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REVIEW

Mast cells and eosinophils: the two key effector cells in allergic inflammation

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Abstract The allergic inflammatory response is composed of two main phases—the early and the late. The early phase initiates when an allergen activates the tissue resident mast cell, triggering the release of a variety of granule-stored and newly formed mediators. As the inflammatory response progresses, blood borne inflammatory cells—in particular, eosinophils—are recruited into the inflamed tissue. Eosinophil activation and consequent release and production of several pro-inflammatory mediators results in the late phase reaction. A chronic allergic inflammation always features prominent tissue eosinophilia. In this review, we will discuss the possible channels of communication, both soluble and physical, between mast cells and eosinophils that can occur in the late and chronic stages of allergy. Such interactions, that we have termed "the allergic effector unit", may modulate the severity and/or duration of the allergic inflammatory reaction.

Keywords Mast cells · Eosinophils · Allergic inflammation

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Abbreviations

Ig	Immunoglobulin
SCF	Stem cell factor
PG	Prostaglandin
LT	leukotriene
IL	Interleukin
GM-CSF	Granulocyte-macrophage colony-stimulating factor
TNF-α	Tumor necrosis factor alpha
TGF-β	Transforming growth factor-β
FGF	Fibroblast growth factor
VEGF	Vascular endothelial growth factor
NGF	Nerve growth factor
EPO	Eosinophil peroxidase
MBP	Major basic protein
ECP	Eosinophil cationic protein
EDN	Eosinophil derived neurotoxin
PAF	Platelet activating factor
IFN-γ	Interferon-gamma
MAPK	Mitogen-activated protein kinase
PAR2	Proteinase-activated receptor 2
AP-1	Activator protein-1
MMPs	Metalloproteinases
DNAM-1	DNAX accessory molecule 1
PVR	Poliovirus receptor
LFA-1	Leukocyte function-associated antigen 1
ICAM-1	Intercellular adhesion molecule 1

Allergic inflammation

Allergy is one of the most widespread diseases in the Western world, and its incidence—which seems to be connected to the industrial and "hygienic" modern way of

life—is estimated to increase every year. It comprises several pathologies such as asthma, conjunctivitis, rhinitis, eczema, etc. The tendency to develop an allergy is known as atopia and is linked to both genetic and environmental factors [1, 2]. Allergic inflammation is a multifactorial response that evolves as a reaction to an innocuous substance, an allergen, which first leads to the production of specific IgE, and then to the aggregation of IgE occupied high-affinity receptors (FcεRI) expressed on the mast cell surface. The ensuing cascade of intracellular events results in mast cell activation and degranulation leading to the release of specific pro-inflammatory mediators, which orchestrate the immediate, early-phase of the allergic process within minutes of allergen exposure [3]. This phase, named the "early phase" of allergy, is characterized by vasodilation, increased vascular permeability, vascular leakage and oedema. Concomitantly, the recruitment of inflammatory cells, i.e., macrophages, T cells, eosinophils, basophils, and perhaps invariant natural killer T cells takes place [4]. These cells and mainly the eosinophils cause the onset of the late phase that usually occurs a few hours after the early phase [5–7]. When the allergic stimulus is continuously present, or other noxious stimuli appear in the patient environment, the allergic inflammation process may become chronic [4, 8, 9]. A common feature of chronic allergic inflammation is tissue remodeling. In asthma this is caused by subepithelial fibrosis, goblet cell hyperplasia, myofibroblast hyperplasia, smooth muscle cell hyperplasia and hypertrophy, which finally results in thickening of the airway wall [4, 10].

Although the allergic response involves many inflammatory cells, the two main effector cells operating this complex response are the mast cells and the eosinophils. Despite the fact that these cells are characteristic respectively of the early and late phases of this process, it is also evident that they can co-exist in the tissues during the late and chronic stages of allergic inflammation. Earlier observations have suggested that these two cells are capable of communicating via soluble mediators. More recently we have put forward the hypothesis that they can also interact via actual physical contact.

In this article, we discuss the possibility that allergic inflammation is modulated and maintained primarily by the complex interactions between mast cells and eosinophils, that we have termed "the allergic effector unit".

Mast cells and eosinophils in allergic inflammation

Mast cells are highly granulated FcεRI bearing tissue-dwelling cells, which develop from myeloid progenitors expressing CD34, CD117 (c-kit) and CD13, under the influence of stem cell factor (SCF). They are widely distributed in connective tissues and mucosal surfaces [5, 6, 11, 12]. In humans at least two main kinds of mast cell phenotypes exist, the first contains tryptase and the second stores tryptase, chymase carboxypeptidase A and cathepsin-G [13].

Their activation through the high affinity receptor FcεRI initiates the immediate secretion of various granular preformed mediators (such as tryptase, chymase, histamine and proteoglycans) as well as of newly-synthesized mediators such as arachidonic acid metabolites (e.g., PGD_2, LTB_4, LTC_4) [4], and the later production of many cytokines, chemokines and growth factors (e.g., IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-11, IL-13, GM-CSF, TNF-α, TGF-β, b-FGF, VEGF, NGF) [5, 11, 14]. IgE-dependent activation is mediated through signal transduction initiated by Lyn, Syk and Fyn kinases from the Src family [15]. Mast cells homeostasis is regulated by IgE and the Th_2-associated cytokines IL-4, IL-10, and TGF-β1, which down regulate important effector proteins (e.g., c-Kit, FcεRI) in long-term mast-cells cultures [16, 17]. Among the released mast cell mediators, histamine as well as the lipid mediators have an important role in the recruitment of Th_2 lymphocytes and of eosinophils to the inflammatory site, and in maintaining the allergic process [18].

