Pediatr Allergy Immunol 2009: 20: 512–518
DOI: 10.1111/j.1399-3038.2008.00798.x

PEDIATRIC ALLERGY AND IMMUNOLOGY

The role of mast cells in eosinophilic esophagitis

Lucendo AJ, Bellón T, Lucendo B. The role of mast cells in eosinophilic esophagitis.
Pediatr Allergy Immunol 2009: 20: 512–518.

Alfredo J. Lucendo[1], Teresa Bellón[2] and Baltasar Lucendo[2]

[1]Department of Gastroenterology, Hospital General de Tomelloso, Tomelloso, Spain, [2]Research Unit, Hospital Universitario La Paz, Madrid, Spain

Eosinophilic esophagitis (EE) is a chronic inflammatory disease of the esophagus which is characterized by the presence of dense infiltrate of eosinophilic leukocytes restricted to this organ mucosa. Accumulating published evidence suggests a strong role of mast cells in the inflammatory infiltrate in the physiopathology of EE. We have reviewed published articles with relevant information about the presence and possible role of mast cells in EE. Although mast cells have been studied indirectly in EE, reported data allow us to confirm that the number of mast cells infiltrating the esophageal epithelium in adult and child patients with EE is higher with respect to the normal state and in gastroesophageal reflux disease. Mast cells linked to IgE, which are not found in other conditions, have been identified in EE. Despite that fact, an anaphylactic reaction history after exposure to allergens is not common in these patients. Therefore, the mast cells' function in EE could be dependent on T lymphocytes, as suggested by a mast cell gene expression analysis. Bi-directional crosstalk is established between mast cells and eosinophils, hence establishing interesting hypotheses regarding their relationship to EE physiopathology. Mast cells' function as an immune response leader seems to substitute for their effector functions in EE, while at the same time opening new research pathways for consideration of these cells as a therapeutic target in EE. However, the inefficiency of therapies that inhibit mast cell functions while they are effective in other respiratory tract diseases results in the need for specific studies to identify the real function of such complex cells in the physiopathology of EE. There is indirect proof of the role of mast cells in EE, while many doubts exist about their activation mechanism, which does not seem to be IgE-mediated. Specific approach studies are needed to clarify the function of these cells in the physiopathology of EE, which could be a possible therapeutic target.

Key words: mast cells; eosinophilic esophagitis

Dr. Alfredo J Lucendo, Department of Gastroenterology, Hospital General de Tomelloso, Vereda de Socuéllamos, Tomelloso, Spain
Tel.: +34 926525927
Fax: +34 926525870
E-mail: alucendo@vodafone.es

Accepted 1 July 2008

Eosinophilic esophagitis (EE) is an increasingly recognized clinicopathologic syndrome (1), which is characterized by esophageal and/or upper gastrointestinal symptoms in association with dense infiltration of esophageal mucosa by eosinophilic leukocytes and absence of pathologic gastroesophageal reflux (GER) (2). This disease affects both children and adults who frequently present food or aeroallergen sensitization, elevated IgE values in serum, and response to elemental or eliminatory diets or antiallergic therapies (3). For these reasons, EE has been considered as an immunoallergic disorder. As a result of this identification, we are obliged to consider the esophageal mucosa as an active immunological surface capable of participating in immunoallergic responses following exposure to food- or air-borne allergens in those sensitized patients subjected to specific testing. This newly discovered function of the esophagus contrasts with its traditional role as a simple muscular tube responsible for the transportation

of food to the stomach and provides us with further insight into food allergies and their various manifestations. Although little is known about the physiopathology of EE, available evidence highlights the central role of eosinophilic leukocytes. The activation of these cells leads to release cytotoxic proteins contained in their cytoplasmatic granules. Varying degrees of intensity in histopathological damage induced by eosinophils lead to the extensive polymorphism on the endoscopic findings characterizing EE (4, 5). However, several reports have noted that the inflammatory epithelial infiltrate in EE contains also an increased number of mast cells, as has been described in both pediatric (6–8) and adult cases (1, 9, 10) of the disease.

