sir James Black*, in 1988, for the development of an H2R antagonist (Black, et al., 1957).

All four HRs are GPCRs (Panula, et al., 2015) and are expressed on various cell types (Ennis, et al., 2013; Panula, et al., 2015). The detailed structure of HRs, their signaling mechanism and ligands, their role in various physiological and pathophysiological conditions and their pharmacological functions have been recently reviewed (Panula, et al., 2015).

Mast cells and basophils are well established prominent sources of preformed histamine in humans, and through this mediator play an important role in causing the symptoms of allergy, acting on target organs such as lungs, skin and intestine. Importantly, histamine also modulates the functions of eosinophils and Th2 cells (Ohsawa & Hirasawa, 2014).

In humans, mast cells express H1R, H2R and H4R while the expression of H3R is limited to brain mast cells. Eosinophils express all four HRs (Gibbs & Levi-Schaffer, 2012; Migalovich-Sheikhet, et al., 2012; Ennis, et al., 2013) (Figure 2). Histamine binding to H1R on mast cells leads to the activation of phospholipase A2 and phospholipase D and downstream of the transcription factor NF- κ B through Gq/11 and G β γ (Banu & Watanabe, 1999). The activation of H1R *via* histamine stimulates the further release of histamine and other mediators, increases the expression of adhesion molecules and chemotaxis of eosinophils and neutrophils, enhances the antigen-presenting cell capacity, increases the co-stimulatory activity of B cells, and downregulates IgE production (Simons & Akdis, 2009). The first anti-histamine drugs developed were the H1R antagonists. Even though H1R expression on human skin mast cells has been reported to be low (Lippert, et al., 2004; Gibbs

& Levi-Schaffer, 2012), H1R antagonists can inhibit mast cell activation at high doses and can so be used as mast cell stabilizing drugs (Levi-Schaffer & Eliashar, 2009). In allergic rhinitis, H1R antagonists are very effective in reducing the symptoms and significantly improving the quality of life by reducing sneezing, rhinorrhea and nasal itching (Simons & Akdis, 2009). H1R antagonists reduce levels of IL-31, a key cytokine in atopic dermatitis. The usefulness of H1R antagonists in various allergic conditions besides allergic rhinitis, such as in allergic conjunctivitis, urticaria and anaphylaxis is well known (reviewed in (Simons & Akdis, 2009)).

The H2R plays an important role in allergic inflammatory responses by mediating bronchial smooth muscle relaxation, vasodilation and mucus production in the airway (Parsons & Ganellin, 2006). Histamine, *via* H2R, inhibits eosinophil, mast cell and neutrophil chemotaxis, IL-12 production by dendritic cells and suppresses Th2 cells and cytokine formation (Simons & Akdis, 2009).

The expression of H3R appears to be low in peripheral tissues while it is high in neuronal mast cells and eosinophils, and therefore H3R is not considered an important target in allergy. H3R and H4R have 40% sequence homology and are functionally similar (Morse, et al., 2001; Zhu, et al., 2001).

H4R, the newest defined receptor, is highly expressed on human neutrophils, basophils, mast cells and eosinophils, displaying a defined role in eosinophil chemotaxis (M. O'Reilly, et al., 2002; Simons & Akdis, 2009). H4R increases calcium flux in human eosinophils and, together with H2R, enhances IL-16 production in lymphocytes (Parsons & Ganellin, 2006; Simons & Akdis, 2009). Jemima et al. (2014) characterized the role of H4R on human mast cells, specifically HMC-1 and LAD-2 cell lines, and CBMC by stimulating them with histamine as well as with a selective H4R agonist. They found that H4R activation increased calcium influx, degranulation, cytokine release and cysteinyl leukotriene and LTB₄

production (Jemima, et al., 2014). Moreover, a recent study carried out on LAD-2 showed that H4R mediates TNF- α and IL-8 release *via* multiple signaling pathways (i.e. PI3K, Ca²⁺-calcineurin-NFAT and MAPKs), thus pointing out the importance of this receptor (X. F. Chen, et al., 2016). Several data demonstrate a role of H4R in chronic itch, particularly in allergic inflammatory states (reviewed in (Shim & Oh, 2008; Jeffry, et al., 2011)).

Even though selective H1R, H2R and H3R antagonists exist, an effective H4R antagonist is still elusive (Sadek & Stark, 2016). The first selective H4R antagonist, JNJ 7777120 (Jablonowski, et al., 2003), has been reported to have anti-inflammatory activity *in vitro* and *in vivo* (Thurmond, et al., 2004). This compound inhibited histamine-induced chemotaxis and calcium influx in BMMC. Studies on H4R knockout mice and mice treated with the H4R antagonist, alone or in combination with H1R-antagonists, showed a decrease in scratching behaviors and chronic allergic inflammation (Ohsawa & Hirasawa, 2014). Another selective H4R antagonist, JNJ 39758979, has been shown to be effective in reducing histamine-induced pruritus in a randomized clinical study in healthy subjects without significantly decreasing wheal or flare (Kollmeier, et al., 2014). (Table 1). The H4R in particular is gaining importance in asthma, and both animal and clinical studies are ongoing that target this receptor (Kiss & Keseru, 2014; Grosicki & Kiec-Kononowicz, 2015; Thurmond, 2015). Optimal H4R antagonists have not yet been developed and studied.

CRTH2/DP2: the receptor for the mast cell cardinal arachidonic acid metabolite, PGD₂

The chemokine receptor homologous molecule expressed on T helper type 2 cells (CRTH2), also known as DP2, is a GPCR for PGD₂ and its metabolites (Hirai, et al., 2001; Nagata & Hirai, 2003; Kostenis & Ulven, 2006). PGD₂ is the major arachidonic acid metabolite released by IgE-activated mast cells and has an important role in allergy and other pathophysiological conditions involving mast cells, eosinophils and Th2 cells (Pettipher, 2008). PGD₂ also binds to DP1, a GPCR family receptor. DP2, first discovered on human

Th2, is also present on the surface of human eosinophils (Figure 2), basophils, macrophages and dendritic cells and intracellularly in mast cells (Nagata, et al., 1999a; Nagata, et al., 1999b; Moon, et al., 2014b). During inflammation, DP2 mediates the chemotaxis of these cells in response to PGD2 (Nagata, et al., 1999a; Shiraishi, et al., 2005; Moon, et al., 2014b). DP2 expression profile on various human tissues and peripheral blood leucocytes is discussed in (Nagata & Hirai, 2003). DP1 and DP2 share very little homology and differ in their signaling mechanisms (Mesquita-Santos, et al., 2011). DP1 signals through elevation of cAMP, while DP2 activation leads to the increase of intracellular calcium, reduction in cAMP (Sawyer, et al., 2002) and downstream activation of PI3K (Xue, et al., 2007).

PGD2 interaction with DP2 and DP1 leads to local vasodilatation, which contributes to the formation of edema, eosinophil and Th2 cell recruitment, stimulation of Th2 cytokine synthesis and, in asthma, bronchoconstriction and mucus production (Gervais, et al., 2001; Hirai, et al., 2001). Few studies though would show that PGD2 contributes to allergen induced pulmonary eosinophilia also *via* DP1 (Matsuoka, et al., 2000; Arimura, et al., 2001). Nevertheless clinical studies of the DP1 antagonist laropipran failed to prove any efficacy in asthmatic and allergic rhinitis patients (Philip, et al., 2009). It has been shown that chemotaxis of eosinophils in response to PGD2 is ultimately determined by a balance between two opposing downstream signaling pathways: the cAMP-dependent inhibitory pathway activated *via* DP1 and the prevailing stimulatory pathway activated *via* DP2 (Monneret, et al., 2001; Kostenis & Ulven, 2006; Sandig, et al., 2007). This indicates a strong role of DP2 over DP1 in eosinophil chemotaxis (Almishri, et al., 2005). The activation of DP2 by PGD2 on eosinophils changes their morphology, induces their migration from the bone marrow (Heinemann, et al., 2003; Schratl, et al., 2007), and enhances their degranulation and chemotactic responsiveness (Gervais, et al., 2001; Heinemann, et al., 2003;

Bohm, et al., 2004). Moreover, on eosinophil DP2 expression has been found to be elevated in patients with atopic dermatitis (Yahara, et al., 2010).

Recently NVP-QAV680, a novel selective antagonist of DP2 has been developed (Sandham, et al., 2013). When tested in human CBMC/peripheral blood eosinophil co-cultures (AEU) NVP-QAV680 decreased tryptase release from IgE-activated mast cells, indicating a role for PGD₂/DP2 axis in the AEU (Seiff M., Migalovich-Sheikhet H., Sandham D., Dubois G., Elishmereni M., Levi-Schaffer F., unpublished data). Importantly, MK-7246 and Compound A, two other selective DP2 antagonists, have been shown to reduce inflammation in animal asthma models (Lukacs, et al., 2008; Gervais, et al., 2011).

OC000459, another DP2 antagonist (N. Barnes, et al., 2012), demonstrating promising potential as oral treatment for asthma in a first clinical trial has been moved to phase 2 studies to assess its effectiveness in preventing or attenuating asthma exacerbation symptoms after rhinovirus infection (Imperial College London, et al., 2016). The DP2 antagonist, AZD1981 has been investigated in phase 2 clinical trials in patients with moderate to severe COPD with no serious adverse effects (AstraZeneca, 2013). Moreover, its efficacy has been evaluated in uncontrolled asthmatic patients under inhaled CS treatment (AstraZeneca, 2014) with improvement of lung functionality and a good safety profile (Table 1). Of the DP2 antagonists available, setipiprant also showed therapeutic potential, decreasing the allergen induced airway responses in allergic asthmatic subjects (Diamant, et al., 2014). Lately, preliminary studies on healthy subjects have been conducted with a novel DP2 antagonist, ACT-453859 (Actelion, 2015), which showed good tolerability even at high doses and a prolonged half-life (Gehin, et al., 2015). Based on their properties on eosinophils and other cells involved in allergic inflammation, several DP2 antagonists have been developed and extensively studied as one of the current and most promising drugs in the treatment of allergic diseases (Pettipher, et al., 2007; Pettipher & Hansel, 2008; Schuligoi, et al., 2010;

Ulven & Kostenis, 2010; Pettipher & Whittaker, 2012; Townley & Agrawal, 2012; C. Lamers, et al., 2013; Norman, 2014).