Eosinophils are bone marrow-derived granulocytes recruited from the peripheral blood to the inflamed tissue. Their presence or that of their specific basic mediators (see below) usually correlates with allergic symptoms [5, 19–21]. Eosinophils differentiate and undergo trafficking under the regulation of the transcription factors GATA-1&2, and c/EBP, the chemokine eotaxin, and the CD4+ Th_2 cell-derived survival cytokines IL-3, IL-5 and GM-CSF [5, 14, 21–26]. They contain highly specific basic granule mediators, e.g., eosinophil peroxidase (EPO), major basic protein (MBP), eosinophil cationic protein (ECP) and eosinophil derived neurotoxin (EDN) which altogether seem to be toxic to respiratory epithelial cells, may alter smooth muscle contraction responses, and are capable of promoting oxidative stress. In addition, eosinophils secrete preformed and de novo synthesized cytokines, chemokines and growth factors (e.g., IL-4, IL-6, IL-8, IL-10, IL-13, GM-CSF, SCF, NGF, TGF-β) as well as lipid mediators upon activation (e.g., PAF, LTC_4, and PGE_2) [5, 14, 19, 21, 27, 28]. Receptors for the pro-inflammatory mediators C5a and PAF, the cytokines IL-2, IL-3, IL-5, IFN-γ, and GM-CSF, the immunoglobulins IgG and IgA, the chemokine CCR3, and other receptors are expressed on the eosinophils [5, 20–22, 29].

Mast cells and eosinophils, the two components of "the allergic effector unit": soluble interactions

The proximity of mast cells and eosinophils in allergic inflammation and the fact that they can stimulate each other even in the absence of an exogenously added activator [30–32] has generated several hypotheses on a cross-talk between the two cells. In fact, some in vitro studies have suggested possible pathways of soluble cross-talk between these cells [33–38]. Data accumulated over the years have indicated that eosinophils and mast cells can affect each other's viability, functionality, trafficking and activation (Fig. 1).

Eosinophils produce SCF [33], the major cytokine regulating activation, differentiation, maturation and survival of mast cells [39–41]. Similarly, eosinophil-derived NGF can influence mast cell survival via its trkA receptor [42, 43]. In addition, early observations showed that the basic proteins stored in eosinophils granules activate mast cells [34]. Eosinophil MBP was found to activate rat peritoneal and human lung mast cells during co-culture with fibroblasts and to release histamine through a mechanism involving the fibroblast-derived membrane form of SCF. This form of SCF induced responsiveness to MBP is a non-IgE-dependent activation, that is similar to the one caused by other basic secretagogues [35, 36, 44]. In another study, it has been shown that human heart mast cells but not human lung and skin mast cells in suspension released histamine, tryptase and PGD_2 when incubated with ECP and MBP [44, 45]. An additional possible mast cell–eosinophil interaction can take place between the major eosinophil chemokine, eotaxin which binds selectively to heparin, a mediator abundantly released from mast cell granules [46]. Last but not least, eosinophils MBP binds heparanase, produced by both mast cells and eosinophils, and inhibits its activity [47].

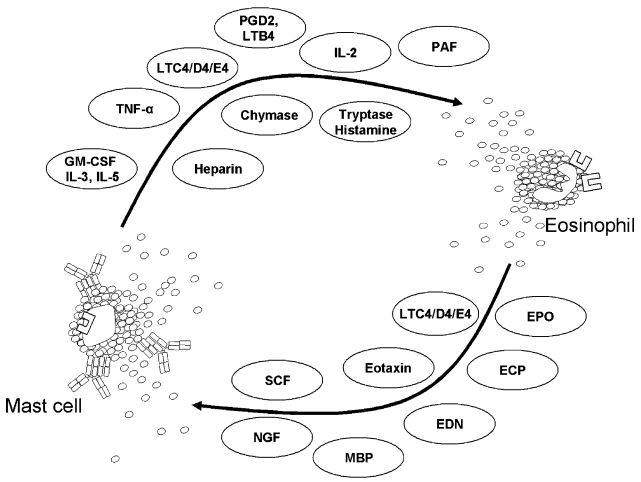

Fig. 1 Mast cell–eosinophil soluble interactions: some of the soluble mediators secreted by mast cells or eosinophils modulating the reciprocal interactions between these two cells in "the allergic effector unit"

Mast cells produce and secrete several cytokines that are known to modulate eosinophil biology [38]. Mast cells produce GM-CSF, IL-3 and IL-5 which represent the main cytokines involved in eosinophil growth, differentiation, chemotaxis, survival and activation [38, 48]. In addition, mast cells synthesize and release TNF-α and IL-2 which promote eosinophil survival, activation, and chemotaxis [48–51]. Interestingly, the enhanced viability of eosinophils incubated with mast cell sonicates was found to relate to TNF-α, which increased the expression of GM-CSF [48]. This effect was inhibited by blocking TNF-α receptors and/or GM-CSF [50]. As mentioned above, TNF-α can modulate eosinophil chemotaxis by inducing eotaxin expression from epithelial and endothelial cells. It also activates the MAPK pathway in eosinophils [38, 50]. TNF-α secreted during the acute phase is also responsible for the capability of eosinophils to produce both Th1- and Th2-associated chemokines [52]. In fact, TNF-α is a very important player in the mast cell–eosinophil interaction, as mast cells are the only cells known to store and release it immediately upon activation [53].