Mast cells have a central function in innate immunity against parasites and bacteria as well as in allergic diseases as they constitute the main effector cells in the IgE-associated responses (11). They are distributed in virtually all the body's vascular tissues (12), and they have been described as resident cells in mucosa and in connective tissues, hence they can be subdivided into two different categories based on immunohystochemical criteria (13), MC_T or MC_{TC}, on the principle of the presence of tryptase (MC_T) or both tryptase and chymase (MC_{TC}) (14). This phenotypic diversity is not only a descriptor of tissue location (15) but also implies regulation of cytokine gene expression, and is associated with functional differences (16) (Table 1). It has long been known that mast cells take part in inflammatory processes in such a way that these cells are present and recruited towards sites of inflammation. Their effector functions accomplished through the release of substances stored in cytoplasmatic granules has been classically recognized as mast cells have mediators that are able to develop an inflammatory response, like tryptases and proteases (17, 18), eicosanoids, reactive oxygen species, and nitric oxide. Mast cell activation because of various T cell-dependent or independent paths or micro-environmental components leads to a differential release of the mediators, which mast cells have in their biological armoury. This paper aims to review published experience in identifying mast cells in EE and to provide a physiopathological explanation of their possible roles in disease mechanisms.

Table 1. Distribution, preformed mediators, and responses of human mast cells [modified from Ryan J and Huff TF(12)]

	MC_{TC}	MC_T
Tissue distribution		
Skin	++	–
Intestinal submucosa	++	+
Small intestine mucosa	+	++
Alveolar wall	–	++
Bronchial/bronchiolar mucosa	+	++
Areas of dense fibrosis	+	–
Nasal mucosa	++	++
Vascular wall	++	–
Selective loss in T-cell deficiency	No	Yes
Preformed mediators		
Histamine	Yes	Yes
α- and β-Tryptase	Yes	Yes
Chimase	Yes	No
Carboxipeptidase A	Yes	No
Cathepsin G	Yes	No
Response to no IgE-mediated stimuli	Strong	Present
Inhibitory effect of cromoglycate	No	Yes

MC_{TC}, tryptase and chimase-positive mast cells; MC_T, tryptase-positive mast cells;
++, wide distribution; +, some distribution; –, no distribution.

Mast cells in epithelial samples of EE

We have long known that apart from eosinophilic leukocytes, the EE epithelial inflammatory infiltrate is characterized by the presence of a dense population of T lymphocytes, mainly CD8+ (9, 19), and furthermore by an increased density of mast cells compared with normal controls. The main role that these mast cells play in respiratory and skin allergic diseases and in the immediate hypersensitivity reactions is well known, as mast cell are the main effectors in IgE-mediated allergic reactions. However, their possible implication in the physiopathology of EE has not been systematically considered, despite the fact that they have been identified both in children (6–8) and adult (9, 10) patients.

Mast cells are identified mainly through immunohistochemical staining of tryptase, a cytoplasmic enzyme highly characteristic of these cells. The first evidence of the presence of mast cells as constitutive cells in the EE inflammatory infiltrate was reported by Atwood et al. (1) who described scattered mast cells that did not form bands in the lamina propria in a series of adult patients. Later on, Justinich et al. (6) reported that mast cells detection could be included in the histopathologic evaluation of EE in infants and children after studying a small series of patients wherein mucosal mast cells increased significantly (parallel with eosinophil increases) in allergic esophagitis vs. GER-induced esophagitis and control tissue. Subsequently, Nicholson et al. (20) described two cases of EE associated with esophageal leimyomatosis that shared a common profile characterized by CD45RO-positive primed T-lymphocytes, activated (EG2-positive) eosinophils, and tryptase-positive mast cells, together with gene expression of interleukin

(IL)-4. These authors suggested the possibility that there was a common underlying allergic component in both disorders. A similar case was reported by Morris et al. (21) in which infiltration of eosinophils and mast cells confined to the esophageal muscularis propria resulted in dysphagia.

The first consideration of the possible etiologic role played by mast cells in EE comes from Straumann et al. (22), who also found a high density of these cells in a number of patients with EE. Despite EE being associated with a cell-mediated type Th2 hypersensitivity reaction, they suggested that an IgE-mediated reaction could also contribute to the physiopathology of the disease. A later paper from Gupta et al. (23) confirmed an increase in the intra-epithelial mast cell number in children with EE compared with healthy controls. In this work, the authors did not find an increase in IL-4 gene expression [which is a key regulator for mast cells (24)]. This fact hindered their ability to clearly implicate these cells in the physiopathology of EE. Mast cell distribution was scattered in the thickness of the esophageal epithelium with a tendency to occupy the deepest layers (7, 9, 23). Thus, mast cells are strategically positioned at the interface between the external and internal environments to enable them to respond rapidly to stimuli with mediator and cytokine secretion.

