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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.

Contents

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; CRTH2, 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; PGD2, Prostaglandin D2; PGE2, Prostaglandin E2; PIR, Paired Ig-like Receptor; S1P, Sphingosine-1-phosphate; sCD48, soluble CD48; SCF, Stem Cell Factor; SEB, *S. aureus* 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; 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) (Fig. 1), is the interplay between mast cells and eosinophils *via* both physical and soluble interactions (Minai-Fleminger et al., 2010; Elishmereni et al., 2011, 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-αR (Temkin et al., 2003), eosinophil major basic protein (MBP)/CD29 (β1 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) (Fig. 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 (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

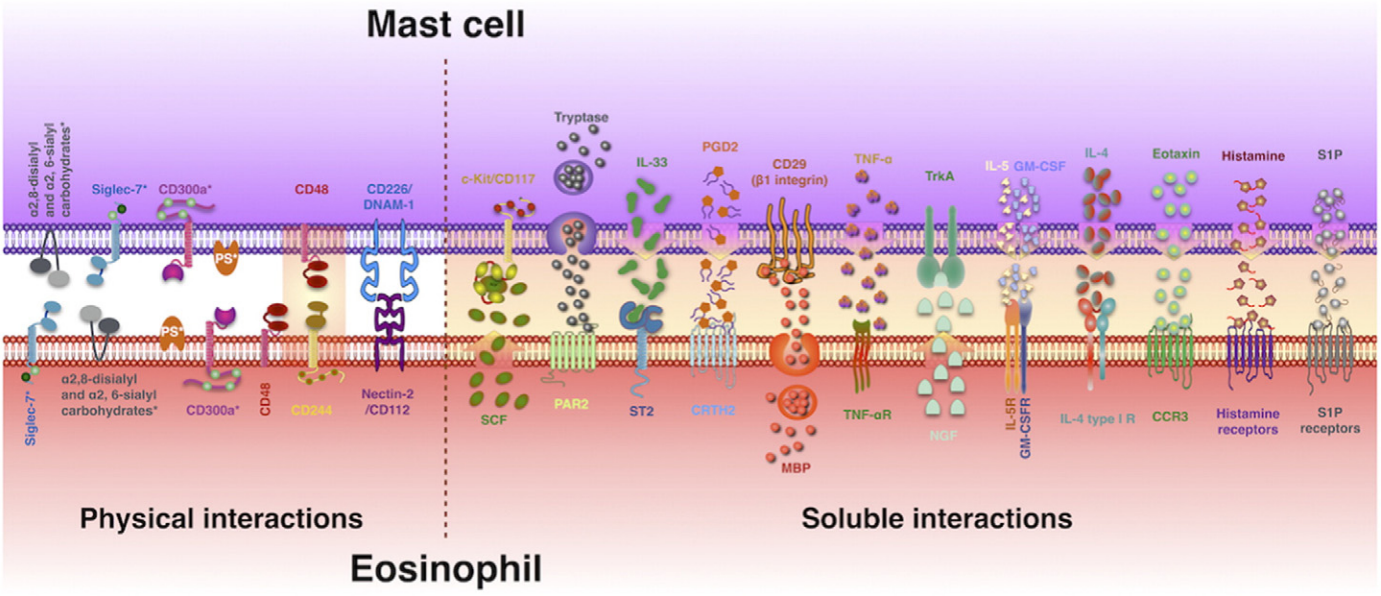

Fig. 1. Schematic representation of the "Allergic Effector Unit": physical interactions and soluble crosstalk Mast cells and eosinophils showing surface receptor/ligand couples and receptors binding released mediators as described in the text.