Thymic stromal lymphopoietin receptor: a chief control for allergic inflammation

Thymic stromal lymphopoietin (TSLP) receptor is a heterodimer composed of the TSLP receptor α -chain and IL-7R α -chain (reviewed in (Cianferoni & Spergel, 2014)). TSLP, mainly produced by epithelial and endothelial cells, binds to the TSLPR. It is an IL-7 like cytokine that has recently received attention as an important player in allergic diseases and thus a valid candidate to be targeted therapeutically. In fact, it induces the release of pro-inflammatory Th2 mediators by mast cells and eosinophils through TSLPR, functionally present on the surface of these cells (Figure 2) (Cook, et al., 2012; Migalovich-Sheikhet, et al., 2012). Furthermore, TSLP has been shown to delay human eosinophil apoptosis and to promote their chemotaxis and adhesion properties (C. K. Wong, et al., 2010). On mast cells, TSLP affects their development, inducing proliferation and differentiation from progenitors (Han, et al., 2014). It also induces chemokine and cytokine synthesis (Kaur, et al., 2012).

The expression of TSLP has been reported to be elevated in patients with severe asthma (Shikotra, et al., 2012) and atopic dermatitis, where the stratum corneum TSLP level was correlated to the severity of the disease (Sano, et al., 2013). While no progress has been reported in targeting its receptor, an anti-human TSLP mAb (IgG2 λ), AMG 157 has been developed, decreasing allergen induced bronchoconstriction and different parameters of airway inflammation before and after allergen challenge (Gauvreau, et al., 2014). AMG 157 has completed phase 1 studies in atopic dermatitis, and is currently in phase 2 studies for the treatment of asthma (Amgen, 2011; Celeste Porsbjerg, et al., 2016) and for the induction of tolerance in individuals with cat allergy in combination with antigen-specific immunotherapy (National Institute of Allergy and Infectious Diseases & Immune Tolerance Network, 2016).

Although no results have been posted yet, AMG 157 is expected to decrease AHR in asthmatic patients already on therapy with inhaled CS and might possibly become a new anti-asthmatic drug.

ST2 and IL-33: emerging players in allergy

The IL-33 receptor ST2 (also known as T1) is composed of a transmembrane form and a soluble form and is mainly expressed on mast cells, eosinophils and other immune cells (Figure 2). Its ligand IL-33, a member of the IL-1 superfamily, induces the formation of ST2 complex (reviewed in (Saluja, et al., 2015)). ST2 and IL-33 are presently recognized to have an important role in the development of asthma and atopic dermatitis.

IL-33 expression has been reported to increase in airway smooth muscle cells (Prefontaine, et al., 2009) and epithelial cells in bronchial asthma (Prefontaine, et al., 2010) and to be associated to pediatric eosinophilic esophagitis (Judd, et al., 2016). IL-33 is known to initiate and amplify innate type 2 responses in ILC2 as its signaling is crucial for determining airway eosinophilia and IL-5/IL-13 production from lung ILC2 after allergen challenge (Bartemes, et al., 2012). Importantly, IL-33 has been found also to be generated by mast cells after IgE-mediated activation. In addition, deficiency of ST2 or Ab-mediated blockade of either ST2 or IL-33 abrogated the late phase inflammatory response in a passive cutaneous anaphylaxis model, emphasizing the key role of IL-33/ST2 axis for the progression of IgE-dependent inflammation (Hsu, et al., 2010).

IL-33, mainly secreted by bronchial epithelial cells, has been shown to directly stimulate mast cells to produce IL-1 β and IL-6, inducing Th17 differentiation following OVA challenge (K. A. Cho, et al., 2012). Importantly, mast cell chymase (Roy, et al., 2014) cleaves the full-length IL-33 to make its active form that is ten times more potent than the full-length

protein (Lefrancais & Cayrol, 2012). Moreover, IgE-activated mast cells substantially produce and release soluble ST2 in both human and mouse systems (Bandara, et al., 2015).

To further stress the role of this cytokine in exacerbating inflammation, intraperitoneal administration of IL-33 has been reported to cause splenomegaly and eosinophilia, to elevate levels of serum IgA and IgE and to induce pro-inflammatory IL-4, IL-5 and IL-13. Moreover, IL-33 treated mice showed large amounts of mucus in the airway epithelium and inflammatory infiltrates of eosinophils, neutrophils and other cells in the gastro-intestinal tract (Schmitz, et al., 2005). IL-33 also induces murine eosinophil differentiation from hematopoietic cells in an IL-5 dependent manner and, most importantly, its presence, together with the ST2 receptor, is required for the expression of CCR3 on differentiating eosinophils (Stolarski, et al., 2010).

From these findings it can be deduced that neutralization of IL-33 as well as blockade of ST2 represent important strategies to suppress allergy and the mast cell-eosinophil interplay. Neutralization of IL-33 has been accomplished by the mAb AMG 282 which is currently in phase 1 clinical trials for atopic asthma (Amgen, 2016b) and chronic rhinosinusitis with nasal polyps (Amgen, 2016a).

In general, the approach of blocking ST2 is not easy to carry out since the soluble form is known to function as a decoy receptor for IL-33 that, in contrast to membrane ST2, attenuates the Th2 inflammatory responses (Oboki, et al., 2010). This means that neutralization of the membrane ST2 might be also accompanied by blocking of its soluble form. Nevertheless IL-33 targeting is very promising for the therapy of allergy. Still we should not forget that IL-33 has a plurifunctional profile, for example, it is a key factor in protective antiviral T cell responses (Peine, et al., 2016).

Sphingosine-1-phosphate receptors are differentially expressed on mast cells and eosinophils

The sphingosine-1-phosphate (S1P) receptors, i.e. S1PR₁ – S1PR₅, are GPCRs that bind the sphingolipid signaling molecule S1P, produced by various cells and notably also by IgE-activated mast cells (Kulinski, et al., 2016). S1PRs are differently expressed on a number of human immune cells (Idzko, et al., 2002; Spiegel & Milstien, 2003; Martino, et al., 2007; Marsolais, et al., 2011). CBMC express S1PR₁ and S1PR₂ (Mackle, et al., 2008), while eosinophils express all S1PRs except for the S1PR₂ (Idzko, et al., 2002) (Figure 2). S1PR₁ expression was found to be significantly upregulated by allergen challenge in allergic rhinitis patients; interestingly, this increased expression was abolished in corticosteroid-treated patients (Mackle, et al., 2008).

S1PR₁ was found to be essential for CBMC migration but apparently has no role in degranulation or cytokine and chemokine release, while S1PR₂ positively regulates both allergen induced degranulation and chemokine secretion (Olivera, 2008; Price, et al., 2008). Moreover, on rodent mast cells S1PR₁ and S1PR₂ function in an autocrine manner to fine-tune mast cell functions (Olivera, 2008; Price, et al., 2008).

Because of these evidences, S1P and its receptors have been regarded as relevant objectives in allergy treatment. S1PR₁ activation by agonists has inhibitory functions. Indeed, its activation effectively downregulates allergic inflammation. For example, FTY720 (2-amino-2-(2-[4-octylphenyl]ethyl)-1,3-propanediol), an agonist (after phosphorylation by sphingosine kinase 2) for S1PR₁ (Hogenauer, et al., 2008), alleviated allergic airway inflammation by reducing eosinophil and T cell accumulation and the development of AHR (Sawicka, et al., 2003; Idzko, et al., 2006). Other selective agonists targeting S1PR₁ for therapeutic purposes have been developed (Ryan & Spiegel, 2008). The S1PR₁ selective agonist SEW2871 showed anti-inflammatory activity *in vitro* (Hughes, et al., 2008) and *in*

vivo (S. Pan, et al., 2006). In an allergen induced asthma model, another selective agonist for S1PR₁, CYM5442 (Marsolais, et al., 2011) inhibited CCL5 and CCL17 airway release and accumulation of activated T cells and eosinophils (Marsolais, et al., 2011). S1PR₂ activation leads to mast cell degranulation, cytokine and chemokine release (Oskeritzian, et al., 2010) and regulation of pro-inflammatory cytokine production (Kulinski, et al., 2016). Remarkably, anti-S1P mAbs inhibited mast cell activation. Furthermore, in *in vivo* acute allergic reaction models, airway infiltration and mast cell activation, serum levels of histamine, cytokines and chemokines (i.e. MCP-1/CCL2, MIP-1 α /CCL3 and RANTES/CCL5) are downregulated (Oskeritzian, et al., 2015). These studies highlight the therapeutic potential of S1PRs. Since S1PR₁ has anti-inflammatory and S1PR₂ has pro-inflammatory properties the best strategy could be a combination of targeting both by using an agonist for S1PR₁ and an antagonist for S1PR₂. However, much research is still needed to develop selective modulators of S1PRs activity for therapeutic purposes (Juif, et al., 2016).

Cannabinoid receptors: from the central nervous system to the periphery to stop inflammation

The cannabinoid receptors CB₁ and CB₂ belong to the GPCR family. CB₁ and CB₂ have been differentiated based on sequence (they share 48% amino acid homology), signaling, tissue distribution and their reactivity towards agonists and antagonists (Howlett, et al., 2002; Lu & Mackie, 2016). Both CB₁ and CB₂ bind Δ^9 -tetrahydrocannabinol, a cannabinoid derived from *Cannabis sativa* (Gaoni & Mechoulam, 1964) and a pharmacologically active synthetic analog of Δ^9 -tetrahydrocannabinol (Howlett, et al., 2002; Svizenska, et al., 2008).