Mast cell activation demonstrated through ultrastructural changes in their cytoplasmatic granules as detected by electronic transmission microscopy and also by positive immunostaining against IgE has been proposed by Kirsch et al (7) as a differentiating element between EE and/or GERD in the case of children with a medium range of eosinophilic density (7 to 24 eosinophils/high power field (HPF)) in the esophageal epithelium. These findings which have been also observed in the case of adults with EE (9) highlight the possible function of IgE in the physiopathology of the disease as immunostaining was demonstrated in the epithelium of patients with EE and not in healthy controls or GERD.

The presence of intra-epithelial mast cells in EE has been established as a differentiating element between this disease and GERD (6) even when the number of eosinophils in GERD is generally much lower than the number considered as the diagnostic criterion for EE (25). The treatment with topical steroids has demonstrated that apart from reducing the number of eosinophils in the esophageal epithelium, it simultaneously significantly reduces the infiltration of mast cells (9, 26) in those patients who reach histologic normalization. Blanchard et al. (8) conducted important research that has opened new avenues of understanding of the molecular physiopathology and the genetics of EE. Among the results observed, they described a direct correlation between the number of eosinophils and mast cells/HPF that infiltrated the esophageal epithelium of 13 children with EE, and the correlation between the inflammatory infiltrate and the severity of tissue damage, expressed as hyperplasia of basal cells. This work demonstrated through a microarrays analysis and immunofluorescence microscopy that various mast cell characteristic genes, such as the genes coding for tryptase, chymase, and carboxypeptidase A3, are induced in EE, although with very different expression levels. For example, some mast cell-specific genes were increased twofold (chymase), whereas others were increased sixfold (tryptase) or 20-fold (carboxypetidase A3) showing dissociation from the threefold change in mast cell levels. Because of this finding of tryptase expression without chymase (MC_T), the authors suggested the involvement of T-cell-dependent mucosal mast cells in the inflammatory process (16). Bhattacharya et al. (27) showed that EE is particularly characterized by strong upregulation of the eotaxin-3/CCL26 gene and their results were confirmed in a recent work. The grade of tissue eosinophilic infiltration has been positively correlated with the tissue expression of eotaxin-3/CCL26 mRNA in the esophageal epithelium (28), and the presence of a polymorphism of a single nucleotide has been demonstrated ($+2496T > G$, rs2302009) in eotaxin-3/CCL26 gene that strengthens its possible role in the pathology of disease (8). It is interesting to note that mast cells also express CCR3 and respond to CCR3 ligands (29–31). Thus, eotaxin-3/CCL26 may also target mast cells in EE.

Discussion of the possible role of mast cells in EE

The symptomatic manifestations of EE (dysphagia, chest pain, heartburn, vomiting, food impaction) are common to other inflammatory chronic processes, among which GERD stands out. Both entities can show alterations in the pH probe recording (4) and even similar endoscopic findings (32). It is important to distinguish between both diseases as patients with EE do not usually respond to acid-reducing treatments (33) even to high doses (2), but they do respond to anti-inflammatory therapies (19, 26) and/or in removing allergenic triggers (34–37). Both EE and GERD have been associated with infiltration of the esophageal epithelium by eosinophilic leuko-

