



Mast cells and eosinophils in allergy: Close friends or just neighbors

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ABSTRACT

Mast cells are mostly known for their role in allergic diseases although in recent years it has become clear that they have a role in other diseases and in the body's defense against microbes. In most cases, but especially in allergy, eosinophils are present in the tissue within proximity of mast cells. Due to this spatio-temporal correlation we and others have postulated and described a crosstalk between these two cells, mediated via their released mediators and physical interactions, that is able to modulate each other's function and ultimately the outcome of the allergic inflammatory reaction. This review will focus on the functional unit between mast cells and eosinophils that we have named the "Allergic Effector Unit" and specifically highlight its role in allergy.

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1. Allergy

Allergy, or type I hypersensitivity, is a term used to describe immunoglobulin E (IgE) mediated diseases characterized by mast cells' activation and tissue infiltration as well as activation of inflammatory cells. Allergy, like several other diseases, is the result of an interplay between genetic and environmental factors. Atopy represents the genetic predisposition to develop a hypersensitivity to otherwise non-harmful substances. When atopic individuals are exposed to allergens, sensitization occurs in a T-helper type-2 (Th-2) dependent pathway that is characterized by the production of several cytokines, principally interleukin (IL) -4 and IL-13. This, in turn, causes the generation of allergen-specific IgE antibodies by plasma cells (Rantala et al., 2013).

The inflammatory response due to an allergic reaction (allergic inflammation) usually occurs in two phases. The *early phase* starts within minutes of allergen exposure, subsequent to sensitization, and is due to cross-linking of allergen specific IgE molecules bound to their high affinity receptors FcεRI expressed on mast cells. This causes degranulation of mast cells and release of preformed granule mediators such as histamine and neutral proteases (detailed below) as well as the synthesis of lipid-derived mediators (Moon et al., 2014). At a later time mast cells also produce and release cytokines, chemokines and growth factors. Mast cells' activation results in the onset of a *late phase reaction* in which

various inflammatory cells and mainly the eosinophils are recruited from the blood circulation to the inflamed tissue and assume an activated phenotype. The classic pathway of the early phase is characterized by IgE bound FcεRI activated mast cells (Rivera and Gilfillan, 2006). Other non-IgE dependent mechanisms of stimulation are also known to take place especially in the late phase and chronic outcome of allergic inflammation (Ben-Zimra et al., 2013).

2. Mast cells

Mast cells are important players in host homeostasis maintenance not only in response to pathogens, snake venoms, and during wound healing but also in a series of inflammatory diseases (Cemerski et al., 2012). However, their recognized pathogenic key role is in their IgE-dependent activation that causes the allergic response. Importantly mast cells after a first activation survive and regenerate by re-synthesizing their released mediators and by renewing their susceptibility to be reactivated by IgE-dependent and independent stimuli (Levi-Schaffer and Riesel, 1989; Levi-Schaffer and Riesel-Yaron, 1990; Levi-Schaffer and Shalit, 1989).

It is noteworthy that infiltrating eosinophils have been detected in the proximity of mast cells in the allergic inflamed tissues and importantly also in several other diseases such as mastocytosis (Maric et al., 2007), cancer (Khatami, 2014), gastric carcinomas (Caruso et al., 2007), Crohn's disease (Xu et al., 2004), intestinal adhesions (Xu et al., 2002), *Trypanosoma cruzi* (Martins et al.,

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2015), rosacea (Cribier, 2013), eosinophilic esophagitis (Abonia et al., 2010), and bullous pemphigoid (Ujji et al., 2012). Mast cells' regenerative potential, a tissue precursor pool and long life span (Levi-Schaffer and Riesel, 1989) are responsible for eosinophils' continuous influx and prolonged survival in an inflamed tissue (reviewed in Walsh et al., 2010). Due to these observations we have focused our studies in the last 15 years on the possible crosstalk of mast cells and eosinophils.