CB₁ is most abundantly expressed in the central nervous system, while CB₂ is expressed primarily in cells of the immune and hematopoietic systems (Howlett, et al., 2002; Pacher, et al., 2006). CB₁ and CB₂ are both expressed on mast cells (Samson, et al., 2003) and CB₂ is found on eosinophils (Oka, et al., 2004) (Figure 2).

Both CB₁ and CB₂ are targeted by endocannabinoids and synthetic cannabinoids. Two endocannabinoids have been well characterized, 2-arachidonoylglycerol and anandamide (Howlett, et al., 2002). 2-arachidonoylglycerol acts as a full agonist to both CB₁ and CB₂, but with higher affinity for CB₂, while anandamide acts only as a partial agonist for both receptors (Nikan, et al., 2016). CB₁ mediates primarily the psychoactive effects of cannabinoids, while CB₂ mainly mediates anti-inflammatory and immunomodulatory actions (Rom & Persidsky, 2013). Activation of cannabinoid receptors on various immune cells regulates cell migration and the production of cytokines and chemokines (discussed in (Cabral, et al., 2015)). CB₁ and CB₂ on mast cells have anti-inflammatory effects. CB₁ downregulates mast cell degranulation by elevation of cAMP levels (Small-Howard, et al., 2005), while CB₂ downregulates the release of pro-inflammatory mediators (Pini, et al., 2012). Blocking of CB₁ on mast cells in the human hair follicles stimulates degranulation and increases cell numbers without affecting mast cell proliferation *in situ* (Sugawara, et al., 2012). It has also been reported that inhibition of mast cell activation and neurogenic inflammation by a mechanism mediated *via* CB₁ and CB₂ could decrease the pain in sickle cell anemia (Vincent, et al., 2016). Activation of CB₁ expressed on bronchial nerve endings has bronchodilatory effects and therefore might be beneficial in AHR and asthma (Pini, et al., 2012).

Regarding eosinophils, 2-arachidonoylglycerol has been reported to induce chemotaxis of these cells *via* CB₂ activation (Oka, et al., 2004; Kishimoto, et al., 2006) and reported to be increased by IL-5 in a Lyn-dependent manner (Larose, et al., 2014). Selective agonist JWH-133 has been shown to not only induce a migratory response in both human and mouse peripheral blood eosinophils, but also to induce eosinophil shape change, CD11b surface expression, adhesion and production of reactive oxygen species. Similarly, systemic application of this selective agonist worsened AHR and enhanced eosinophil counts in

bronchoalveolar lavages in a mouse model of acute airway inflammation (Frei, et al., 2016) suggesting the importance of an antagonistic approach directed to the CB₂ receptor in eosinophilic reactions. Indeed the specific CB₂ antagonist SR144528 attenuates both the recruitment of eosinophils and ear swelling in a murine chronic contact dermatitis model (Oka, et al., 2006).

Based on the fact that cannabinoids have been shown to play an important role in downmodulating allergic respiratory disorders (Pacher, et al., 2006; Pini, et al., 2012), selective modulators of CB₁ and CB₂ have been developed over the past decades, and studies are underway to exploit the endocannabinoid system for therapeutic purposes (Console-Bram, et al., 2012; Rom & Persidsky, 2013). The CB₂ agonist Gp1a has been shown to downregulate IgE levels in antigen-immunized mice (Newton & Klein, 2012). In patients with allergic asthma, allergen challenge was found to increase anandamide levels in the bronchoalveolar fluid (Zoerner, et al., 2011). Recently, anandamide was reported to increase human airway epithelium permeability through arachidonic acid metabolites (Shang, et al., 2016) indicating a potential role in enhancing asthma severity. In contrast, the CB₁/CB₂ agonist CP55,940 can effectively prevent antigen-induced asthma-like reactions in guinea pigs (Giannini, et al., 2008). Altogether, these studies indicate that CB₁, CB₂ and endocannabinoids are potential but complex therapeutic targets for the treatment of allergic inflammation. On mast cells, CB₁/CB₂ activation is anti-inflammatory while on eosinophils CB₂ activation is pro-inflammatory. Therefore, a differential approach using CB₁/CB₂ agonists and antagonists in the treatment of allergic conditions will be required, agonists targeting CB₁/CB₂ on mast cells without penetrating the blood-brain barrier and antagonists targeting CB₂ on eosinophils to downregulate them.

Bradykinin receptors: from asthma to hereditary angioedema

Two bradykinin receptors have been identified: B1R, an inducible receptor, and B2R, a constitutive receptor, both belonging to the GPCR family (Leeb-Lundberg, et al.). Bradykinin, a vasoactive, pain inducing and pro-inflammatory kinin released during acute inflammation is the main B1R and B2R ligand. Bradykinin contributes to bronchial asthma symptoms due to its ability to mediate smooth muscle contraction, increase nitric oxide, prostaglandin and cytokine synthesis and raise pulmonary arterial pressure leading to bronchial obstruction (Sabatini, et al., 2013; Ricciardolo, et al., 2016).

B1R and B2R, expressed on eosinophils (Figure 2), are upregulated in asthmatic patients (C. M. Bertram, et al., 2009). These two receptors are also expressed on neutrophils in both asthmatic and healthy subjects (C. Bertram, et al., 2007). Even though bradykinin activity involves predominantly the constitutive B2R (Sabatini, et al., 2012; Sharma, 2014), the inducible B1R also plays an important role, since its activation induces neutrophil chemotaxis during asthma. In consequence, blocking B1R might contribute to a decrease of airway inflammation (C. Bertram, et al., 2007; C. M. Bertram, et al., 2009).

In addition, B2R antagonists can inhibit the progressive airway obstruction in asthma due to a decrease in airway remodeling (Sabatini, et al., 2013; Ricciardolo, et al., 2016). Actually, bradykinin induces contractility and differentiation of lung fibroblasts into myofibroblasts through the activation of the constitutive B2R (Vancheri, et al., 2005; Holgate, et al., 2010). Myofibroblasts are able to produce and release several cytokines and chemokines (i.e. IL-6, IL-8, IL-10, TNF- α), inflammatory mediators (i.e. platelet activating factor, prostaglandin E2 (PGE2)) and growth factors (i.e. GM-CSF, SCF, transforming growth factor β) that contribute to the maintenance of the inflammatory response (Baum & Duffy, 2011). *De novo* expression of α -smooth muscle actin, a common molecular marker for fibroblast differentiation, is typical of this transition into myofibroblasts (Hinz, et al., 2007).

Interestingly, *in vitro* studies show that the CS budesonide and the β_2 -adrenoceptor agonist formoterol, alone or in combination, are able not only to reduce the bradykinin-mediated differentiation of fibroblasts (Kelly, et al., 2010), but also to completely block it (Sabatini, et al., 2012), thus preventing the expression of α -smooth muscle actin.

Icatibant (Hoe 140), a B2R antagonist, was found to display a potential profile as an anti-asthmatic treatment (Akbari, et al., 1996). When compared to R954, an antagonist of B1R, in a murine asthma model icatibant was reported to increase vascular endothelial growth factor levels while R954 both inhibited eosinophil activation, proliferation, migration and enhanced the production of transforming growth factor β and vascular endothelial growth factor, both involved in tissue repair (Vasquez-Pinto, et al., 2010).

Even though icatibant showed some anti-asthmatic properties in older studies, no further findings have been reported. Recently, icatibant has been licensed for the treatment of acute attacks of hereditary angioedema in adults (FDA News Release, 2011; Farkas, 2016). Nevertheless, the B1R antagonist R954 can be considered as a promising therapeutic approach in asthma treatment. This compound has recently been evaluated in a pre-clinical pharmacokinetic and toxicology study (Gobeil, et al., 2014), showing a good profile for early clinical studies.

Mas-related gene X2: the novel understanding of mast cell driven anaphylaxis like responses

The Mas-related gene X (MrgX) is a subset of Mrg receptors, a large family of almost 50 members of GPCRs. Mrg receptor expression is largely restricted to sensory neurons of the dorsal root ganglion and for this reason believed to have a role in nociception (reviewed in (Burstein, et al., 2006)). Specifically, MrgX₂ and other members of the Mrg family were thought to be expressed only on human neuronal populations and to mediate pain sensation. Most interestingly MrgX₂ was recently found also to be expressed by human mast cells

(Figure 2) where it is activated by antimicrobial peptides such as LL-37 (similarly to formyl peptide receptor (FPR)), causing calcium mobilization and degranulation (Subramanian, et al., 2011). Strikingly MrgX₂ expression is elevated in skin mast cells in patients with chronic urticaria and is accompanied by eosinophil infiltration in most of the studied patients (Fujisawa, et al., 2014).

Recently, the mouse orthologue of the human MrgX₂, named Mrgprb2, has been characterized. Both the human and mouse receptors are identified as the main mast cell receptor for a range of cationic secretagogues, including inflammatory peptides/small molecule drugs associated with allergic type reactions or systemic pseudo-allergic/anaphylactoid reactions. Activation of Mrgprb2 by basic secretagogues has been shown to activate murine mast cells both *in vitro* and *in vivo*, to release histamine and to mediate inflammation, while its absence in Mrgprb2 knockout mice abolished these effects (McNeil, et al., 2015). Importantly, eosinophil derived MBP and EPO have been shown to stimulate human skin mast cells through MrgX₂ (Fujisawa, et al., 2014), which is yet another example of the powerful crosstalk between mast cells and eosinophils. In summary, it seems that MrgX₂ might represent an important target which, if selectively blocked, could reduce drug-induced anaphylactoid reactions.