Chymase, a mast cell-specific protease, and PAF can also regulate eosinophil infiltration, activation and degranulation [54, 55]. Tryptase, the other mast cell preformed neutral protease, is capable as well of activating and degranulating eosinophils through binding to the protease-activated receptor PAR2 on eosinophils [28, 56]. Incubation of freshly isolated human peripheral eosinophils with rat and human mast cell sonicate caused a tryptase-mediated synthesis and release of the two pro-inflammatory cytokines IL-6 and IL-8 by eosinophils through activation of the MAPK/AP-1 pathway [28, 47]. Furthermore, histamine can elevate the expression of adhesion molecules and increase pro-inflammatory cytokine production by eosinophils [18]. Activated mast cells and eosinophils produce and secrete arachidonic acid-derived metabolites [4, 57]. For example, mast cells secrete PGD_2, LTB_4, LTC_4 and LTE_4 which may act as a potent chemoattractant for eosinophils or neutrophils, induce the recruitment of these cells to the bronchial mucosa of human asthmatic patients, influence eosinophil adhesion and induce IL-8 secretion from eosinophils [4, 19, 58–61]. Eosinophils also represent a major source of LTC_4, LTD_4 and LTE_4 [62–64] which are capable of promoting mast cells degranulation [65]. Since both cells express receptors for these metabolites [57, 66], this implies autocrine signaling functions as well.

Mast cells and eosinophils, the two components of "the allergic effector unit": physical interactions

Physical contact communication is considered highly important in modulating interactions and transferring information between cells as well as regulating activities at the whole organ level. This kind of communication is considered more efficient, accurate and reliable than paracrine-mediated systems. Previous immunology studies, concerning T lymphocytes and antigen-presenting cells, have pointed out the indispensable role of direct cell–cell contact as a significant communication route capable of influencing major features such as cell activation, regulation and function [67, 68]. Cell–cell interaction increases T cells proliferation through molecules engaged specifically when the cells touch each other, and not due to diffusible factors [69, 70]. In most cases, contact-dependent communication, through receptor–ligand pairs, constitutes a highly precise method of interaction for the efficient and simultaneous distribution of multiple signals, activating, co-activating or inhibiting. Some information has been accumulated over the years on contact-dependent communications between cells in the inflammatory process. In chronic allergic inflammation, the physical interactions between cells have been shown to significantly influence the severity of the disease. For example, it was shown that the outcome of the cross-talk between stimulated T lymphocytes and monocytes or macrophages is the production of proinflammatory cytokines such as IL-1 and TNF-α [71]. These cytokines, produced by stimulated monocytes and macrophages, play a role in inducing connective tissue cells to produce large amounts of matrix metallo-proteinases (MMPs), which in turn degrade extracellular matrix components (e.g., collagens and proteoglycans) [71]. In addition, in co-cultures with activated T lymphocytes [72], there was an increase in mast cell IgE-dependent activation, most likely through contact-mediated effects [73]. The close proximity in the co-culture with activated T cells, caused mast cells to degranulate and release IL-4, IL-6, IL-8, oncostatin M and TNF-α, probably through receptor–ligand interactions [74–77].

These studies led us to hypothesize that physical contact between mast cells and eosinophils can take place and might be active in allergy, and various other inflammatory conditions in which both of these two cells have a role. Interestingly, two recent studies by Caruso et al. [78] and by Piazuelo et al. [79] demonstrated the formation of mast cell–eosinophil couples in gastric carcinomas and chronic gastritis, respectively, showing a clear cut interface. In addition, the cross-talk between mast cells and eosinophils was also proven in Crohn's disease and *Ascaris* infection [80]. Yet a direct communication between mast cells and eosinophils has not been documented in the context of allergic inflammation, despite their close proximity in allergic tissues.

Concerning allergic inflammation we found that human tissue sections taken from chronic allergic inflammatory diseases such as atopic dermatitis and allergic rhinitis often show well-defined mast cell–eosinophil couples. Moreover, preliminary observations in vitro by our group, using both light and electron microscopy, have established the formation of well-defined mast cell–eosinophil couples when these cells are co-cultured (Minai-Fleminger and Levi-Schaffer, unpublished data). Interestingly, we have shown that these couples exhibit a close interface in contrast to arbitrarily adjacent cells. Moreover, analysis of live imaging shows mast cells actively moving towards eosinophils using pseudopod or nanotube-like structures (Elishmereni and Levi-Schaffer, unpublished data).

