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Mechanism of Eosinophilic Esophagitis

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The esophagus is the only segment in the gastrointestinal (GI) tract that is devoid of eosinophils; whereas, most of the other leukocytes reside in the esophagus at baseline in healthy state (1, 2). The esophagus is lined with mucous membrane and muscles that act with peristaltic action to move swallowed food down to the stomach. The epithelium of the esophagus is squamous but not keratinized like skin; therefore keratinocytes are directly exposed to the esophageal content. This indicates that esophageal epithelium may have a significant role in the induction of esophageal inflammation. The accumulation of eosinophils in the esophageal mucosa is the cardinal pathological finding that occurs secondary to several unrelated diseases and is reported in a number of esophageal diseases such as hypereosinophilic syndrome, eosinophilic gastroenteritis, drug reactions, fungal/parasitic infections, gastroesophageal reflux (GERD), and eosinophilic esophagitis (EoE) (1-11). (EoE or EE- For consistency thru the monograph we would like to call eosinophilic esophagitis EoE. EoE has been increasingly confused with erosive esophagitis in the adult gi world-)) EoE is a commonly observed medical problem and is well documented in pediatric patients, but the adult form has only recently gained recognition as a distinct entity. EoE is characterized by an increase in esophageal eosinophilia, basal cell hyperplasia and the number of other esophageal abnormalities that include furrows, the formation of fine concentric mucosal rings (corrugated esophagus), and esophageal strictures (narrowing) (3-9), associated with extensive tissue remodeling and fibrosis (10,11).

Clinical characteristics of eosinophilic esophagitis (EoE)

Esophageal eosinophils are not pathognomonic for EoE since eosinophil infiltration in the esophagus occurs in a variety of states including GERD. Differentiating EoE from other esophageal disorders, specifically GERD is often a challenge (23). Patients with primary EoE commonly report symptoms that include difficulty feeding, vomiting, chest pain, dysphagia, and food impaction (19,24-26); these symptoms appear to occur sequentially as disease progresses from infancy into adulthood (27). Dysphagia and food impaction are commonly observed in adult EoE patients (28-30). However, longitudinal studies from childhood into adulthood are not yet available. EoE patients are predominantly young males (19,24) and have relatively high levels of eosinophils in the esophageal mucosa, extensive epithelial hyperplasia,

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and a high rate of atopic disease compared to patients with GERD (22,31). In particular, esophageal eosinophil levels of $>24/\text{hpf}$ have been reported to correlate with lack of responsiveness to anti-GERD therapy (12,32); these concentrations may be diagnostic of EoE rather than GERD, especially in patients already on anti-GERD therapy. A recent expert panel established as part of the First International Group of EoE Researchers (FIGERS) recommended that a cutoff of 15 eosinophils/hpf is sufficient for the diagnosis of EoE provided that GERD has been eliminated as the diagnosis (33); for research purposes a higher threshold level was recommended. Additionally, esophageal biopsies from EoE demonstrate a thickened mucosa with basal layer hyperplasia and papillary lengthening. Radiographic and endoscopic studies have shown many findings, including small caliber esophagus, strictures, mucosal rings, ulcerations, whitish papules and polyps (8,21,25,26,36,37). EoE has been found to be associated with esophageal dysmotility but the etiology of the motor disturbances is unclear. The eosinophil and mast cell activation and degranulation has been postulated as a possible etiology of EoE pathogenesis (13,34,35).

Food and environmental allergens are linked to EoE

Food allergies affect an estimated 6% of children and 3.7% of adults in the US and during the past decade food allergy and its manifestations have substantially increased (53,54). Food allergies can be classified into those that are IgE-mediated and those that are non-IgE-mediated. IgE-mediated reactions develop when food-specific IgE antibodies residing on mast cells and basophils come into contact with and bind to circulating food allergens and activate the cells to release potent mediators and cytokines. In non-IgE-mediated food allergic disorders, multiple inflammatory cells and their mediators play a role in immunopathogenesis. The majority of EoE patients (90%) have evidence of food and aeroallergen hypersensitivity yet only a subset (10-30%) has a history of food anaphylaxis (38). Recent literature on pediatric patients with EoE confirms that nearly all patients respond to an elemental diet with resolution of symptoms and normalization of biopsies (38); reintroduction of foods causes symptoms and esophageal eosinophilia to return (39). Interestingly, patients with EoE have also been reported to exhibit seasonal variations in their symptoms and changes in their esophageal eosinophil levels. The mucosal eosinophil counts were elevated during the spring and summer and were suppressed during the winter (40), indicating a role for aeroallergens. Additionally, studies of animal models have also linked EoE to aeroallergens and allergic diseases (41). These findings indicate that sensitization pathways could occur in human EoE and antigen presenting cells (APCs) may play an important role in the pathogenesis of EoE. An average of 3 to 6 foods per patient were directly linked to the development of esophageal eosinophilia and the common foods identified were milk, egg, soy, chicken, wheat, beef, corn, and peanuts (38,39). Taken together, this provides supportive evidence that food and aeroallergen sensitization is causally involved in EE. (Figure 1)