Mast cells are highly granulated tissue cells that develop from myeloid progenitor cells expressing CD34, CD117 (c-kit) and CD13, and they mature in the tissues under the regulation of stem cell factor and other cytokines (Gilfillan et al., 2011). In addition to their primary activating receptor FcεRI, they also express various activating and inhibitory receptors (e.g. CD48, TSLPR (thymic stromal lymphopoietin receptor), histamine receptor (H)1, C3a and C5a, Substance P receptor, ECB2 (endocannabinoid receptor 2), CD300a, FcγRIIb, Siglec-7 (Sialic acid-binding immunoglobulin-type lectins), etc.), that are potential therapeutic targets (Gibbs and Levi-Schaffer, 2012; Harvima et al., 2014; Migalovich-Sheikhet et al., 2012). Mast cells contain an array of preformed granule-associated mediators and some cytokines (i.e. tumor necrosis factor (TNF) alpha) (Lundequist and Pejler, 2011; Zhang et al., 2011) that are released upon activation followed by synthesis of cytokines, chemokines, and growth factors (Bachelet et al., 2006a; Bloemen et al., 2007; Gilfillan et al., 2011).

3. Eosinophils

Eosinophils are granulocytic leukocytes, containing a bilobed nucleus and are mostly associated with the pathogenesis of various parasitic helminth infections (Klion and Nutman, 2004), allergic diseases, and several other inflammatory conditions (Weller, 2009). Eosinophils' numbers are classically elevated in the peripheral blood during the late phase of allergic inflammation, and usually remain high longer than other inflammatory cells (Amini-Vaughan et al., 2012). Interestingly eosinophils can process and present a variety of microbial, viral, and parasitic antigens like professional antigen presenting cells (Akuthota et al., 2010), although under certain *in vitro* conditions they fail to do so (van Rijt et al., 2003).

Eosinophils develop in the bone marrow from myeloid progenitor cells, under tight regulation of transcription factors, namely GATA-1 (a zinc family finger member), PU.1 (an ETS family member) and C/EBP (CCAAT/enhancer-binding protein family) members, and migrate (under CCR3 dominant regulation) into tissues in physiological and in pathological conditions such as allergy. The development and expansion of eosinophils is positively regulated mainly by granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3 and IL-5 that have been referred to as the "eosinophils survival cytokines". The receptor IL-5Rα is especially important as it is expressed early by common myeloid progenitors of eosinophils and can mediate eosinophils' differentiation, maturation, survival, chemotaxis, and effector functions (Lacy et al., 2014).

Eosinophils cytoplasmic secondary granules contain specific high cationic proteins, i.e. major basic protein, eosinophil peroxidase, eosinophil cationic protein, eosinophil-derived neurotoxin and other mediators (Blanchard and Rothenberg, 2009), playing important roles in inflammation, allergy, parasitic infection, tissue injury and tumors.

Eosinophils contain a large array of preformed cytokines, chemokines and growth factors (e.g., IL-4, IL-6, IL-8, IL-10, IL-13, GM-CSF, transforming growth factor beta (TGF-β)) that they can promptly release upon stimulation. Eosinophils are also a rich source of *de novo* synthesized lipid mediators (e.g., platelet

activating factor (PAF), leukotriene C4, and prostaglandin E2) (Blanchard and Rothenberg, 2009; Travers and Rothenberg, 2015). Eosinophils express various receptors for activating stimuli such as IL-2, C5a and PAF, interferon (IFN)-γ (Neves et al., 2008), IL-3, IL-5, GM-CSF, chemokine receptor 3 (CCR3), RANTES (Regulated on Activation, Normal T Expressed and Secreted) (Gregory et al., 2003) and the immunoglobulin A (Decot et al., 2005), which cause them to degranulate. Moreover they also express CD48, 2B4 (Munitz et al., 2005), pattern recognition receptors (PRRs) (Kvarnhammar and Cardell, 2012) and histamine receptors that signal via various mechanisms/pathways (summarized in (Davoine and Lacy, 2014). This would indicate their capacity to be involved in several kinds of pathologies. Eosinophils also express inhibitory receptors such as Siglec-8, CD300a and others (Bochner, 2009; Nissim Ben Efraim et al., 2013).

4. Mast cells–eosinophils interactions

Cells have been shown to communicate with each other through a variety of mechanisms. Communication pathways can comprise the classical receptor–ligand interaction, the transfer of proteins, lipids, genetic materials through micro-RNA found in the extracellular space (Rayner and Hennessy, 2013) and vesiculation events taking place either at the plasma membrane (Lee et al., 2011) or within exosomes (Robbins and Morelli, 2014).