Studies conducted in our laboratory have established several lines of evidence for mast cell–eosinophil cross-talk through a ligand–receptor interface (Fig. 2). One example of such a ligand–receptor interface is the relationship between DNAM-1 and Nectin-2 [81]. DNAM-1 (DNAX Accessory Molecule 1, CD226) is an adhesion molecule expressed on mast cells, regulating its activity state and as a consequence its degranulation [82] and also on T lymphocytes as a co-stimulatory molecule important for antitumor activity [83]. One molecule identified as a functional ligand of DNAM-1 is Nectin-2 (CD112) [84], which was found to be highly expressed on both mast cells and eosinophils and to mediate the augmented IgE-dependent activation observed in a mast cell–eosinophil co-culture [81]. DNAM-1 is also expressed on human NK cells and upon binding to its ligand PVR or Nectin-2 will initiate a reaction of cell cytotoxicity [85]. We found that mast cell activation induced by FcεRI was enhanced in co-culture with eosinophils as a response to the physical cross-talk mediated by the CD226/CD112 interactions [81]. Further exploring the possibility of contact-based communication, we also found an interaction between the CD2 family receptor 2B4 (CD244) expressed on eosinophils, which functions as an activation molecule [86], and its high affinity ligand CD48 molecule, which is expressed by mast

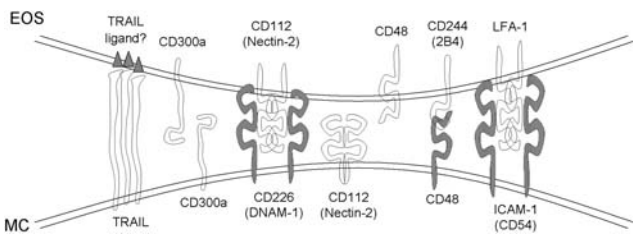

Fig. 2 Mast cell–eosinophil physical interactions: some of the possible receptor–ligand couples between human mast cells and eosinophils that we have been investigating

cells [72]. Through this pathway, CD48 can bind 2B4 and activate eosinophils to release EPO, IFN-γ and IL-4 [86]. On the other hand, eosinophils also express the CD48 receptor. This expression was shown to be up-regulated by IL-3 in atopic asthmatic patients or by allergen challenge in a murine model of experimental asthma. In addition, cross-linking of CD48 on human eosinophils initiated activation cascade and enhanced release of eosinophil granule proteins [87]. However, it has not yet been established whether there is a specific receptor on mast cells for this molecule.

Other ligand–receptor interactions between mast cells and eosinophils may be mediated through LFA-1 (leukocyte function-associated antigen 1, also known as $\alpha_L\beta_2$ integrin), a molecule expressed by eosinophils which also co-stimulates IgE-mediated activation [74, 88], and represents a ligand for ICAM-1 (intercellular adhesion molecule 1, CD54) receptor expressed on murine peritoneal and human uterine mast cells [74, 88–90]. This pathway can be activated after mast cell degranulation and will result in the recruitment of eosinophils to the site of inflammation. The same process of ligand–receptor interaction can also occur between mast cells and T cells which similarly express the LFA-1 molecule on their surface [74].

Finally, mast cells and eosinophils express an array of inhibitory receptors. We have recently found that both cells express the inhibitory receptor CD300a [82, 91] whose ligand is still unknown and could potentially be expressed in an autocrine or paracrine fashion on these cells [81, 82]. In addition, eosinophils express the integrin $\alpha_V\beta_3$ [92], which is a cognate ligand of the inhibitory receptor gp49B1 on murine mast cells [93]. Furthermore, a recent study by our group suggests another mast cell–eosinophil interaction through TRAIL and TRAIL-R. Eosinophils were shown to express TRAIL-R on their cell surface [94] as pro-survival molecules [95, 96]. Mast cells are known to express TRAIL-R on their cell surface that transduces a pro-apoptotic signal [95, 96]. Mast cell TRAIL was found in their cytoplasm (Berent-Maoz and Levi-Schaffer, unpublished data). The complete significance of both the pro-apoptotic and the pro-survival TRAIL-mediated pathways in allergic responses is not fully understood.

Altogether, these findings might suggest the feasibility of a physical contact between mast cells and eosinophils, which might contribute to the modulation of allergic reactions.

Conclusions

Throughout the course of allergic inflammation, "the allergic effector unit", the functional interface between mast cells and eosinophils, represents a central functional entity. Mast cells and eosinophils reside in a "niche" in the late and chronic phases of the inflammatory process, which enables the close proximity and tight interactions between the two cell types. These interactions, which can be mediated through soluble and physical pathways of communication, are possibly involved in modulating the severity and/or duration of the allergic response.

Additional in vivo studies should be conducted in order to better understand the importance of "the allergic effector unit", and perhaps to define better a new target for treating allergic inflammation.