CD48 and CD244 (2B4): the couple has to be “divorced”

The CD48 receptor is a glycosylphosphatidylinositol (GPI)-anchored cell surface receptor of the CD2/SLAM family (Elishmereni, et al., 2011). Structurally, CD48 is composed of two Ig-like domains – one variable (V)-like domain and –one constant 2 (C2)-like domain, but does not contain a transmembrane domain. CD48 is anchored to the cell surface by a GPI anchor which includes a phosphoethanolamine linker, glycan core and a phospholipid tail. CD48 is expressed on mast cells, eosinophils and nearly all hematopoietic cells including basophils, and its expression is regulated by viral and bacterial products and immune associated proteins

(McArdel, et al., 2016). CD48 functions as an important co-stimulatory molecule in lymphocyte activation (Yashiro-Ohtani, et al., 2000), facilitating cell adhesion (Yokoyama, et al., 1991; Barber & Long, 2003) and innate responses to bacterial infection (Shin, et al., 2000; Shin & Abraham, 2001).

Since CD48 is expressed on the key effector cells of allergy (Figure 2) and on basophils (Munitz, et al., 2006a; Munitz, et al., 2007), its importance in allergy is evident. CD48 is one of the 291 signature genes in mouse models of asthma/allergic airway inflammation (Zimmermann, et al., 2003). Its expression is upregulated on eosinophils in peripheral blood and in bronchial biopsies of asthma patients (Gangwar, R. S., Minai-Fleminger, Y., Seaf, M., Gutgold, A., Shikotra, A., Chauhan, A., Holgate, S., Bradding, P., Howarth, P., Eliashar, R., Berkman, N. and Levi-Schaffer, F, unpublished data) as well as in skin lesions of atopic dermatitis patients (Minai-Fleminger, et al., 2014). CD48 expression is also upregulated in eosinophils of a murine model of experimental asthma (Munitz, et al., 2006a; Munitz, et al., 2007) and in both eosinophils and mast cells during bacterial infections in mice (Rocha-de-Souza, et al., 2008). On both mast cells and eosinophils CD48 is a receptor for *S. aureus* and its exotoxins (Rocha-de-Souza, et al., 2008; Minai-Fleminger, et al., 2014) and on mast cells CD48 also binds *E. coli* and *M. tuberculosis* (Malaviya, et al., 1999; Munoz, et al., 2003).

Due to lack of a transmembrane domain, CD48 has a limited ability to signal on its own. However, the GPI linker allows it to associate with cholesterol-rich lipid rafts and associated signaling molecules (McArdel, et al., 2016). Crosslinking of CD48 on human peripheral blood eosinophils by anti-CD48 mAbs initiated an activation cascade and enhanced release of eosinophil granule proteins (Munitz, et al., 2006a). Moreover, we found that *S. aureus* toxins can differentially induce Lyn, Fyn, Erk1, and Erk2 phosphorylation in human eosinophils.

Like other GPI molecules, CD48 has also a soluble form (sCD48), which previously was detected only in the human serum of patients with lymphoproliferative disorders (G. M.

Smith, et al., 1997) and more recently in primary Sjögren's syndrome patients (Nishikawa, et al., 2016). We have recently found that serum sCD48 levels are significantly upregulated in human asthma patients as compared to healthy individuals and to allergic rhinitis and atopic dermatitis patients (Minai-Fleminger, et al., 2013). Human peripheral blood eosinophils activated by *S. aureus* enterotoxin B (SEB) *in vitro* release EPO, ECP and IL-8, induce the formation of sCD48 by cell-associated phospholipase C and phospholipase D, and upregulate CD48 transcription (Minai-Fleminger, et al., 2014; Gangwar & Levi-Schaffer, 2016). sCD48 was also detected in a murine SEB-induced peritonitis model in which eosinophil infiltration is a prominent event (Gangwar & Levi-Schaffer, 2016).

The broad expression pattern of CD48 on immune cells and its upregulated expression on mast cells and eosinophils in allergic inflammation and when complicated by bacterial infection make CD48 a central receptor mediating key cellular interactions and regulating the outcome of the allergic response. In both mice and humans, CD244 (2B4), a CD2 like molecule of the SLAM family, is a high affinity ligand of CD48, whereas CD2 has only low affinity for CD48 (McArdel, et al., 2016).

The high-affinity ligand of CD48, CD244, has not yet been extensively studied in allergy. CD244 was first identified on natural killer cells and T lymphocytes showing multiple functions. Structurally, CD244 consists of a N-terminal V-like Ig domain, a C2-like Ig domain and type 1 transmembrane proteins including four cytoplasmic Immunoreceptor Tyrosine-based Switch Motifs (ITSM) (McNerney, et al., 2005). Phosphorylation of tyrosine residues in these motifs facilitates binding of a SLAM-associated protein (SAP) which regulates the final functional outcome (Waggoner & Kumar, 2012). The first ITSM motif is sufficient for 2B4-mediated natural killer cell activation while the third ITSM is responsible for inhibitory signals (Eissmann, et al., 2005). CD244 is an important molecule for antiviral immunity and its crosslinking activates natural killer cell cytotoxicity. In humans, CD244 is

expressed on all natural killer cells, most of the CD8⁺ T cells, $\gamma\delta$ T cells, monocytes, basophils, (McArdel, et al., 2016), and eosinophils (Figure 2) in which its expression and activating function were first described by us (Munitz, et al., 2005). Although CD244 is not expressed on human mast cells, it is expressed on mouse mast cells as well as on mouse eosinophils and, functionally, exhibits both inhibitory and stimulatory effects, respectively, on these cells (Elishmereni, et al., 2014; Gangwar & Levi-Schaffer, 2014). Human natural killer cells express two isoforms of CD244, CD244 short and CD244 long that differ in a small portion of the extracellular domain. Depending upon the CD244 isoform, the interaction with its receptor CD48, the degree of CD244 crosslinking and the availability of SAP, CD244 can induce either activation or inhibition of natural killer cells (Lee, et al., 2004; D. Yuan, 2008; Mathew, et al., 2009). All these interactions make CD244 signaling very complex and, in the absence or non-functionality of SAP (for example in X-linked lymphoproliferative disease), mixed effects are to be expected (Watzl & Claus, 2014).

As mentioned above, the most important players in the pro-inflammatory physical crosstalk within the AEU are mast cell CD48 and eosinophil 2B4 (Figure 1) (Minai-Fleminger, et al., 2010; Elishmereni, et al., 2011; Arthur & Bradding, 2016). This CD244-CD48 mediated cell-cell interaction increases the survival of eosinophils and the activation of mast cells (Minai-Fleminger, et al., 2010; Elishmereni, et al., 2011; Elishmereni, et al., 2013).

Experimental approaches to prevent CD48 mediated activation of effector cells of allergic inflammation by neutralizing or blocking CD48 have been explored in experimental systems *in vitro* and *in vivo*. CD48 blocking on human peripheral blood eosinophils results in decreased activation after SEB activation (Minai-Fleminger, et al., 2014). Notably, neutralization of CD48 by anti-CD48 mAb reduces lung inflammation in an experimental murine asthma model (Munitz, et al., 2007). Using a murine model of atopic dermatitis we have recently demonstrated that skin inflammation is significantly reduced in CD244

knockout mice (Elishmereni, et al., 2014), as well as in CD48 knockout mice (Gangwar, R. S., Seaf, M., Fyhrquist, N., Karra, L., Alenius, H. and Levi-Schaffer, F. unpublished data). These findings indicate that in the case of an impaired physical AEU formation, allergic inflammation is significantly reduced. Therefore, another therapeutic approach could be to prevent the formation of AEU by blocking either CD48 on mast cells or CD244 on eosinophils. This could be achieved by single-chain Fv Abs with blocking properties. sCD48 can act as a decoy receptor (Levi-Schaffer & Gangwar, 2016). In a recent study we showed that sCD48 has an anti-inflammatory role in SEB induced eosinophilic inflammation. *In vitro*, sCD48 blocked SEB-induced eosinophils degranulation and chemotaxis (Gangwar & Levi-Schaffer, 2016). *In vivo*, sCD48 significantly reduced peritoneal inflammation in the SEB-induced murine peritonitis model (Gangwar & Levi-Schaffer, 2016). sCD48 can also bind to CD244 expressed by eosinophils and inhibit human CBMC-induced eosinophil survival in the AEU (Elishmereni, et al., 2011). It should be noted here that there are other receptor-ligand pairs expressed in both mast cells and eosinophils which also can take part in forming the physical AEU such as CD300a/phosphatidylserine, CD112 (nectin-2)/CD226 (DNAM-1) and Siglec-7 and its ligands (α 2,8-disialyl and α 2,6-sialyl carbohydrates) (Figure 1).

Moreover, blocking of CD244 on eosinophils (*in vitro*) by sCD48 resulted in decreased eosinophil activation by an anti-CD244 mAb (Gangwar, R. S., Minai-Fleminger, Y., Seaf, M., Gutgold, A., Shikotra, A., Chauhan, A., Holgate, S., Howarth, P., Bradding, P., Eliashar, R., Berkman, N. and Levi-Schaffer, F, unpublished data). Based on the above data on the key importance of CD48 and CD244 in allergic inflammation, future therapeutical approaches could be considered. These might include the blocking of CD48 on mast cells/eosinophils or blocking of CD244 on eosinophils by synthetic receptor/ligand analogs. This approach has

been explored in collagen-induced arthritis murine model by using small peptides to block the CD2-CD48 interaction with CD58 (A. Gokhale, et al., 2013; A. S. Gokhale, et al., 2015).

Other activating receptors: serotonin receptor, purinergic receptors, corticotropin-releasing hormone receptor

In addition to the receptors described above, mast cells and eosinophils express several additional activating receptors. However, the usefulness of some of them in terms of developing a future drug for allergy is doubtful either because of contrasting functions of the receptors, or because their activation will interfere with physiological functions of cells other than mast cells or eosinophils. The therapeutic potential of some other receptors is only beginning to be explored.