In the course of allergic inflammation, in addition to mast cells and eosinophils, other inflammatory cells such as basophils, neutrophils, Th-2 and CD8+ lymphocytes, invariant natural killer (iNK) cells and the more recently described innate lymphoid cells ILC2 (Walker et al., 2013) can possibly interact to regulate the allergic inflammation reaction.

Nevertheless, mast cells and eosinophils are the key effector cells due to their characteristic preformed mediators and their capacity to produce and release several other mediators that are mainly responsible for the symptoms of allergic diseases. Therefore we have put forward the hypothesis that primarily mast cell–eosinophil interactions with one another and their micro-environment can dictate the evolution of allergic inflammation from its onset to its possible resolution and/or to chronicity and tissue remodeling.

In this review we will discuss the mast cell–eosinophil bidirectional soluble and physical crosstalk, describing first the effects of mast cells on eosinophils and then how eosinophils can affect the mast cells.

4.1. Mast cells–eosinophils interactions: the allergic effector unit

We have hypothesized that mast cells together with eosinophils form a functional unit that we named "the allergic effector unit", by having a soluble and physical crosstalk (Elishmereni et al., 2011; Minai-Fleminger et al., 2010). Further we have assumed that the allergic effector unit can enhance these cells' functions thus amplifying the late phase and chronic outcomes of allergic inflammation. As mentioned above mast cells after being first activated retain their survival and regenerate in the inflamed tissues. At the same time eosinophils display an increased survival and therefore these two cells can communicate via several released mediators and by membrane bound ligands and their respective receptors. Importantly several of the allergic effector unit activating signals, as described below (among them the mast cells stimulating signals that are not carried out through the classical IgE/allergen interactions), are not currently targets of anti-allergic drugs and therefore could be one of the reasons for the lack of complete effects seen in some patients.

4.1.1. The allergic effector unit: soluble crosstalk

The first important observation in hypothesizing a mast cell–eosinophil crosstalk is that mast cells synthesize eosinophil survival cytokines that can also induce eosinophil chemotaxis, the first step in their interaction. In addition to IL-5, GM-CSF and IL-3, TNF- α and IL-2 that have also been reported to promote eosinophil chemotaxis, viability and activation (Levi-Schaffer et al., 1998; Shakoory et al., 2004; Temkin et al., 2003) are generated by mast cells. In particular, TNF- α modulates eosinophil chemotaxis through induction of eotaxin expression from epithelial and endothelial cells and activation of mitogen-activated protein kinases (MAPK) pathways (Temkin and Levi-Schaffer, 2001). Other mast cell products which promote eosinophil chemotaxis and recruitment into sites of allergic response are histamine (through H4R), prostaglandin D2 (through the chemoattractant receptor-homologous molecule on Th-2 (CRTH2)) and eotaxin itself (through the chemokine receptor CCR3) (Hirai et al., 2001; Menzies-Gow et al., 2004). LTC4, LTD4 and LTE4, can also be released by mast cells and function as potent chemoattractants for eosinophils, promote their adhesion and induce IL-8 production (Minai-Fleminger and Levi-Schaffer, 2009). The mast cell specific granule mediators tryptase and chymase can stimulate eosinophil activation and degranulation and the generation and release of IL-6 and IL-8 via MAPK/AP-1 pathway, by cleavage of protease-activated receptor 2 (PAR-2) (Temkin et al., 2002). In addition, human mast cells and also IgE-stimulated murine mast cell lines and bone marrow derived mast cells can generate mature forms of IL-33 (Hsu et al., 2010), which are very potent for induction of type-2 innate immune responses. IL-33 induces massive expansion of eosinophils and innate lymphoid cells (ILC2) and high levels of IL-5 and IL-13 secretion in lungs and bronchoalveolar lavage fluids in mice (Lefrancais et al., 2014) thus further fueling tissue eosinophilia. As expected, mice treated with anti-IL-33 antibody after ovalbumin challenge, showed a decreased number of eosinophils in bronchoalveolar lavage fluid (Lee et al., 2014). Mast cell derived histamine augments both eosinophil expression of adhesion molecules and synthesis of pro-inflammatory cytokines (Gelfand, 2004) and platelet-activating factor, which regulates eosinophil degranulation.