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References

1. Eder W, Ege MJ, von Mutius E. The asthma epidemic. N Engl J Med. 2006;355:2226–35.
2. Lawson JA, Senthilselvan A. Asthma epidemiology: has the crisis passed? Curr Opin Pulm Med. 2005;11:79–84.
3. Williams CM, Galli SJ. The diverse potential effector and immunoregulatory roles of mast cells in allergic disease. J Allergy Clin Immunol. 2000;105(5):847–59.
4. Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. Nature 2008;454:445–54.
5. Bloemen K, Verstraelen S, Van Den Heuvel R, Witters H, Nelissen I, Schoeters G. The allergic cascade: review of the most important molecules in the asthmatic lung. Immunol Lett. 2007;113:6–18.
6. Bischoff SC. Role of mast cells in allergic and non-allergic immune responses: comparison of human and murine data. Nat Rev Immunol. 2007;7:93–104.
7. Metz M, Grimbaldeston MA, Nakae S, Piliponsky AM, Tsai M, Galli SJ. Mast cells in the promotion and limitation of chronic inflammation. Immunol Rev. 2007;217:304–28.
8. Holgate ST. The epidemic of allergy and asthma. Nature 1999;402:B2–4.
9. Kay AB. Allergy and allergic diseases. First of two parts. N Engl J Med. 2001;344:30–7.
10. Bischof RJ, Snibson KJ, Velden JV, Meeusen EN. Immune response to allergens in sheep sensitized to house dust mite. J Inflamm (Lond). 2008;5:16.
11. Bachelet I, Levi-Schaffer F, Mekori YA. Mast cells: not only in allergy. Immunol Allergy Clin North Am. 2006;26:407–25.
12. Tsai M, Grimbaldeston MA, Yu M, Tam SY, Galli SJ. Using mast cell knock-in mice to analyze the roles of mast cells in allergic responses in vivo. Chem Immunol Allergy. 2005;87:179–97.
13. Matsumoto M, Kunimitsu S, Wada K, Ikeda M, Keyama A, Kodama H. Mast cell distribution, activation, and phenotype in xanthoma. J Am Acad Dermatol. 2007;56:1006–12.
14. Prussin C, Metcalfe DD. 5. IgE, mast cells, basophils, and eosinophils. J Allergy Clin Immunol. 2006;117:S450–6.