Among the most interesting activating receptors are the serotonin receptors. Serotonin is one of the best characterized neurotransmitters and vasoactive amines that regulates several physiologic functions in the central nervous system and in the periphery (Berger, et al., 2009; Ahern, 2011; Baganz & Blakely, 2013; Durk, et al., 2013). Serotonin has been shown to modulate adhesion, migration and cytokine production in mast cells, eosinophils and monocytes/macrophages (Kushnir-Sukhov, et al., 2006; Muller, et al., 2009; Durk, et al., 2013; B. N. Kang, et al., 2013). The serotonin receptor 1a, coupled to adenylyl cyclase *via* Gi-protein, is expressed on both human (skin) and murine mast cells (Kushnir-Sukhov, et al., 2006; Ritter, et al., 2012) and its activation causes inflammation due to the migration of mast cells and their adherence to the site, apparently without mast cell degranulation (Nordlind, et al., 2008). However, the exploitation of serotonin receptors as potential pharmacological targets for anti-allergic therapy could be risky due to the wide expression of these receptors in the central nervous system and their many roles in important physiological functions such as memory, anxiety and cardiovascular functioning.

Purinergic receptors (PRs), identified as the ones that mediate relaxation of gut smooth muscle in response to adenosine 5'-triphosphate (ATP), represent another class of important receptors expressed by mast cells, eosinophils, neutrophils and macrophages, being involved in regulating their apoptosis and cytokine secretion (Lister, et al., 2007; Volonte & D'Ambrosi, 2009; Cekic & Linden, 2016). Specifically, the subtypes P2XR and P2YR are expressed on eosinophils and are responsible for eosinophil chemotaxis (Idzko, et al., 2001; Ferrari, et al., 2006). On murine mast cells, ATP-induced stimulation of the subtype P2X7R (Cekic & Linden, 2016) triggers the production of IL-6 and TNF- α (Lister, et al., 2007) and in human mast cells induces degranulation and mediator release (Wareham & Seward, 2016). The corticotropin-releasing hormone (CRH) receptor consists of two subtypes (CRHR₁ and CRHR₂), expressed both in the central nervous system and in the periphery. They bind to CRH, a peptide hormone involved in the regulation of the hypothalamic-pituitary-adrenocortical axis. CBMC express the subtype CRHR₁ that, when stimulated by CRH, triggers the release of vascular endothelial growth factor (J. Cao, et al., 2006; O'Kane, et al., 2006). Moreover, CRH is able to enhance the release of vascular endothelial growth factor from allergic mast cells and to induce the expression of the Fc ϵ RI gene in these cells (Asadi & Theoharides, 2012). CRH and its receptors might be specific targets when psychological stress worsens asthma, atopic dermatitis and other mast cell driven diseases.

4.2. Inhibitory receptors on mast cells and eosinophils as therapeutic targets

Inhibitory receptors have been broadly studied in the context of natural killer cells and T cells whose activation mainly by major histocompatibility complex (MHC) class I ligands is a major focus in cancer research (Turnis, et al., 2015). After the discovery that mast cells and eosinophils exhibit a series of functional inhibitory receptors, we and others have proposed to consider them as a target for anti-allergic treatment (reviewed by (Karra, et al., 2009). Notably, while in the field of activating receptors the neutralization of ligands is a much-

exploited approach, in the case of inhibitory receptors, activation of the receptors by specific ligands has been less investigated.

Typical inhibitory receptors are characterized by the intracellular immunoreceptor tyrosine based inhibitory motif (ITIM) and are classified according to their structure in two different families: Ig receptor superfamily (characterized by a single V-type Ig like domain in their extracellular portion) and calcium dependent lectin superfamily (reviewed by (Karra, et al., 2009). Once activated by their specific ligands or mAbs, these receptors undergo phosphorylation of the ITIM tyrosine residues followed by recruitment of cytoplasmic SH2 containing phosphatases such as SHP-1, SHP-2, SHIP-1, leading to further dephosphorylation steps and finally to inhibitory signaling.

Some inhibitory receptors have been described to occur uniquely on murine mast cells (reviewed in (Karra, et al., 2009)) and eosinophils, for example leukocyte immunoglobulin-like receptor B4, also known as glycoprotein 49B1 (Norris, et al., 2007) and paired Ig-like receptors (PIR-A and PIR-B) (Munitz, et al., 2008) while others are expressed on both murine and human cells being sometimes structural homologues or functional paralogues. Although many of these receptors have been characterized in the past, their therapeutic exploitation in the field of allergy has not been investigated, in contrast to cancer immunotherapy where a flourishing use of immunological checkpoints has recently begun with encouraging data. In the cancer field, an excellent example of inhibitory receptor is Programmed cell death-1 interacting with its ligand that inhibits T lymphocyte proliferation, survival and effector functions. This pathway has been targeted by a mAb (MDX-1106) in trials/already approved for advanced metastatic solid tumors (Zitvogel & Kroemer, 2012; FDA News Release, 2014). We will discuss here the most recent advances in inhibitory receptor targeting mast cells and eosinophils. In the case of inhibitory receptors, the strategy

is to activate rather than block their machinery since this will lead to downregulation of mast cell and eosinophil functions and hence of allergy.

FcγRIIb: the pioneer of ITIM containing inhibitory receptors

FcγRIIb is the low affinity receptor for IgG, composed of an extracellular portion (two Ig-like domains) and expressed in humans in two different forms denominated as FcγRIIb₁ and FcγRIIb₂ (reviewed by (Malbec, et al., 2002)). It is the first receptor in which the ITIM was discovered (reviewed in (Lehmann, et al., 2012)). FcγRIIb is broadly expressed on cells of the innate immune system including mast cells and eosinophils (Figure 2) as well as on cells of the adaptive immune system. On mast cells, FcγRIIb has been shown to crosslink to the adjacent activating FcεRI by the same multivalent ligand to form immune complexes and inhibit FcεRI-dependent murine mast cell activation (Daeron, et al., 1995). In a murine model of allergic airway inflammation, FcγRIIb deficient mice exhibited strong allergic lung inflammation accompanied by increased bronchoalveolar lavage fluid cellularity, eosinophilia and mucin content upon ragweed extract challenge, suggesting its possible involvement in airway disease (Dharajiya, et al., 2010).

In general, functional activation of FcγRIIb has been shown to occur only following co-aggregation with ITAM-containing receptors that leads to ITIM phosphorylation, recruitment of SHIP-1 and a negative response (reviewed by (Daeron, et al., 2008)). Wu et al. (2014) have shown that functional single nucleotide polymorphisms of the gene encoding FcγRIIb are risk factors for atopy, possibly being responsible for increased sensitivity to allergens (J. Wu, et al., 2014).

FcγRIIb has been targeted by the Ab XmaB7195 directed against B cells expressing inhibitory receptors and tested in humanized mouse models of Ig production (S. Y. Chu, et al., 2012). This Fc-engineered Ab links FcγRIIb and the IgE B-cell receptor, both inhibiting

plasma cell differentiation/production of IgE and neutralizing its soluble form (S. Y. Chu, et al., 2012). Since the final goal of this therapeutic Ab was, as for omalizumab, to suppress IgE production, the efficacy of the two Abs (XmAb7195 vs omalizumab) was compared. Relative to the activity of omalizumab, XmAb7195 has a much higher affinity for human IgE and FcγRIIb, significantly reducing both free and total IgE levels. Thus, it is an excellent candidate for the therapy of allergic asthma (S. Y. Chu, et al., 2012). Since FcγRIIb appears to be a crucial modifier in the development of allergy, it might be the missing element in its treatment.

The CD300a and CD300f inhibitory receptor: applying brakes to mast cell and eosinophil activation

The human CD300 family has eight members (CD300 a-h), all characterized by a single extracellular Ig V-like domain but with diverse intracellular portions and signaling pathways. In addition to their single receptor functions, the members of the CD300 family form heterocomplexes (homodimers and heterodimers). CD300a and CD300c are paired receptors on the cell surface, having >80% similarity in their amino acid composition but showing inhibitory and activating profiles, respectively.

Except for CD300g, whose distribution is limited to endothelial cells (Takatsu, et al., 2006), all CD300 family members are found on leukocytes (Borrego, 2013). CD300a is expressed on the surface of natural killer cells (Cantoni, et al., 1999) and on multiple subsets of T and B cells (Clark, et al., 2007; Silva, et al., 2011). Moreover, CD300a is present in a vast repertoire of myeloid lineages such as plasmacytoid dendritic cells, myeloid dendritic cells, monocytes, macrophages, neutrophils, basophils (Gibbs, et al., 2012), lung, skin and nasal polyps and, last but not least, mast cells (Bachelet, et al., 2005) and eosinophils (Munitz, et al., 2006b) (Figure 2).

Identified physiological ligands for the two inhibitory receptors of this family (human CD300a and CD300f) are lipids and specifically phosphatidylserine and phosphatidylethanolamine for CD300a (Zenarruzabeitia, et al., 2015), and ceramide, sphingomyelin and phosphatidylcholine for CD300f (Izawa, et al., 2014). Phosphatidylserine and phosphatidylethanolamine are expressed at the early stage of cell death/apoptosis as membranal “flags” for phagocyte engulfment whereas ceramide is a major chemical component of cell membranes including those of normal skin. Several skin diseases are characterized by alterations in the permeability of the epidermal barrier, most likely due to variations in ceramide composition. There might be a connection between the state of inflammation and the ‘non-binding’ of some members of the inhibitory receptor family of their physiological ligands.

CD300a has four tyrosine residues in its cytoplasmic portion, three of which are consensus sequences for ITIM. Phosphorylation of the ITIM tyrosines is accompanied by recruitment/activation of SHP-1 and SHIP-1 in mast cells and of SHP-1 in eosinophils (Bachelet, et al., 2005; Munitz, et al., 2006b).