To dissect the mast cell–eosinophil crosstalk, *in vitro* studies were performed using cell monocultures consisting of either mast cells or eosinophils in the presence of respective selected mediators or of respective cell sonicates or cell co-cultures. In the first studies human peripheral blood eosinophils were usually incubated with Rat mast cell sonicates, showing enhanced viability of eosinophils due to mast cell derived TNF- α which in turn, was capable of augmenting the eosinophils' production of GM-CSF, through nuclear factor-kappa B (Levi-Schaffer et al., 1998; Temkin and Levi-Schaffer, 2001) and inhibiting their apoptosis (Kankaanranta et al., 2014). Interestingly, TNF- α has been reported to cause eosinophils' production of both Th-1 and Th-2 associated chemokines (Liu et al., 2007). All these mediators are potential therapeutic targets (Gibbs and Levi-Schaffer, 2012; Harvima et al., 2014; Migalovich-Sheikhet et al., 2012), and indeed a selective antagonist of H4R and of CRTH2 downregulated the allergic inflammation in experimental animal models and in clinical trials (Somma et al., 2013).

Regarding the influence of eosinophils on mast cells, the first most important finding by our group has been that eosinophils produce stem cell factor, which is the fundamental cytokine coordinating differentiation, maturation, survival and activation of mast cells (Hartman et al., 2001). Freshly isolated and cultured human peripheral blood eosinophils were found to express both isoforms of stem cell factor at the mRNA level and to synthesize the protein backbone of stem cell factor (Hartman et al., 2001). Stem cell factor co-localized with major basic protein suggesting

that its release, together with major basic protein and other granule-associated mediators, occurs in a prompt fashion upon eosinophils activation (Hartman et al., 2001). Eosinophils also produce nerve growth factor (Noga et al., 2003) that prompts mast cell survival and activation via TrkA receptors (Kritas et al., 2014), and can be affected by nerve growth factor in an autocrine manner resulting in the release of eosinophil peroxidase (Solomon et al., 1998). Next it was described that eosinophils are capable of promoting mast cell degranulation through the release of LTC4, LTD4 and LTE4 (Bandeira-Melo et al., 2002; Bandeira-Melo and Weller, 2003) and since the same receptors are also present on mast cell surfaces, this represents an interesting autocrine signaling function too.

Moreover it was shown that upon incubation with eosinophil major basic protein, eosinophil peroxidase, and eosinophil derived cationic protein, Rat peritoneal mast cells released histamine in a dose dependent manner (Zheutlin et al., 1984), which in turn can promote superoxide production in eosinophils (Pincus et al., 1982). Following the evidence of eosinophil major basic protein effects on Rat mast cells, a complex relationship between eosinophil major basic protein and mast cell functions was found also in human cells. Other studies showed that human heart mast cells when incubated with eosinophil derived cationic protein and major basic protein released histamine, tryptase and prostaglandin D2 (Patella et al., 1996; Zheutlin et al., 1984). It was further found that depending on their phenotype, mast cells can immediately respond or not respond to IgE-independent stimuli such as eosinophil major basic protein. For example human cord blood derived mast cells and even freshly isolated purified human lung mast cells are unresponsive to eosinophil major basic protein, while after co-culture with human lung or 3T3 fibroblasts they acquire responsiveness. This is due to the fibroblast-derived membrane form of stem cell factor that induces the expression of Gi3 (Piliponsky et al., 2003). We speculated that in the tissues in which mast cells reside they are in close contact with the membrane form of stem cell factor provided by various structural cells and hence responsive to these non-IgE-dependent stimuli. Notably eosinophil major basic protein was found to specifically activate fibroblast derived-membranal stem cell factor-primed cord blood derived mast cells through binding to integrin-beta 1 to release histamine, IL-8, GM-CSF, prostaglandin D2, and TNF- α (Ben-Zimra et al., 2013). Interestingly it was recently found that in addition to eosinophil major basic protein, eosinophil peroxidase also induces histamine release from human skin mast cells through the G protein-coupled Mas-related gene X2 (MrgX2) receptor that also binds antimicrobial peptides (such as LL-37) and basic neuropeptides (such as Substance P) (Fujisawa et al., 2014; Subramanian et al., 2011).