15. Roth K, Chen WM, Lin TJ. Positive and negative regulatory mechanisms in high-affinity IgE receptor-mediated mast cell activation. Arch Immunol Ther Exp (Warsz). 2008; 56:385–99.
16. Ryan JJ, Kashyap M, Bailey D, Kennedy S, Speiran K, Brenzovich J, et al. Mast cell homeostasis: a fundamental aspect of allergic disease. Crit Rev Immunol. 2007;27:15–32.
17. Shelburne CP, Ryan JJ. The role of Th2 cytokines in mast cell homeostasis. Immunol Rev. 2001;179:82–93.
18. Gelfand EW. Inflammatory mediators in allergic rhinitis. J Allergy Clin Immunol. 2004;114:S135–8.
19. Jacobsen EA, Ochkur SI, Lee NA, Lee JJ. Eosinophils and asthma. Curr Allergy Asthma Rep. 2007;7:18–26.
20. Rosenberg HF, Phipps S, Foster PS. Eosinophil trafficking in allergy and asthma. J Allergy Clin Immunol. 2007;119:1303–10. quiz 1311–2.
21. Rothenberg ME, Hogan SP. The eosinophil. Annu Rev Immunol. 2006;24:147–74.
22. Hogan SP. Recent advances in eosinophil biology. Int Arch Allergy Immunol. 2007;143(Suppl 1):3–14.
23. Mattes J, Foster PS. Regulation of eosinophil migration and Th2 cell function by IL-5 and eotaxin. Curr Drug Targets Inflamm Allergy. 2003;2:169–74.
24. Lopez AF, Begley CG, Williamson DJ, Warren DJ, Vadas MA, Sanderson CJ. Murine eosinophil differentiation factor. An eosinophil-specific colony-stimulating factor with activity for human cells. J Exp Med. 1986;163:1085–99.
25. Rothenberg ME, Pomerantz JL, Owen WF Jr, Avraham S, Soberman RJ, Austen KF, et al. Characterization of a human eosinophil proteoglycan, and augmentation of its biosynthesis and size by interleukin 3, interleukin 5, and granulocyte/macrophage colony stimulating factor. J Biol Chem. 1988;263: 13901–8.
26. Nerlov C, Graf T. PU.1 induces myeloid lineage commitment in multipotent hematopoietic progenitors. Genes Dev. 1998;12: 2403–12.
27. Eliashar R, Levi-Schaffer F. The role of the eosinophil in nasal diseases. Curr Opin Otolaryngol Head Neck Surg. 2005;13:171–5.
28. Temkin V, Kantor B, Weg V, Hartman ML, Levi-Schaffer F. Tryptase activates the mitogen-activated protein kinase/activator protein-1 pathway in human peripheral blood eosinophils, causing cytokine production and release. J Immunol. 2002;169: 2662–9.
29. Adamko D, Odemuyiwa SO, Moqbel R. The eosinophil as a therapeutic target in asthma: beginning of the end, or end of the beginning? Curr Opin Pharmacol. 2003;3:227–32.
30. El Gazzar M, El Mezayen R, Nicolls MR, Marecki JC, Dreskin SC. Downregulation of leukotriene biosynthesis by thymoquinone attenuates airway inflammation in a mouse model of allergic asthma. Biochim Biophys Acta. 2006;1760:1088–95.
31. Ohnishi H, Miyahara N, Gelfand EW. The role of leukotriene B(4) in allergic diseases. Allergol Int. 2008;57.
32. Landgraf MA, Landgraf RG, Carvalho MH, Fortes ZB. Modulation of lung allergic inflammation and malnutrition. Neuroimmunomodulation 2008;15:194–206.
33. Hartman M, Piliponsky AM, Temkin V, Levi-Schaffer F. Human peripheral blood eosinophils express stem cell factor. Blood 2001;97:1086–91.
34. O'Donnell MC, Ackerman SJ, Gleich GJ, Thomas LL. Activation of basophil and mast cell histamine release by eosinophil granule major basic protein. J Exp Med. 1983;157:1981–91.
35. Piliponsky AM, Gleich GJ, Nagler A, Bar I, Levi-Schaffer F. Non-IgE-dependent activation of human lung- and cord blood-derived mast cells is induced by eosinophil major basic protein and modulated by the membrane form of stem cell factor. Blood 2003;101:1898–904.
36. Piliponsky AM, Pickholtz D, Gleich GJ, Levi-Schaffer F. Human eosinophils induce histamine release from antigen-activated rat peritoneal mast cells: a possible role for mast cells in late-phase allergic reactions. J Allergy Clin Immunol. 2001;107:993–1000.
37. Puxeddu I, Ribatti D, Crivellato E, Levi-Schaffer F. Mast cells and eosinophils: a novel link between inflammation and angiogenesis in allergic diseases. J Allergy Clin Immunol. 2005;116: 531–6.
38. Shakoory B, Fitzgerald SM, Lee SA, Chi DS, Krishnaswamy G. The role of human mast cell-derived cytokines in eosinophil biology. J Interferon Cytokine Res. 2004;24:271–81.
39. Bischoff SC, Dahinden CA. c-kit ligand: a unique potentiator of mediator release by human lung mast cells. J Exp Med. 1992;175:237–44.
40. Dastych J, Metcalfe DD. Stem cell factor induces mast cell adhesion to fibronectin. J Immunol. 1994;152:213–9.
41. Meininger CJ, Yano H, Rottapel R, Bernstein A, Zsebo KM, Zetter BR. The c-kit receptor ligand functions as a mast cell chemoattractant. Blood 1992;79:958–63.
42. Hermes B, Welker P, Feldmann-Boddeker I, Kruger-Krasagakis S, Hartmann K, Zuberbier T, et al. Expression of mast cell growth modulating and chemotactic factors and their receptors in human cutaneous scars. J Invest Dermatol. 2001;116:387–93.
43. Tam SY, Tsai M, Yamaguchi M, Yano K, Butterfield JH, Galli SJ. Expression of functional TrkA receptor tyrosine kinase in the HMC-1 human mast cell line and in human mast cells. Blood 1997;90:1807–20.
44. Zheutlin LM, Ackerman SJ, Gleich GJ, Thomas LL. Stimulation of basophil and rat mast cell histamine release by eosinophil granule-derived cationic proteins. J Immunol. 1984;133:2180–5.
45. Patella V, de Crescenzo G, Marino I, Genovese A, Adt M, Gleich GJ, et al. Eosinophil granule proteins activate human heart mast cells. J Immunol. 1996;157:1219–25.
46. Ellyard JI, Simson L, Bezos A, Johnston K, Freeman C, Parish CR. Eotaxin selectively binds heparin. An interaction that protects eotaxin from proteolysis and potentiates chemotactic activity in vivo. J Biol Chem. 2007;282:15238–47.
47. Temkin V, Aingorn H, Puxeddu I, Goldshmidt O, Zcharia E, Gleich GJ, et al. Eosinophil major basic protein: first identified natural heparanase-inhibiting protein. J Allergy Clin Immunol. 2004;113:703–9.
48. Levi-Schaffer F, Temkin V, Malamud V, Feld S, Zilberman Y. Mast cells enhance eosinophil survival in vitro: role of TNF-alpha and granulocyte-macrophage colony-stimulating factor. J Immunol. 1998;160:5554–62.
49. Hoenstein R, Admon D, Solomon A, Norris A, Moqbel R, Levi-Schaffer F. Interleukin-2 activates human peripheral blood eosinophils. Cell Immunol. 2001;210:116–24.
50. Temkin V, Levi-Schaffer F. Mechanism of tumour necrosis factor alpha mediated eosinophil survival. Cytokine 2001;15:20–6.
51. Temkin V, Pickholtz D, Levi-Schaffer F. Tumor necrosis factors in a murine model of allergic peritonitis: effects on eosinophil accumulation and inflammatory mediators' release. Cytokine 2003;24:74–80.
52. Liu LY, Bates ME, Jarjour NN, Busse WW, Bertics PJ, Kelly EA. Generation of Th1 and Th2 chemokines by human eosinophils: evidence for a critical role of TNF-alpha. J Immunol. 2007;179:4840–8.
53. Malaviya R, Ikeda T, Ross E, Abraham SN. Mast cell modulation of neutrophil influx and bacterial clearance at sites of infection through TNF-alpha. Nature 1996;381:77–80.
54. Takafuji S, Tadokoro K, Ito K, Nakagawa T. Release of granule proteins from human eosinophils stimulated with mast-cell mediators. Allergy 1998;53:951–6.
55. Wong CK, Ng SS, Lun SW, Cao J, Lam CW. Signalling mechanisms regulating the activation of human eosinophils by