CD300a expression on mast cells, *in vitro*, is downregulated by eosinophil MBP and eosinophil-derived neurotoxins. This finding points to a crucial pro-inflammatory crosstalk between mast cells and eosinophils in allergic inflammation. On CBMC, CD300a crosslinking with either FcεRI or c-Kit (*in vitro*) results in inhibition of IgE-induced degranulation (Bachelet, et al., 2005) and SCF mediated differentiation and survival (Bachelet, et al., 2008). The activation of CD300a on mast cells is accompanied by a decrease in intracellular calcium influx and de-phosphorylation of SYK (Bachelet, et al., 2005). CD300a expression on peripheral blood eosinophils is increased in hypoxia, one of the main characteristics of inflamed tissues, and by GM-CSF, and these effects are abolished by inhibition of hypoxia-inducible factor-1 (Nissim Ben Efraim, et al., 2013).

Activation of CD300a has also been found to inhibit human eosinophil chemotaxis, survival and release of pro-inflammatory mediators such as TNF- α , IL-1 β , interferon- γ (in response to eotaxin), GM-CSF and IL-5. Moreover, CD300a crosslinking inhibits human eosinophil-mediated murine fibroblast proliferation, suggesting that CD300a activation might be important in bronchial asthma and atopic dermatitis, where negative modulation of fibroblasts is required (Munitz, et al., 2006b).

CD300a on mast cells has been the target of bispecific Ab fragments generated by its conjugation with anti-human IgE (IE1M) and tested in different murine models of allergic disease. IE1M has been shown to potently inhibit the allergic response in a murine model of passive cutaneous anaphylaxis and to abrogate asthma (Bachelet, et al., 2006). A similar approach has been used in a chronic model of experimental asthma in which CD300a was co-aggregated with CCR3 (bispecific LC1) (Alvarez-Errico, et al., 2004).

Recently, another member of the CD300 family, CD300f has been found to inhibit human cell function *via* its ITIM (Alvarez-Errico, et al., 2004) (reviewed in (Borrego, 2013)). Specifically, CD300f inhibits Fc ϵ RI mediated mast cell activation (*in vitro* (Izawa, et al., 2014)) and significantly downregulates mast cell-dependent allergic responses including passive anaphylactic reactions and chronic airway inflammation ((Izawa, et al., 2012)). Furthermore, human peripheral blood eosinophils from allergic rhinitis patients have been shown to express high levels of CD300f (Moshkovits, et al., 2014).

In the mouse, the CD300f orthologue, LMIR3, regulates eosinophil homeostasis, inhibiting eotaxin induced eosinophil migration, actin polymerization and calcium influx (Moshkovits, et al., 2014). However, despite being an inhibitory receptor, in IgE-independent murine aeroallergen models carrying a strong IL-4 signature, CD300f physically associates with IL-4R- α , potentially amplifying IL-4R- α mediated responses (Moshkovits, et al., 2015). Therefore, further research is needed to understand whether CD300f might be a valuable target for

future anti-allergic drugs. On the other hand, CD300a seems so far to be a key regulator of the allergic setting and a candidate to be targeted by specific Abs for the treatment of allergy, with particular emphasis on airway inflammation and tissue remodeling in asthma. Finally, the relevance of blocking the activating functions of some CD300 family members requires further studies.

Sialic acid-binding immunoglobulin-like lectins (Siglecs): new targets for mast cells and eosinophils in allergy and beyond

The Siglec superfamily comprises Ig-type carbohydrate-binding proteins (lectins), consisting of two subsets according to their sequence similarities and evolutionary conservation. The first subset comprises the highly conserved sialoadhesin (Siglec-1), CD22 (Siglec-2), myelin-associated glycoprotein MAG (Siglec-4) and Siglec-15. The second subset includes CD33 (Siglec-3)-related Siglecs, Siglec-5-12, Siglec-14 and Siglec-16, all expressed in humans but quite variably in other species.

Siglecs are broadly expressed on the surface of numerous immune cells where they play regulatory functions (reviewed in (Crocker, et al., 2007)). CD22 and most of CD33-related Siglecs are ITIM bearing, recruiting phosphatases and inositol phosphatases, although some of them such as Siglec-14 and Siglec-16 have recently been identified as DAP-12 coupled ‘activating’ molecules (H. Cao & Crocker, 2011). Siglec members bind glycans terminating in sialic acid residues which are widely expressed on the surface of many cells comprising bacteria and tumor cells, thus opening another chapter of interactions and possible activation pathways (M. K. O'Reilly & Paulson, 2010). In particular, several pathogens as well as neoplastic cells might express sialic acids on their surface as a mechanism of immune evasion so that a Siglec-mediated inhibitory response might take place following ligand recognition (Hudak, et al., 2014). Apart from Siglec-4, Siglec-6 and the ‘non sialic acid

binding' Siglec-XII, all other Siglecs are found on the surface of various leukocyte subsets and mast cells (Kiwamoto, et al., 2012).

Although being highly specific for B cells, the inhibitory CD22 has been found intracellularly in human mast cells (Yokoi, et al., 2006) and on murine gastrointestinal eosinophils in which it negatively regulates function and survival (Wen, et al., 2012). In general, CD33-related Siglecs inhibit or promote apoptosis in leukocytes, but as of now there is no information on similar effects in mast cells (Park & Bochner, 2011).

Siglec-7 is expressed on human natural killer cells in which it has been shown to modulate cytotoxicity (Nicoll, et al., 2003) as well as on human eosinophils and mast cells (Munitz, et al., 2006b) (Figure 2). Siglec-7 has been found, once co-crosslinked to FcεRI, to inhibit human mast cell degranulation and cytokine release, further proving that targeting inhibitory receptors in allergic diseases might limit allergic reactions (Mizrahi, et al., 2014). Preliminary data on eosinophils indicate that also these cells are subject to a Siglec-7 downregulatory function (Legrand F., Landolina N, Levi-Schaffer F, Klion A, unpublished data). No paralog of Siglec-7 exists in the mouse, thus rendering it difficult to assess its role in models of allergic diseases.

Siglec-8 is expressed on human eosinophils and mast cells and has a functional paralog in the mouse named Siglec-F (Bochner, 2009). The activation of Siglec-8 on eosinophils by mAbs promotes human eosinophil apoptosis, using mechanisms involving caspase and reactive oxygen species (Nutku, et al., 2005). A stronger Siglec-8 mediated pro-apoptotic effect was observed under stimulation with IL-5, IL-33 or GM-CSF (Na, et al., 2012). A similar inhibition of the anti-apoptotic effect of both IL-5 and GM-CSF was observed when CD300a was crosslinked on eosinophils cultured in the presence of these cytokines (Munitz, et al., 2006b). In addition, engagement of Siglec-8 on human mast cells results in inhibition of FcεRI dependent mediator release as observed for Siglec-7 (Yokoi, et al., 2008).

In vivo studies have shown that administration of monoclonal and polyclonal Abs targeting Siglec-F decreases both blood and tissue eosinophil count and eosinophil mediated inflammation (Zimmermann, et al., 2008). Additionally, binding of the constitutively expressed glycoproteins Muc4 and Muc5b to Siglec-F and the ensuing control of eosinophilia has recently been characterized in the murine lungs. Mice deficient in Muc5b in the lungs show exaggerated eosinophilic inflammation and decreased rates of eosinophil apoptosis in response to IL-13 administration, suggesting that Muc5b engagement mediates a pro-apoptotic pathway *in vivo* as a resolving mechanism for eosinophilic inflammation (Kiwamoto, et al., 2015).

These encouraging results strongly underline the potential of Siglecs (especially of Siglec-8 and perhaps of Siglec-7) to both downregulate mast cell activation and decrease the number of eosinophils. In other words, mAbs or specific ligands (glycans) for the inhibitory Siglecs (Magesh, et al., 2011) may be global tools to “apply brakes” in the early phase of allergy, to “relieve the flames” in the late phase of allergy, and to control hypereosinophilic syndromes.

Leukocyte Ig-like receptor: a rising new target in allergy

The leukocyte Ig-like receptor (LIR), composed of extracellular Ig-like portions, long cytoplasmic domains and up to four ITIMs associating with SHP-1 (Colonna, et al., 1997), comprises the inhibitory receptors LIR-1–LIR-3, LIR-5 and LIR-8. LIR-1 is expressed by progenitors of mast cells (Cosman, et al., 1997), but there is some controversy whether it is also present on eosinophils (Tedla, et al., 2003; Munitz, et al., 2006b) and some other cells (Figure 2). LIR-2 and LIR-3 are expressed on the surface of both eosinophils and mast cell progenitors (Tedla, et al., 2008). Both LIR-1 and LIR-2 recognize MHC class I molecules. LIR-1 has been reported to bind a MHC class I homolog encoded by human cytomegalovirus UL18 (Chapman, et al., 2000) and LIR-2 has been shown to bind several angiopoietin-like proteins, oligomeric β -amyloid and others (reviewed in (X. Kang, et al., 2016)).

Most of the work on LIR-1 and LIR-2 in the framework of allergy has been carried out with the mouse orthologue, the inhibitory PIR-B expressed by both mast cells and eosinophils (Munitz, et al., 2008). PIR-B, mainly expressed on the cell surface, has also an activating isoform named PIR-A. PIR-B activation on mast cells causes tyrosine phosphorylation and SHP-1 recruitment. Its crosslinking with Fc ϵ RI or c-Kit inhibits IgE or SCF mediated mast cell activation, respectively (C. C. Chen, et al., 2002).