cytes, but their density in EE is much higher in normal conditions. The human esophagus contains T lymphocytes (from which about 75% are CD8+), density of which increases in GERD and especially in EE (9). Similar data have been reported regarding mast cells and some authors propose the existence of a continuous phenotype between EE and GERD (38). At the same time, there are some doubts about the possibility that GERD by itself could develop a pathologic role in the origin of EE (39). A possible relationship between increasing incidence of eosinophils-related foregut disorders and the widespread availability and massive use of acid-reducing therapies (40) has been suggested as it was proven that these drugs significantly increase allergic sensitization in both mice and humans, thus reducing the degradation of antigens by gastric acid and secondarily increasing sensitization potential (2, 41) and generating specific IgE. Overall, 71–78% of pediatric EE patients and 60–69% of adult EE patients had elevated total IgE levels (2). Furthermore, patients usually present high levels of aeroallergens or foods-specific IgE (42, 43). Several investigations in humans (42, 44, 45) and mice (46) support the idea that EE could be driven by aeroallergens. With respect to food-specific IgE, EE patients have no history of anaphylaxis to those foods to which they have a positive test. However, we have evidence of the development of EE by means of an immediate hypersensitivity reaction triggered after ingesting food in patients with high levels of serum-specific IgE against those foods (10). The high rate of concurrent atopic diatheses in these patients suggests that elevated IgE levels are probably not linked specifically to EE.

The most extensively studied mechanism leading to mast cells' activation and degranulation is antigen cross-linking of IgE antibodies on their surface. This cross-linking not only results in the rapid release of autacoid mediators but also in the sustained synthesis and release of cytokines, chemokines, and growth factors (47). The mechanism of mast cell activation in EE is not clear, but what we know leads us to think that in the majority of patients it is not IgE-mediated. There are multiple alternate mechanisms that lead to the release of mediators by mast cells, independent of IgE, for instance, through expression of *Toll-like receptors* (11) or by non-immunologic mechanisms (48, 49), such as after exposure to acid GER (50–52) or to bile acids (53). The enteric nervous system plays a role in regulating allergic inflammatory cells, such as lymphocytes, mast cells, and eosinophils (54). This morphologic and functional association between immune cells and nerve cells has been described mainly for mast cells (55), where substance P could play an important role (56). This ability to signal independently of IgE can be induced in an antigen-independent manner prior to a T-cell encounter with antigens and it has the potential to influence the initiation of an adaptive immune response as well as the later effector phase (57).

Between these IgE-independent mechanisms, particularly relevant is the ability of certain eosinophil-derived proteins, mainly major basic protein (MBP), to induce mast cell degranulation in an especially attractive hypothetical mast-cell/eosinophil interaction. Mann and Leung (58) hypothesized that upon antigen exposure, esophageal mast cells increase histamine levels and subsequently induce the accumulation of eosinophils in sensitized individuals. Secondarily, eosinophilic chemotactic factors could result in further eosinophilic accumulation and degranulation. Inversely, some of the proteins contained in the eosinophils' granules, particularly MBP, can induce mast cell degranulation and the production of tumor necrosis factor-α, thus the existence of an interaction between both cell types can be suggested as a feedback loop that increases the inflammatory response (59). Other Th2 cytokines released by mast cells define an environment that helps allergic inflammatory processes (11), recruitment of T lymphocytes, eosinophils' medullar proliferation, and induce B-cell class switching to IgE. Some of them, such as IL-4, IL-5, IL-13 (60), granulocyte-macrophage colony stimulating factor, and eotaxines (57) have been widely implicated in the physiopathology of EE (61).

Beyond their effector functions, mast cells have an increasingly recognized immunoregulatory function (62). Histamine participates in the early phase of allergic response binding to H1 type receptors, but through other receptors (H2 to H4) histamine can modulate immune responses (63, 64) acting on dendritic cells and T-lymphocytes (57). Mast cells by themselves could promote a local humoral environment, providing the initiation, perpetuation, and even the resolution of inflammatory responses and playing a central role in orchestrating inflammation (65). Available evidences with respect to the presence of mast cells taking part in the epithelial inflammatory infiltrate in EE support the idea that the mast cells' function could be highly relevant in the physiopathology of EE, although to the date their role has not been well characterized. Furthermore, in pediatric cases of EE, ultrastructural changes have been found by electron

microscopy, in addition to positive IgE-immunostaining, indicating mast cells activation (7). These data have also been corroborated in adults (9). Mast cells activation through their high affinity IgE receptors (FCεRI) could initiate immediate responses which are characterized by a strong increase in vascular permeability and angioedema, which have not been clinically observed in EE. However, spongiosis or enlargement of intercellular spaces is a typical finding in the histopathological analysis of esophageal epithelial samples in these patients (66).