mast-cell-derived chymase: implications for mast cell-eosinophil interaction in allergic inflammation. Immunology 2009;126(4): 579–87.
56. Vliagoftis H, Lacy P, Luy B, Adamko D, Hollenberg M, Befus D, et al. Mast cell tryptase activates peripheral blood eosinophils to release granule-associated enzymes. Int Arch Allergy Immunol. 2004;135:196–204.
57. Boyce JA. Mast cells and eicosanoid mediators: a system of reciprocal paracrine and autocrine regulation. Immunol Rev. 2007;217:168–85.
58. Saban MR, Saban R, Bjorling D, Haak-Frendscho M. Involvement of leukotrienes, TNF-alpha, and the LFA-1/ICAM-1 interaction in substance P-induced granulocyte infiltration. J Leukoc Biol. 1997;61:445–51.
59. Schain F, Tryselius Y, Sjoberg J, Porwit A, Backman L, Malec M, et al. Evidence for a pathophysiological role of cysteinyl leukotrienes in classical Hodgkin lymphoma. Int J Cancer. 2008;123:2285–93.
60. Laitinen LA, Laitinen A, Haahtela T, Vilkka V, Spur BW, Lee TH. Leukotriene E4 and granulocytic infiltration into asthmatic airways. Lancet 1993;341:989–90.
61. Sehmi R, Wardlaw AJ, Cromwell O, Kurihara K, Waltmann P, Kay AB. Interleukin-5 selectively enhances the chemotactic response of eosinophils obtained from normal but not eosinophilic subjects. Blood 1992;79:2952–9.
62. Bandeira-Melo C, Weller PF. Eosinophils and cysteinyl leukotrienes. Prostaglandins Leukot Essent Fatty Acids. 2003;69:135–43.
63. Bandeira-Melo C, Bozza PT, Weller PF. The cellular biology of eosinophil eicosanoid formation and function. J Allergy Clin Immunol. 2002;109:393–400.
64. Weller PF. Lipid, peptide and cytokine mediators elaborated by eosinophils. In: Smith JH, Cook RM, editors. Immunopharmacology of eosinophils. The Handbook of Immunopharmacology. London: Academic Press; 1993. p. 25–42.
65. Kaneko I, Suzuki K, Matsuo K, Kumagai H, Owada Y, Noguchi N, et al. Cysteinyl leukotrienes enhance the degranulation of bone marrow-derived mast cells through the autocrine mechanism. Tohoku J Exp Med. 2009;217:185–91.
66. Bandeira-Melo C, Woods LJ, Phoofolo M, Weller PF. Intracrine cysteinyl leukotriene receptor-mediated signaling of eosinophil vesicular transport-mediated interleukin-4 secretion. J Exp Med. 2002;196:841–50.
67. Grakoui A, Bromley SK, Sumen C, Davis MM, Shaw AS, Allen PM, et al. The immunological synapse: a molecular machine controlling T cell activation. Science 1999;285:221–7.
68. Monks CR, Freiberg BA, Kupfer H, Sciaky N, Kupfer A. Three-dimensional segregation of supramolecular activation clusters in T cells. Nature 1998;395:82–6.
69. Kashiwakura J, Yokoi H, Saito H, Okayama Y. T cell proliferation by direct cross-talk between OX40 ligand on human mast cells and OX40 on human T cells: comparison of gene expression profiles between human tonsillar and lung-cultured mast cells. J Immunol. 2004;173:5247–57.
70. Nelson CM, Chen CS. Cell-cell signaling by direct contact increases cell proliferation via a PI3 K-dependent signal. FEBS Lett. 2002;514:238–42.
71. Dayer JM, Burger D. Cytokines and direct cell contact in synovitis: relevance to therapeutic intervention. Arthritis Res. 1999;1:17–20.
72. Malaviya R, Gao Z, Thankavel K, van der Merwe PA, Abraham SN. The mast cell tumor necrosis factor alpha response to FimH-expressing Escherichia coli is mediated by the glycosylphosphatidylinositol-anchored molecule CD48. Proc Natl Acad Sci USA. 1999;96:8110–5.
73. Brill A, Baram D, Sela U, Salamon P, Mekori YA, Hershkoviz R. Induction of mast cell interactions with blood vessel wall components by direct contact with intact T cells or T cell membranes in vitro. Clin Exp Allergy. 2004;34:1725–31.
74. Inamura N, Mekori YA, Bhattacharyya SP, Bianchine PJ, Metcalfe DD. Induction and enhancement of Fc(epsilon)RI-dependent mast cell degranulation following coculture with activated T cells: dependency on ICAM-1- and leukocyte function-associated antigen (LFA)-1-mediated heterotypic aggregation. J Immunol. 1998;160:4026–33.
75. Salamon P, Shoham NG, Gavrieli R, Wolach B, Mekori YA. Human mast cells release Interleukin-8 and induce neutrophil chemotaxis on contact with activated T cells. Allergy 2005;60: 1316–9.
76. Salamon P, Shoham NG, Puxeddu I, Paitan Y, Levi-Schaffer F, Mekori YA. Human mast cells release oncostatin M on contact with activated T cells: possible biologic relevance. J Allergy Clin Immunol. 2008;121:448–455. e5.
77. Stopfer P, Mannel DN, Hehlgans T. Lymphotoxin-beta receptor activation by activated T cells induces cytokine release from mouse bone marrow-derived mast cells. J Immunol. 2004;172: 7459–65.
78. Caruso RA, Fedele F, Zuccala V, Fracassi MG, Venuti A. Mast cell and eosinophil interaction in gastric carcinomas: ultrastructural observations. Anticancer Res. 2007;27:391–4.
79. Piazuelo MB, Camargo MC, Mera RM, Delgado AG, Peek RM Jr, Correa H, et al. Eosinophils and mast cells in chronic gastritis: possible implications in carcinogenesis. Hum Pathol. 2008;39: 1360–9.
80. Beil WJ, McEuen AR, Schulz M, Wefelmeyer U, Kraml G, Walls AF, et al. Selective alterations in mast cell subsets and eosinophil infiltration in two complementary types of intestinal inflammation: ascariasis and Crohn's disease. Pathobiology 2002;70: 303–13.
81. Bachelet I, Munitz A, Mankutad D, Levi-Schaffer F. Mast cell costimulation by CD226/CD112 (DNAM-1/Nectin-2): a novel interface in the allergic process. J Biol Chem. 2006;281: 27190–6.
82. Bachelet I, Munitz A, Moretta A, Moretta L, Levi-Schaffer F. The inhibitory receptor IRp60 (CD300a) is expressed and functional on human mast cells. J Immunol. 2005;175:7989–95.
83. Shibuya A, Campbell D, Hannum C, Yssel H, Franz-Bacon K, McClanahan T, et al. DNAM-1, a novel adhesion molecule involved in the cytolytic function of T lymphocytes. Immunity 1996;4:573–81.
84. Bottino C, Castriconi R, Pende D, Rivera P, Nanni M, Carnemolla B, et al. Identification of PVR (CD155) and Nectin-2 (CD112) as cell surface ligands for the human DNAM-1 (CD226) activating molecule. J Exp Med. 2003;198:557–67.
85. Pende D, Bottino C, Castriconi R, Cantoni C, Marcenaro S, Rivera P, et al. PVR (CD155) and Nectin-2 (CD112) as ligands of the human DNAM-1 (CD226) activating receptor: involvement in tumor cell lysis. Mol Immunol. 2005;42:463–9.
86. Munitz A, Bachelet I, Fraenkel S, Katz G, Mandelboim O, Simon HU, et al. 2B4 (CD244) is expressed and functional on human eosinophils. J Immunol. 2005;174:110–8.
87. Munitz A, Bachelet I, Eliashar R, Khodoun M, Finkelman FD, Rothenberg ME, et al. CD48 is an allergen and IL-3-induced activation molecule on eosinophils. J Immunol. 2006;177:77–83.
88. Forbes E, Hulett M, Ahrens R, Wagner N, Smart V, Matthaei KI, et al. ICAM-1-dependent pathways regulate colonic eosinophilic inflammation. J Leukoc Biol. 2006;80:330–41.
89. Fox CC, Jewell SD, Whitacre CC. Rat peritoneal mast cells present antigen to a PPD-specific T cell line. Cell Immunol. 1994;158:253–64.
90. Guo CB, Kagey-Sobotka A, Lichtenstein LM, Bochner BS. Immunophenotyping and functional analysis of purified human uterine mast cells. Blood 1992;79:708–12.