Once activated, PIR-B regulates IL-5 induced eosinophil development and function as a suppressor of PIR-A pro-apoptotic activities. *In vivo*, bone marrow eosinophils from PIR-B knockout mice undergo apoptosis. Moreover, aeroallergen induced lung eosinophilia and stimulation of lung Th2 cells is impaired in these mice (Ben Baruch-Morgenstern, et al., 2014). Activation of gp49B1, the closest known mouse orthologue of LIR-5, inhibits SCF-induced mast cell secretion. Moreover, activation of mast cells obtained by injection of SCF in gp49B knockout mice results in increased degranulating mast cell numbers and causes tissue swelling, underlining the relevance of this molecule in the context of inflammatory conditions where mast cells are activated (Feldweg, et al., 2003). Although much therapeutic potential can be associated with LIRs, further evaluation of their role in human disease is required to understand whether they could be a valid target for future drugs.

SIRP- α and CD200R

Other potentially relevant inhibitory receptors of the Ig superfamily are the signal regulatory protein SIRP- α and CD200R, expressed by both mast cells and eosinophils (Figure 2) (Ghannadan, et al., 2002) as well as by other hematopoietic cells. SIRP- α is a membrane glycoprotein receptor belonging to the SIRP family, characterized by three Ig-like domains in its extracellular portion and four ITIMs in its cytoplasmic region that upon phosphorylation recruit SHP-1 and SHP-2, thus mediating a negative signal. SIRP- α binds to a broadly

expressed Ig like glycoprotein named CD47, having the potential to signal itself, which indicates that SIRP- α /ligand interaction might result in two-way signaling (reviewed in (van Beek, et al., 2005)).

In murine mast cells, SIRP- α is a negative regulator of IgE-mediated activation (Y. F. Pan, et al., 2013). Activation of SIRP- α with specific Abs on the surface of murine eosinophils inhibits the release of mediators whereas eosinophils with mutated SIRP- α fail to be inhibited (Verjan Garcia, et al., 2011). Moreover, SIRP- α is an important regulator of murine eosinophil homeostasis, having strong effects on eosinophil survival. Because of its clear-cut action on mast cells, SIRP- α may be one of the negative players to attenuate the acute phase of allergic inflammation and possibly be a therapeutic target in eosinophil-associated diseases.

CD200R lacks the ITIM but its crosslinking has been shown to inhibit Fc ϵ RI-mediated mast cell activation, unlike other receptors of the same family. Interestingly, although co-crosslinking to Fc ϵ RI is not critical to exert an inhibitory effect on human mast cells, co-crosslinking of the two receptors shows synergistic effects (Cherwinski, et al., 2005). CD200R mediated inhibition of murine mast cell degranulation has been shown to occur *via* phosphorylation of three tyrosine residues (S. Zhang & Phillips, 2006) in the cytoplasmic domain, recruitment of SHIP and inhibition of Ras/MAPK pathways (S. Zhang, et al., 2004). Notably, asthmatic patients have been reported to have lower expression of CD200R in circulating leukocytes, giving rise to the hypothesis that local delivery of recombinant CD200R might re-establish lung homeostasis (Lauzon-Joset, et al., 2015). In an experimental model of asthma, the administration of recombinant CD200R abrogated AHR, reduced the accumulation of Th2 cells and diminished levels of pro-inflammatory cytokines in bronchoalveolar lavages (Lauzon-Joset, et al., 2015). Although CD200R might receive

attention in the treatment of asthma, its therapeutic profile, as mentioned for PD-1, seems now to be much more relevant to cancer therapy (Coles, et al., 2011).

Other inhibitory receptors: c-lectin mast cell function-associated antigen, platelet-endothelial cell adhesion molecule-1, leukocyte-associated Ig like receptor, E-prostanoid receptors

As described for the activating receptors, there are also a few more inhibitory receptors on mast cells and eosinophils that might be future aims in allergy treatment. One of them is the c-lectin mast cell function-associated antigen (MAFA), a lectin-like type II transmembranal glycoprotein whose expression and function have been well described for rat mast cells and basophils. We know that the human MAFA homolog is expressed on lung mast cells, but we do not yet know its function (M. B. Lamers, et al., 1998). Engagement of MAFA inhibits degranulation and release of cytokines from IgE-activated rat mucosal mast cells (RBL-2H3) *via* phosphorylation of ITIM in its short cytoplasmic tail (Redelinghuys & Brown, 2011) and reduces the proliferation rate of the RBL-2H4 cell line by modulation of the Ras signaling pathway (Abramson & Pecht, 2002).

The Platelet-Endothelial Cell Adhesion Molecule-1 (PECAM-1) is another ITIM bearing Ig immunoreceptor expressed on the surface of both mast cells and eosinophils (Chiba, et al., 1999) as well as other cells. Activation of PECAM-1 inhibits FcεRI-mediated activation of RBL-2H3 by phosphorylation of its two cytosolic ITIMs (Sagawa, et al., 1997b) and recruitment of SHP-2 (Sagawa, et al., 1997a). PECAM-1 knockout mice exhibit a hyperresponsive phenotype, with higher levels of ear swelling and reduced numbers of intact mast cells upon induction of local anaphylaxis (M. X. Wong, et al., 2002). Human eosinophil PECAM-1 interacts with αvβ3 integrin expressed on endothelial cells, increasing adhesion and possibly promoting recruitment of eosinophils to the site of inflammation (Chiba, et al.,

1999). However, an *in vivo* study showed that stimulation of this adhesion molecule with anti-PECAM-1 Ab did not inhibit eosinophil recruitment (Miller, et al., 2001). Therefore, the validity of targeting PECAM-1 for allergy remains doubtful at the present time.

Leukocyte-associated Ig like receptor (LAIR)-1 is a single Ig like domain constitutively present on mast cells (Florian, et al., 2006), eosinophils (Verbrugge, et al., 2006) (Figure 2), and other cells (Meyaard, et al., 1997; Bonaccorsi, et al., 2010) as well as on natural killer cells where it promotes a strong inhibition of their cytotoxicity. On mast cells and eosinophils, activation of both LIRs and LAIRs results in a reduction of preformed mediators and cytokine release (Karra, et al., 2009). Interestingly, a LAIR-1 ligand is collagen (Meyaard, 2008), thus implicating its possible role in multiple inflammatory responses. In the characterization of LAIR-1 knockout mice it was observed that blood eosinophils were significantly elevated only in younger mice, but to date no other studies have been performed (Tang, et al., 2012), rendering the possible targeting of this receptor in allergy still elusive.

E-prostanoid receptors, EP2 and EP4, have been described as inhibitory receptors on both mast cells (Feng, et al., 2006) and eosinophils (Sturm, et al., 2008). PGE₂ binding to EP2 inhibits mast cell degranulation (Kay, et al., 2006), cytokine transcription and FcεRI-mediated eicosanoid production (Feng, et al., 2006) and eosinophil chemotaxis towards eotaxin, PGD₂ and C5a (Sturm, et al., 2008). Similarly, EP4 stimulation inhibits mast cell activity (Feng, et al., 2006), reduces eosinophil chemotaxis, upregulates eosinophil CD11b levels and enhances their production of reactive oxygen species (Luschnig-Schratl, et al., 2011).

Noteworthy, the activation of EP3 *via* PGE₂ results in mast cell exocytosis and eicosanoid formation, highlighting the activating feature of this receptor (Feng, et al., 2006). Since PGE₂ exerts anti-inflammatory effects, (Luschnig-Schratl, et al., 2011), EP2 and EP4 agonists could therefore be an innovative therapeutic alternative in eosinophilic diseases.

5. Future prospective and conclusions

Much progress in therapeutic drug research has been achieved in recent years, with new approaches to cure different diseases due to a better understanding of disease etiopathology. This is also true for allergy, although researchers are still looking for the “best” target and the “best” way for anti-allergic therapy, with patient endotypes recently being taken into account. Mast cells and eosinophils are the recognized main effector cells of allergy and hence, the main cells to be aimed at in therapy. Specific targeting of mast cell activation has been recently achieved, to some extent, through the anti-IgE mAb omalizumab (Xolair), an approved treatment for persistent severe allergic asthma and chronic urticaria. Other still not validated options include the inhibition of FcεRI phosphorylation events with specific inhibitors of SYK and LAT. In a future perspective, targeting of sterol, sphingolipid and protein enriched structures as lipid raft components (Varshney, et al., 2016) that associate with LAT might be a useful approach to negatively regulate FcεRI signaling. With regard to eosinophils, the survival, differentiation and activation of these cells is controlled by the anti-IL-5 mAbs mepolizumab and reslizumab, a treatment that has had some success in the therapy of allergic asthma.

Several other options for mast cell (Migalovich-Sheikhet, et al., 2012) and eosinophil targeting are available (N. A. Landolina & Levi-Schaffer, 2014) and have to be further explored. In addition, novel strategies targeting mast cells and eosinophils either directly or indirectly are being pursued. One such example is the attempt to ‘resolve’ allergic inflammation by exploiting pro-resolving lipid mediators, i.e. lipoxin A4 and resolvin D1, that bind to the ALX/FPR2 (lipoxin A4) and to FPR2 and GPR32 (resolvin D1) (Krishnamoorthy, et al., 2012). In murine models of asthma, lipoxins and FPR2 have been shown to function as potent downregulators of airway inflammation. Specifically, administration of a lipoxin A4 analog inhibited AHR and pulmonary inflammation,

significantly decreasing the levels of Th2 cytokines, eotaxin, prostanoids and other mediators (Levy, et al., 2002).

Additionally, the 'protective' function of lipoxin B4 (whose receptor has not yet been defined) has been recently described in murine models of allergic rhinitis and asthma where it inhibited allergic inflammation more efficaciously than dexamethasone (Karra, et al., 2015). Clinical trials involving patients with infantile eczema showed that topical administration of 15(R/S)-methyl-lipoxin A4 significantly reduced the severity of the disease (S. H. Wu, et al., 2013). Further studies are focusing on the lipoxin-FPR axis in patients with severe asthma in which this interaction is thought not to work properly and thus not to shut down the inflammatory signal as expected (Elliot Israel & National Heart Lung and Blood Institute, 2015). A deeper understanding of lipoxins and other pro-resolving lipid mediators interacting with specific receptors and the expression of these receptors on inflammatory cell types including mast cells and eosinophils in allergy is clearly a promising area of research that may lead to new therapeutic options. Another novel approach is based on human umbilical cord blood-derived stem cells, which is currently under clinical trial for the treatment of moderate to severe atopic dermatitis. Preliminary results attest to an overall reduction of inflammation in the treatment group, which suggests that this might be an effective therapy (H. S. Kim, et al., 2016).