4.1.2. The allergic effector unit: physical interactions

Physical cell–cell interactions require more specific regulation than soluble interactions. The discovery that mast cells and eosinophils form physical couples in allergic inflamed tissues and thus can communicate also by physical contact has shed further light on how these cells can influence each other by a more “immunological” precise mechanism rather than just the released mediators (Elishmereni et al., 2011).

Evidence demonstrating the co-existence of mast cells and eosinophils in a number of non-allergic diseases has been previously shown (Caruso et al., 2007; Martins et al., 2015; Xu et al., 2004). We were the first to put forward the hypothesis and to show the existence of the physical allergic effector unit in allergy in human nasal polyps and asthmatic bronchi, as well as in mouse atopic dermatitis skin (Elishmereni et al., 2011; Elishmereni et al., 2014) and allergic asthma lungs (Galli S. and Levi-Schaffer F., unpublished). Therefore we dissected *in vitro* the modalities of first

human and then of mouse allergic effector unit formation. *In vitro* mast cells and eosinophils in co-culture interacted to form physical contact within 5 min, and this physical allergic effector unit lasted for 3–4 min. Pseudopodia like structures from mast cells appeared to draw near eosinophils facilitating the cell–cell contact (Elishmereni et al., 2011). Short term (60 min) *in vitro* interaction/adherence between human peripheral blood eosinophils and cord blood derived mast cells was found to modify the lipid body content and the granule morphology of co-cultured mast cells and eosinophils, respectively, and to increase the level of released eosinophil peroxidase (Minai-Fleminger et al., 2010). The functionality of the physical contact between these two cells as well as their reciprocal activation was also observed by transfer of eosinophil peroxidase from eosinophils to mast cells and tryptase from mast cells to eosinophils (Minai-Fleminger et al., 2010) via cell membrane contact. Cell surface molecules implicated so far by our group in the human mast cells–eosinophils contact mechanism are the activating receptors/ligands couples of the CD2-family. CD48 which is expressed by mast cells and its high-affinity ligand 2B4 (CD244) expressed on eosinophils (Minai-Fleminger and Levi-Schaffer, 2009; Munitz et al., 2005), and the adhesion molecules DNAM-1, and Nectin-2 (Bachelet et al., 2006b) that convey stimulatory signals in these cells in the time frame of three days of co-culture (Elishmereni et al., 2013).

At both IgE-activated and steroid-inhibited settings of co-culture, eosinophils were more viable due to physical cell–cell contact via CD48-2B4 but also due to soluble mediators such as GM-CSF produced by mast cells (Elishmereni et al., 2011). Moreover, eosinophils increased basal and IgE-stimulated mast cell tryptase and beta-hexosaminidase release involving physical contact mediated via CD48-2B4. Eosinophils in co-culture with mast cells also released more eosinophil peroxidase. In summary in the allergic effector unit (1–2 h or 1–3 days), it was found that the mast cell–eosinophil couples activated, degranulated and released beta-hexosaminidase, tryptase, eosinophil peroxidase, and TNF-alpha (Elishmereni et al., 2013) only because of the stimulatory interaction via 2B4-CD48 contact. Data of the human system were reconfirmed by employing mouse bone marrow derived-mast cells and -eosinophils.

As with many cell types also for eosinophils and mast cells there are known differences between mouse and human cells to be taken into consideration when interpreting data obtained from animal models centering on these cells (recently detailed regarding asthma physiology in (Ray et al., 2015)). Such differences include, for example, the fact that mast cells in rodents are divided into two major phenotypes based on the tissue in which they are located. There are the connective tissue-type mast cells and the mucosal-type mast cells which differ in their biochemical and functional characteristics and rely on IL-3 as a growth and differentiation factor (Rubinchik and Levi-Schaffer, 1994). In humans, mast cells are defined according to their neutral protease content, i.e. mast cells positive for tryptase and mast cells containing tryptase, chymase and carboxypeptidase A (Krishnaswamy et al., 2006; Pejler et al., 2010) and rely on stem cell factor for differentiation as previously mentioned. In addition, mice mast cells but not human, express 2B4 a high affinity ligand/receptor for CD48. Moreover 2B4 on mouse bone marrow derived mast cells was found to be inhibitory while having a stimulatory effect on eosinophil migration and activation (Elishmereni et al., 2014). Eosinophils can secrete different cytokines in response to the same stimuli in human and mouse. Murine eosinophils express the receptor Siglec-F that is considered to be a marker for differentiation and activation. Furthermore their granules' morphology is smaller (Dyer et al., 2013) and their activation limited compared to the human eosinophils.