Several mediators included in mast cells' cytoplasm granules (such as histamine, leukotrienes and platelet activator factor) have the capacity to act on neuromuscular components of the digestive tract wall (67); in this way, they could play an important role in originating motor disturbances observed in many cases of EE (68). Indeed, mast-cell activation and increased mucosal histamine levels have been observed in experimental models of esophagitis (50, 51). Confocal microscopy has shown that mast cells are located close to primary afferent nerve fibres in intestinal allergies, and degranulation of these cells could alter neuron membrane stability (69). Mann and Leung (58) directly implicated mast cells in the genesis of concentric esophageal rings which are found in patients affected with EE during endoscopic exams, generating the hypotheses that the activation of acetylcholine by histamine (liberated in response to antigen mediated stimulation) may cause the contraction of muscle fibers in the muscularis mucosae, resulting in the formation of esophageal rings. Leukotriene C4, another strong mediator, the synthesis of which is induced after mast cell activation (57) shows a long recognized effect on smooth muscle, reported mainly in the bronchial tree (70–72). We have recent evidence demonstrating that EE in patients of pediatric age is associated with fibrous remodeling of the esophageal wall because of subepithelial collagen deposition (73, 74) determined by a molecular mechanism which is dependent on transforming growth factor (TGF)-beta-1 and its signaling molecule phospho-SMAD2/3 proteins. This process has been related to the activation of eosinophils present in the esophageal lamina propria, but not to that of mast cells in the same location (74) despite the fact that these cells also constitute a potential source of TGF-beta.

Drugs acting on mast cells and their derived mediators are a first level strategy for treatment of multiple allergic processes and they have been assayed in EE as well, in particular mast cell stabilizers and leukotriene receptor antagonists. Mast cell stabilisers have been successfully utilized in eosiniphilic gastroenteritis because they are resistant to gastric acid (75, 76), but study by Liacouras et al.(77) did not result in clinical nor histologic improvement with these drugs in a 10-year review, which presented information on 14 EE child patients treated with 100 mg oral cromolyn, four times daily for 1 month. Attwood et al. (78) used high doses of Montelukast (up to 100 mg) in a short series of eight patients diagnosed with EE. Although most patients reported symptomatic improvement after treatment in a telephone-based evaluation, none of them reached resolution of the epithelial inflammation. Gupta et al. (79) determined esophageal mucosal levels of cysteinyl leukotrienes in children with EE and normal controls and found that they were similar in both groups. The poor response to these therapies contrasts with results obtained in other allergic diseases of the airways, and strongly supports the idea that mast cells could present a distinctive functional role and activation pattern in EE. The true consideration of mast cell as a possible therapeutic target in EE depends on uncovering its true function in this disease.

Conclusion

Published data provides indirect evidence of the possible participation of mast cells in the physiopathology of EE, as they are cells capable of acting at multiple levels, with continuing interest in their possible interaction with T lymphocytes and eosinophils. Mast cell activation pathways in EE have not been defined so far, but in most patients it seems not to be IgE-dependent, although the presence of activated IgE-bearing mast cells in children and adults has been observed, distinguishing EE from GERD patients. Studies specifically directed at defining the exact role of mast cells in EE, which could constitute a potential strategy for therapy in EE patients, should be promoted.

References

1. Attwood SE, Smyrk TC, Demeester TR, et al. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci 1993: 38: 109–16.
2. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology 2007: 133: 1342–63.
3. Khan S, Kandula L, Orenstein SR. Educational clinical case series in pediatric allergy and immunology. Pediatr Allergy Immunol 2007: 18: 629–39.
4. Lucendo AJ, Pascual-Turrión JM, Navarro M, et al. Endoscopic, bioptic and manometric findings in eosinophilic esophagitis before and after steroid therapy: a case series. Endoscopy 2007: 39: 765–71.
5. Chang F, Anderson S. Clinical and pathological features of eosinophilic oesophagitis: a review. Pathology 2008: 40: 3–8.