A very recent strategy for treating allergy includes the use of the microRNA-223, targeting the insulin like growth factor 1 receptor and promoting mast cell apoptosis (Gao, et al., 2016). Current approaches to anti-allergic therapy also focus on mast cell genetics and function to identify mutations and abnormalities in order to create a bank of information about anaphylaxis, allergies, asthma and other inherited mast cell diseases (National Institute of Allergy and Infectious Diseases, 2016).

New developments in Ab-based therapy have led to the concept of “sweeping Abs” as a therapeutic tool for anti-allergic therapy (reviewed in (Igawa, et al., 2016)). The conventional Abs are very effective in binding to circulating antigens in plasma and preventing them from binding to IgE, but the limitation is that this antigen-Ab complex is not cleared fast enough from the plasma, leading to increases in overall antigen-Ab concentrations. The “sweeping Ab” is an Ab that incorporates two Abs: one is a variable region that binds to free antigen and the other is the Fc region, which facilitates the uptake of the Ab-antigen complex into the endosome. In this way the antigen is more efficiently cleared from the circulation.

Last, but not least, in the emerging concept of personalized or precision medicine, a mosaic of preventive measures and medical approaches are taking into consideration the enormous variability between individuals that may affect the clinical outcome of certain treatments (Galli, 2016). In the field of allergy, one example is asthma therapy in which the emergence of new pathways defines asthma phenotypes and proper markers for each subtype (Wenzel, 2016) including some of the discussed activating receptors. We therefore believe that there will be no “good” therapy for all different allergic patients, but, according to their phenotype, one or more than one pathway will be targeted in a precise fashion. Moreover, among these therapeutic options, mast cell and eosinophil receptors, either activating or inhibitory, will be the main players.

Conflict of Interest Statement:

The authors declare that there are no conflicts of interest.

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Table 1

Current status of drugs targeting receptor/ligand interactions for allergy therapy as described in the text.

Receptor/target	Drug	Status	Application
IgE	Anti-IgE mAb: omalizumab	Commercially available	severe persistent asthma and chronic urticaria
IgE producing B cells	mAbs targeting CεmX epitope on IgE-B cells: 1. quilizumab 2. h4B12	Clinical trial: 1. Phase 2b 2. Clinical trial completed	moderate to severe allergic asthma, chronic urticaria atopic dermatitis
IL-5 _R	anti-IL-5Rα mAb: benralizumab	Clinical trial: Phase 3	asthma and COPD
IL-5	anti-IL-5 mAb: mepolizumab (Nucala) and reslizumab (Cinqair)	Approved	severe eosinophilic asthma
	anti-IL-5 mAb: mepolizumab	Clinical trial: Phase 3	COPD
GM-CSF	anti-GM-CSF mAb: KB003	Clinical trial: Phase 2	moderate to severe asthma
IL-4Rα	anti-IL-4Rα mAb: dupilumab	Clinical trial: Phase 3	asthma and Moderate to severe atopic dermatitis

IL-4	anti-IL-4 mAb: pascolizumab	Clinical trial: Phase 2	symptomatic steroid naïve asthma
IL-13	anti-IL-13 mAb: lebrikizumab	Clinical trial: Phase 2	severe asthma, COPD
	anti-IL-13 mAb: tralokinumab	Clinical trial: Phase 3	uncontrolled asthma
	anti-IL-13 mAbs: lebrikizumab and Tralokinumab	Clinical trial: Phase 2	persistent moderate to severe atopic dermatitis
CCR3	CCR3 antagonist: GW766944	Clinical trial: Phase 2	Mild to moderate asthma
CRTH2	CRTH2 antagonist: OC000459	Clinical trial: Phase 2	asthma,
	CRTH2 antagonist: AZD1981	Clinical trial: Phase 2	asthma, COPD
TSLP	anti-TSLP mAb: AMG 157	Clinical trial: Phase 2	asthma, atopic dermatitis
IL-33	Anti-IL-33 mAb AMG 282	Clinical trial: Phase 1	atopic asthma, chronic rhinosinusitis

Figure legends

Figure 1. Schematic representation of the “Allergic Effector Unit”: physical interactions and soluble crosstalk

Mast cells and eosinophils showing surface receptor/ligand couples and receptors binding released mediators as described in the text.

Figure 2. Schematic representation of therapeutically useful activating and inhibitory receptors on the surface of human mast cells and eosinophils

The graph depicts receptors discussed in the text. The relatively cell specific receptors and those having a major role on each cell type are shown on the top of mast cell and eosinophil. In addition, the receptors are drawn to show their molecular structure in a schematic manner.

Figure 1

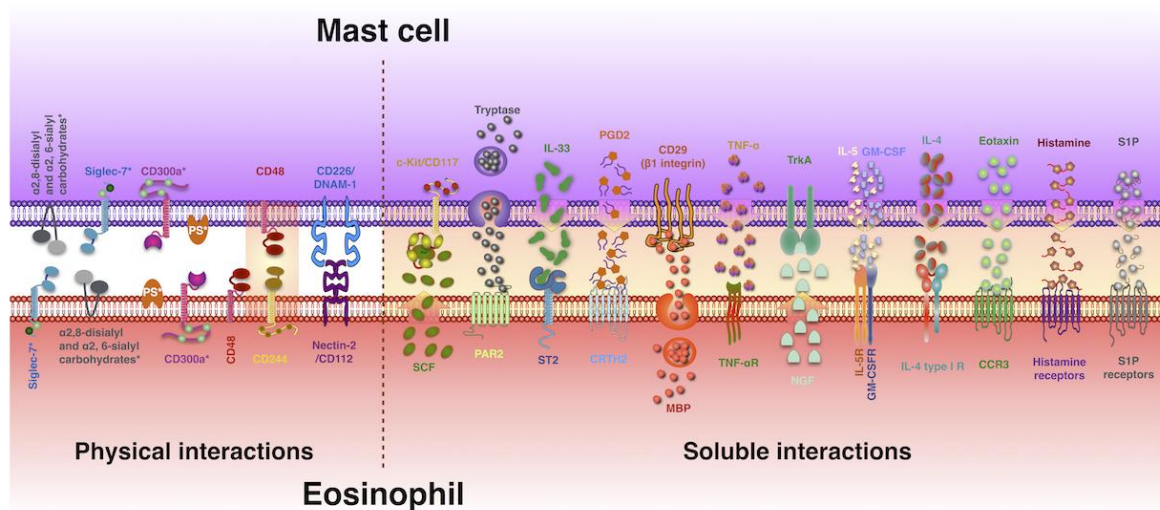
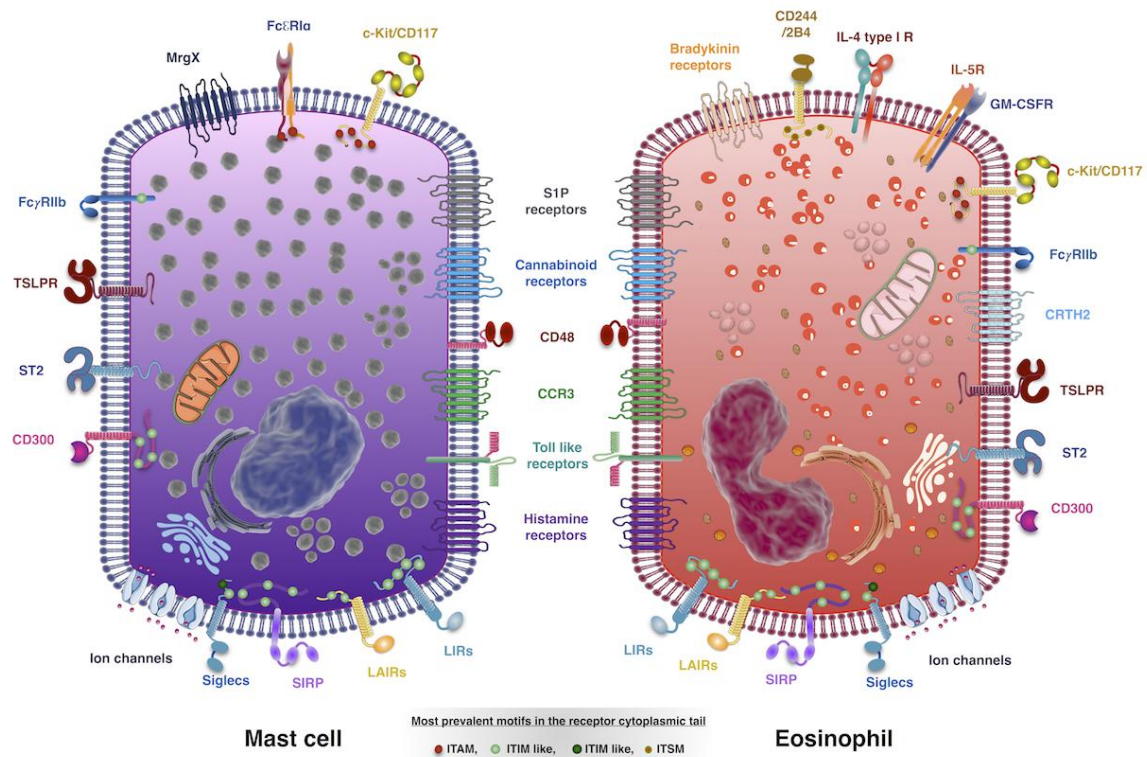


Figure 2



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