Our data on murine models of allergic (atopic dermatitis) and non-allergic (peritonitis) diseases in 2B4-/- mice demonstrated a

dual role of 2B4 in which reduced eosinophil infiltration into the skin (in atopic dermatitis) and peritoneum (in peritonitis) was observed. Also, fewer mast cell–eosinophil pairs (allergic effector unit) were seen in skin of 2B4-/- atopic dermatitis mice (Elishmereni et al., 2014). Similarly atopic dermatitis model in CD48-/- mice also showed diminished allergic inflammation phenotype indicating that in the absence of CD48 less allergic effector unit formation takes place (Gangwar R.S. and Levi-Schaffer F., unpublished). These results indicate the importance of CD48/2B4 in mediating mast cell–eosinophil physical interactions in allergic inflammation. Moreover CD48 has been shown by us to be an important receptor as expressed both by mast cells and eosinophils since it serves in their activating interaction with *S. aureus* and its toxins (Minai-Fleminger et al., 2014; Rocha-de-Souza et al., 2008). *S. aureus* is the main bacteria infecting atopic dermatitis patients' tissues. We can thus speculate a super activated allergic effector unit in which mast cells and eosinophils are at the same time interacting with each other and with the bacteria. Regarding the mast cell–eosinophil physical interaction besides the CD48/2B4, other ligand/receptor couples can be implicated such as the leukocyte function-associated antigen 1 (LFA-1) (also known as integrin alpha L beta 2), a molecule expressed by eosinophils/T cells which also co-stimulates IgE-mediated activation (Inamura et al., 1998). LFA-1 is also the ligand for the intercellular adhesion molecule-1 (ICAM-1, CD54) receptor expressed on murine peritoneal and human uterine mast cells (Guo et al., 1992; Inamura et al., 1998), whose activation after mast cell degranulation will result in the recruitment of eosinophils to the site of inflammation.

5. Conclusions

In recent years mast cells' crosstalk with a variety of immune cell types that exert regulatory and/or effector functions have been studied. Yet at the same time such studies focusing on mast cells–eosinophils crosstalk are scarce. The specific crosstalk between mast cells and eosinophils (the allergic effector unit) that we have defined has great potential to modulate allergic inflammation, in which both cells have pivotal roles (Minai-Fleminger and Levi-Schaffer, 2009). Our data would indicate that in allergic inflammation, the allergic effector unit interactions have a stimulatory activity. Nevertheless we cannot rule out that at later time points a resolution phenotype can take place (Levi-Schaffer et al., unpublished) since both eosinophils and mast cells express a wide array of inhibitory receptors together with their ligands (Karra and Levi-Schaffer, 2011; Mizrahi et al., 2014; Munitz and Levi-Schaffer, 2007).

Future characterization of all the soluble and physical mediated crosstalks between these cells might lead to the identification of novel targets for the treatment of allergy and its consequences. Cell selective receptors or a ligand knockout mice system could be helpful in deciphering the role of a particular receptor/ligand. For example the best possible way to study the function of CD48/2B4 specifically on mast cells and eosinophils in allergic inflammation is by reconstituting mast cells and eosinophils obtained from CD48/2B4 knockout mice into mast cell and eosinophil deficient mice (Sash and GATA mice, respectively). If these studies show the activating roles of these receptors as we defined *in vitro* and also *in vivo* in models of allergy, we foresee that impairing CD48/2B4 interaction specifically on mast cells–eosinophils and/or blocking soluble mediators and/or their receptors will be a successful therapeutic approach to downregulate the allergic response. Since in several other eosinophil-mediated diseases eosinophils and mast cells are also found together in inflamed tissues in close proximity as in the allergic effector unit (Fig. 1) it might be worthwhile to investigate whether comparable mechanisms are