6. Justinich CJ, Kalafus D, Esposito P, et al. Mucosal mast cells distinguish allergic from gastroesophageal reflux-induced esophagitis. J Pediatr Gastroenterol Nutr 1996: 23: 342A.
7. Kirsch R, Bokhary R, Marcon MA, et al. Activated mucosal mast-cells differentiate eosinophilic (allergic) esophagitis from gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr 2007: 44: 20–6.
8. Blanchard C, Wang N, Stringer KF, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. J Clin Invest 2006: 116: 536–47.
9. Lucendo AJ, Navarro M, Comas C, et al. Immunophenotypic characterisation and quantification of the epithelial inflammatory infiltrate in eosinophilic esophagitis through stereology: an analysis of the disease's cellular mechanisms and the esophagus's immunological capacity. Am J Surg Pathol 2007: 31: 598–606.
10. Martín-Muñoz MF, Lucendo AJ, Navarro M, et al. Food allergy and eosinophilic esophagitis: two cases studies. Digestion 2006: 74: 49–54.
11. Krishnaswamy G, Ajitawi O, Chi DS. The human mast cell: an overview. Methods Mol Biol 2006: 315: 13–34.
12. Ryan JJ, Huff TF. Biology of mast cells. In: Adkinson NF Jr, Yunginger JW, Busse WW et al., ed. Middleton's Allergy, Principles and Practice. Philadelphia, PA: Mosby, 2003: 333–46.
13. Hallgren J, Gurish MF. Pathways of murine mast cell development and trafficking: tracking the roots and routes of the mast-cell. Immunol Rev 2007: 217: 8–18.
14. Prussin C, Metcalfe DD. IgE, mast cells, basophils and eosinophils. J Allergy Clin Immunol 2006: 117: S450–6.
15. Schwartz LB. Mast cells and basophils. Clin Allergy Immunol 2002: 16: 3–42.
16. Austen KF, Boyce JA. Mast cell lineage development and phenotypic regulation. Leuk Res 2001: 25: 511–8.
17. Caughey GH. Mast cell tryptases and chymases in inflammation and host defense. Immunol Rev 2007: 217: 141–54.
18. Stevens RL, Adachi R. Protease-proteoglycan complexes of mouse and human mast cells, and importance of their beta trytase-heparin complexes in inflammation and innate immunity. Immunol Rev 2007: 217: 155–67.
19. Teitelbaum J, Fox V, Twarog F, et al. Eosinophilic Esophagitis in children: immunopathological analysis and response to fluticasone propionate. Gastroenterology 2002: 122: 1216–25.
20. Nicholson AG, Li D, Pastorino U, et al. Full thickness eosinophilia in oesophageal leiomyomatosis and idiopathic eosinophilic oesophagitis. A common allergic inflammatory profile J Pathol 1997: 183: 233–6.
21. Morris CD, Wilkinson J, Fox D, et al. Diffuse esophageal leiomyomatosis with localized dense eosinophilic infiltration. Dis Esophagus 2002: 15: 85–7.
22. Straumann A, Bauer M, Fischer B, et al. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. J Allergy Clin Immunol 2001: 108: 954–61.
23. Gupta SK, Fitzgerald JF, Roudratynk T, et al. Cytokine expression in normal and inflamed esophageal mucosa: a study into the pathogenesis of allergic eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2006: 42: 22–6.
24. Bischoff SC, Mayer JH, Manns MP. Allergy and the gut. Int Arch Allergy Immunol 2000: 121: 270–83.
25. Winter HS, Madara JL, Stafford RJ, et al. Intraepitelial eosinophils: a new diagnostic criterion for reflux esophagitis. Gastroenterology 1982: 83: 818–23.
26. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized double-blind, placebo controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. Gastroenterology 2006: 131: 1381–91.
27. Bhattacharya B, Carlsten J, Sabo E, et al. Increased expression of eotaxin-3 distinguishes between eosinophilic esophagitis and gastroesophageal reflux disease. Hum Pathol 2007: 38: 1747–53.
28. Bullock JZ, Villanueva JM, Blanchard C, et al. Interplay of adaptive Th2 immunity with eotaxin-3/C-C Chemokine receptor 3 in eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2007: 45: 22–31.
29. Romagnani P, De Paulis A, Beltrame C, et al. Tryptase-chymase double-positive human mast cells express the eotaxin receptor CCR3 and are attracted by CCR3-binding chemokines. Am J Pathol 1999: 155: 1195–204.
30. De Paulis A, Annunziato F, Di Gioia L, et al. Expression of the chemokine receptor CCR3 on human mast cells. Int Arch Allergy Immunol 2001: 124: 146–50.
31. Ochi H, Hirani WM, Yuan Q, et al. T helper cell type 2 cytokine-mediated comitogenic responses and CCR3 expression during differentiation of human mast cells in vitro. J Exp Med 1999: 190: 267–80.
32. Müller S, Pühl S, Vieth M, et al. Analysis of symptoms and endoscopic findings in 117 patients with histological diagnoses of eosinophilic esophagitis. Endoscopy 2007: 39: 339–44.
33. Ruchelli E, Wenner W, Voytek T, et al. Severity of esophageal eosinophilia predict response to conventional gastroesophageal reflux therapy. Pediatr Develop Pathol 1999: 2: 15–8.
34. Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology 1995: 109: 1503–12.
35. Markowitz JE, Spergel JM, Ruchelli E, et al. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol 2003: 98: 777–82.
36. Spergel JM, Andrews T, Brown-Whitehorn TF, et al. Treatment of eosinophilic esophagitis with specific elimination diet directed by a combination of skin prick and patch test. Ann Allergy Asthma Immunol 2005: 95: 336–43.
37. Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clin Gastroenterol Hepatol 2006: 119: 1097–102.
38. Rothenberg ME. Eosinophilic gastrointestinal disorders. J Allergy Clin Inmunol 2004: 113: 11–28.
39. Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. Am J Gastroenterol 2007: 102: 1301–6.
40. Murch SH. Clinical manifestations of food allergy: the old and the new. Eur J Gastroenterol Hepatol 2005: 17: 1287–91.
41. Untersmayr E, Poulsen LK, Platzer MH, et al. The effect of gastric digestion on codfish allergenicity. J Allergy Clin Immunol 2005: 115: 377–82.
42. Simon D, Marti H, Heer P, et al. Eosinophilic esophagitis is frequently associated with IgE-mediated