91. Munitz A, Bachelet I, Eliashar R, Moretta A, Moretta L, Levi-Schaffer F. The inhibitory receptor IRp60 (CD300a) suppresses the effects of IL-5, GM-CSF, and eotaxin on human peripheral blood eosinophils. Blood 2006;107:1996–2003.
92. Stern M, Savill J, Haslett C. Human monocyte-derived macrophage phagocytosis of senescent eosinophils undergoing apoptosis. Mediation by alpha v beta 3/CD36/thrombospondin recognition mechanism and lack of phlogistic response. Am J Pathol. 1996;149:911–21.
93. Castells MC, Klickstein LB, Hassani K, Cumplido JA, Lacouture ME, Austen KF, et al. gp49B1-alpha(v)beta3 interaction inhibits antigen-induced mast cell activation. Nat Immunol. 2001;2: 436–42.
94. Daigle I, Simon HU. Alternative functions for TRAIL receptors in eosinophils and neutrophils. Swiss Med Wkly. 2001;131: 231–7.
95. Berent-Maoz B, Piliponsky AM, Daigle I, Simon HU, Levi-Schaffer F. Human mast cells undergo TRAIL-induced apoptosis. J Immunol. 2006;176:2272–8.
96. Berent-Maoz B, Salemi S, Mankuta D, Simon HU, Levi-Schaffer F. TRAIL mediated signaling in human mast cells: the influence of IgE-dependent activation. Allergy 2008;63:333–40.