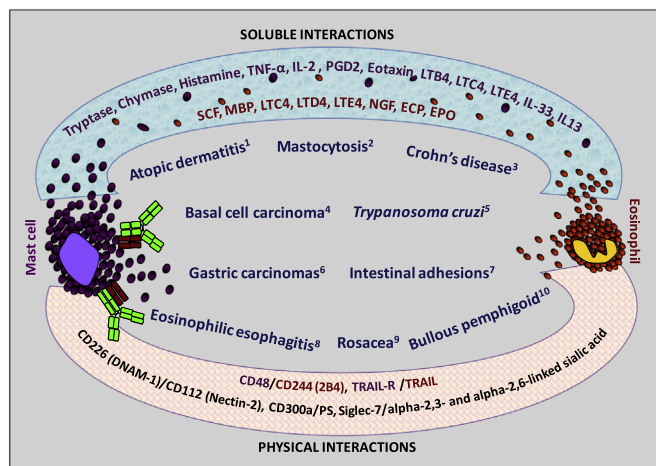


Fig. 1. Schematic representation of mast cell–eosinophil interactions. Soluble mediators released by mast cells and eosinophils affecting each other are shown on the top while the receptors/ligands involved in physical interactions are shown on the bottom. Diseases in which mast cells and eosinophils are found in close proximity are listed in the middle (¹Elishmereni et al., 2014; ²Maric et al., 2007; ³Xu et al., 2004; ⁴Khatami, 2014; ⁵Martins et al., 2015; ⁶Caruso et al., 2007; ⁷Xu et al., 2002; ⁸Abonia et al., 2010; ⁹Cribier, 2013; ¹⁰Ujii et al., 2012).

Table 1

The human and murine allergic effector unit: effects of mast cell–eosinophil crosstalk.

Soluble interactions				
Mast cells influence on eosinophils				
Mast cells	Eosinophils	System	Method	
TNF- α	Chemotaxis, Survival, Activation	Human, Murine	<i>In-vitro</i> , <i>in-vivo</i>	
IL-2	Chemotaxis, Survival, Activation	Human	<i>In-vitro</i>	
GM-CSF, IL-3, IL-5	Differentiation, Chemotaxis, Survival, Activation	Human	<i>In-vitro</i>	
PAF	Infiltration, Activation, Degranulation	Human	<i>In-vitro</i>	
Tryptase, Chymase	Activation, Degranulation	Human	<i>In-vitro</i>	
Histamine, PGD ₂ , Eotaxin	Chemotaxis, Recruitment	Human, murine	<i>In-vitro</i> , <i>in-vivo</i>	
LTC ₄ , LTD ₄ , LTE ₄	Chemotaxis, Activation, Adhesion	Human	<i>In-vitro</i>	
IL-33	Expansion	Murine	<i>In-vivo</i>	
Eosinophils influence on mast cells				
Eosinophils	Mast cells	System	Method	
SCF	Survival, Activation, Maturation, Differentiation	Human, Murine	<i>In-vitro</i>	
NGF	Survival, Activation	Human	<i>In-vitro</i>	
MBP, ECP, EDN, EPO	Activation	Human	<i>In-vitro</i>	
LTC ₄ , LTD ₄ , LTE ₄	Degranulation	Human	<i>In-vitro</i>	
Physical interactions				
Mast cells influence on eosinophils				
Mast cells	Eosinophils	System	Method	
CD48	CD244 (2B4)	Human, Murine	<i>In-vitro</i> , <i>in-vivo</i>	
CD226 (DNAM-1)	CD112 (Nectin-2)	Human	<i>In-vitro</i>	
ICAM-1 (CD54)	LFA-1	Human, Murine	<i>In-vitro</i>	
Eosinophils influence on mast cells				
Eosinophils	Mast cells	System	Method	
CD244 (2B4)	CD48	Human, Murine	<i>In-vitro</i> , <i>in-vivo</i>	
CD112 (Nectin-2)	CD226 (DNAM-1)	Human	<i>In-vitro</i>	
LFA-1	ICAM-1 (CD54)	Human, Murine	<i>In-vitro</i>	

The table summarizes some of the potential interactions between mast cells and eosinophils and their effects via either “soluble interaction” or “physical interaction” as described in the review.

present in these diseases and can be therefore targeted similarly to allergy

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