allergic airway diseases. J Allergy Clin Inmunol 2005: 115: 1090–2.
43. Yamazaki K, Murray JA, Arora AS, et al. Allergen-specific in vitro cytokine production in adult patients with eosinophilic esophagitis. Dig Dis Sci 2006: 51: 1934–41.
44. Onbasi K, Sin Az, Doganavsalgil B, et al. Eosinophil infiltration of the esophageal mucosa in patients with pollen allergy during the season. Clin Exp Allergy 2005: 35: 1423–31.
45. Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. J Allergy Clin Inmunol 2003: 112: 796–7.
46. Mishra A, Hogan SP, Brandt EB, et al. An etiological role for aeroallergens and eosinophils in experimental esophagitis. J Clin Invest 2001: 107: 83–90.
47. Holgate ST. The role of mast cells and basophils in inflammation. Clin Exp Allergy 2000: 30 (Suppl. 1): 28–32.
48. Zheutlin LM, Ackerman SJ, Gleich GJ. Stimulation of basophil and mast cells histamine release by eosinophil granule-derived cationic proteins. J Immunol 1984: 133: 2180–5.
49. Metcalfe DD, Baram D, Mekory YA. Mast cells. Physiol Rev 1997: 77: 1033–79.
50. Barclay RL, Dinda PK, Morris GP, et al. Morphological evidence of mast cell degranulation in an animal model of acid-induced esophageal mucosal injury. Dig Dis Sci 1995: 40: 1651–8.
51. Feldman MJ, Morris GP, Dinda PK, et al. Mast cells mediate acid-induced augmentation of opossum esophageal blood flow via histamine and nitric oxide. Gastroenterology 1996: 110: 121–8.
52. Paterson WG. Role of the mast cell-derived mediators in acid-induced shortening of the esophagus. Am J Physiol 1998: 274: G385–8.
53. Quist RG, Ton-Nu HT, Lillienau J, et al. Activation of mast cells by bile acids. Gastroenterology 1991: 101: 446–56.
54. Bischoff SC. Food allergies. Curr Treat Options Gastroenterol 2007: 10: 34–43.
55. Williams RM, Bienenstock J, Stead RH. Mast cells: the neuroimmune connection. Chem Immunol 1995: 61: 208–35.
56. Koon HW, Pothoulakis C. Immunomodulatory properties of substance P: the gastrointestinal system as a model. Ann NY Acad Sci 2006: 1008: 23–40.
57. Sayed BA, Brown MA. Mast cells as modulators of T-cell responses. Immunol Rev 2007: 217: 53–64.
58. Mann NS, Leung JW. Pathogenesis of esophageal rings in eosinophilic esophagitis. Med Hypotheses 2005: 64: 520–3.
59. Liacouras CA, Bonis P, Putman PE, et al. Summary of the First International gastrointestestinal eosinophil research symposium. J Pediatr Gastroenterol Nutr 2007: 45: 370–91.
60. Blanchard C, Mingler MK, Vicario M, et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. J Allergy Clin Immunol 2007: 120: 1292–300.
61. Lucendo Villarín AJ, De Rezende L. Eosinophilic esophagitis: review of current clinical and physiopathological concepts. Gastroenterol Hepatol 2007: 30: 234–41.
62. Montero Vega MT. New aspects on inflammation in allergic diseases. Allergol Immunopathol (Madr) 2006: 34: 156–79.
63. Jutel M, Blaser K, Akdis CA. The role of histamine in regulation of immune responses. Chem Immunol Allergy 2006: 91: 174–87.
64. Akdis CA, Blaser K. Histamine in the immune regulation of allergic inflammation. J Allergy Clin Immunol 2003: 112: 15–22.
65. Kinet JP. The essential role of mast cells in orchestrating inflammation. Immunol Rev 2007: 217: 5–7.
66. Ravelli AM, Villanacci V, Ruzzenenti N, et al. Dilated intercellular spaces: a major morphological feature of esophagitis. J Pediatr Gastroenterol Nutr 2006: 42: 510–5.
67. Cheung KM, Oliver MR, Vameron DJS, et al. Esophageal eosinophilia in children with dysphagia. J Pediatr Gastroenterol Nutr 2003: 37: 498–503.
68. Lucendo AJ, Castillo P, Martín-Chávarri S, et al. Manometric findings in adult eosinophilic oesophagitis: a study of 12 cases. Eur J Gastroenterol Hepatol 2007: 19: 417–24.
69. Vanderhoff JA, Young RJ. Allergic disorders of the gastrointestinal tract. Curr Opin Clin Nutr Metab Care 2001: 4: 553–6.
70. Holgate ST, Peters-Golden M, Panettieri RA, et al. Roles of cysteinyl leukotrienes in airway inflammation, smooth muscle function, and remodeling. J Allergy Clin Immunol 2003: 1 (Suppl.): S18–34.
71. Fulmer JJ, Khan AM, Elidemir O, et al. Role of cysteinyl leukotrienes in airway inflammation and responsiveness following RSV infection in BALB/c mice. Pediatr Allergy Immunol 2005: 16: 593–601.
72. Landgraf RG, Nossi DF, Sirois P, et al. Prostaglandins, leukotrienes and PAF selectively modulate lymphocyte subset and eosinophil infiltration into the airways in a murine model of asthma. Prostaglandins Leukot Essent Fatty Acids 2007: 77: 163–72.
73. Aceves SS, Newbury RO, Dohil R, et al. Esophageal remodeling in pediatric eosinophilic esophagitis. J Allergy Clin Immunol 2007: 119: 206–12.
74. Chehade M, Sampson HA, Morotti RA, et al. Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2007: 45: 319–28.
75. Moots RJ, Prouse P, Gumpel JM. Near fatal eosinophilic gastroenteritis responded to oral sodium cromoglycate. Gut 1988: 29: 1282–5.
76. Businco L, Cantani A. Food allergy in children: diagnosis and treatment with sodium cromoglycate. Allergol Immunopathol (Madr) 1990: 18: 339–48.
77. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. Clin Gastroenterol Hepatol 2005: 3: 1198–206.
78. Attwood SE, Lewis CJ, Bronder CS, et al. Eosinophilic esophagitis: a novel treatment using Montelukast. Gut 2003: 52: 181–5.
79. Gupta SK, Peters-Golden M, Fitzgerald JF, et al. Cysteinil leukotriene levels in esophageal mucosal biopsies of children with eosinophilic inflamation: are they all the same? Am J Gastroenterol 2006: 101: 1125–8.