Cellular mediators that influence the occurrence of EE

The current understanding of the pathophysiology of EE comes from both basic immunological studies and clinical observation and treatment. A large number of eosinophils were detected in the esophagus following induction of EE in humans as well as in an experimental mouse model of EE. These eosinophils contain a number of toxic granular proteins. Eosinophil granules contain a crystalloid core composed of major basic protein (MBP-1 and -2), and a matrix composed of eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase (EPO) (42). These cationic proteins share certain pro-inflammatory properties but differ in other ways. The MBP, EPO, and ECP have cytotoxic effects on epithelium and ECP and EDN possess anti-viral and ribonuclease activity (44). MBP directly increases smooth muscle reactivity (45) and also triggers degranulation of mast cells and basophils (46). Indeed, evidence is emerging that mast cells and eosinophils both are involved

in EE pathogenesis (47,48). Several studies have shown that mast cells are present in the normal esophagus and their number increases in esophageal biopsies of EE patients (47,48). Interestingly, mast cell gene (like tryptase or carboxypeptidase's 3) induced expression is noticed in the esophageal biopsies of EE patients (47). Mast cells are known to release mediators (such as histamine and proteases) and upon activation they cause pathophysiological alterations in tissues (49,50). Evidence indicates that both eosinophils and mast cells are present in an activated state in EE patients (35,47,52). Activated eosinophils and mast cells generate lipid mediators that stimulate smooth muscle contraction, increased vascular permeability and mucus secretion (51). Moreover, the leukotrienes released by these cells can also recruit inflammatory cells from the circulation, which would be an indirect pathway affecting the inflammatory response. Eosinophils and mast cells are also the source of transforming growth factor (TGF)- β that may induce tissue fibrosis. Of note, the amount of TGF- β is increased in the esophagus of human and mouse models of experimental EoE; therefore, induced TGF- β is capable of modifying clinical symptoms in the esophagus of EoE patients.

Significance of eosinophil-specific receptors and chemokines in EoE pathogenesis

Eosinophil accumulation often occurs in the absence of infiltration by other inflammatory cells. As a result, there has been a considerable amount of research focused on identifying eosinophil specific chemoattractants (53). Eosinophils respond to a variety of chemoattractants including lipids, complement degradation products, and various chemokines including eotaxin, RANTES, and MCPs. Eotaxin was originally identified as the predominant eosinophil chemoattractant and a potent activator of eosinophils (54). The specificity of eotaxin for eosinophils is the result of the exclusive signaling of eotaxin through its receptor, CCR3, which is expressed predominantly on human and mouse eosinophils (53,55-58). Eosinophils express several chemokine receptors, but CCR3 is expressed at the highest level per cell (55,56,59). CCR3 appears to function as the predominant chemokine receptor since CCR3 ligands are generally the most potent eosinophil chemoattractants. Consistent with the expression of CCR3, eosinophils respond to MIP-1, **RANTES**, **MCP-2**, MCP-3, MCP-4, eotaxin-1, eotaxin-2, and eotaxin-3. Both eotaxin-2 and -3 have 30% homology to eotaxin-1 (48,60,61). Recently, we reported that eotaxin-3 is a signature gene for EoE, which is also a powerful eosinophil activating protein (48,61,62). Eotaxin-3 is induced in EoE patients of all ages regardless of gender and the allergic status of the patient and is completely distinct from the gene expression in patients with reflux esophagitis. Previously, it has been shown that eotaxin-3 is a chemoattractant for eosinophils and esophageal epithelium is a rich source of eotaxin-3 in EoE patients (48). This indicates that eotaxin-3 has a critical role in the accumulation of eosinophils in the esophageal mucosa of EoE patients. We recently showed that an eotaxin-3 gene single nucleotide polymorphism is associated with EoE (48). Furthermore, the significance of eotaxin-3 is supported by our previous work demonstrating that mice with genes targeted for the eotaxin receptor, CCR3 were protected from the development of experimental EoE (48).

Molecules involved in the pathogenesis of EoE

IL-5 is the most specific cytokine for eosinophil growth, differentiation, activation, and survival and primes eosinophils to respond to chemoattractants such as eotaxin, an eosinophil selective CC chemokine (63-65). IL-5 also facilitates eosinophil migration from bone marrow to the blood (69). Recent experiments have demonstrated that IL-5 is over-expressed in the esophagus of patients with EoE (66). Additionally, systemic over-expression of IL-5 (via pharmacological or transgenic approaches) promotes eosinophil trafficking to the esophagus in mice (67) and neutralizing anti-IL-5 (TRFK5) treatment in a murine model of EoE restricts eosinophil trafficking to the lung and esophagus (41). Determining the role of IL-5 in EoE is

of importance because two different studies have shown an improvement in the clinical and pathological symptoms of EoE after anti-IL-5 treatment (68). Animal studies have documented that dietary and environmental antigens such as enteric-coated ovalbumin or *Aspergillus* antigen induced esophageal eosinophilia (41,70) was ablated in mice deficient in IL-5 (41, 70). Conversely, transgenic mice overexpressing IL-5 had constitutively elevated number of esophageal eosinophils (71). Eosinophils also produce IL-5; therefore, it is important to understand whether local induction of IL-5 has a role in EoE pathogenesis. We recently showed that local expression of IL-5 is required for the induction of esophageal remodeling in human and experimental EoE.

IL-13 has also been implicated in a variety of allergic conditions including asthma (72), atopic dermatitis (35,73,74), and allergic rhinitis (75-77). The over-expression of IL-13 by pharmacological administration or transgenic approaches induces multiple features of asthma, including eosinophilia, mucus over-production, and airway hyperresponsiveness (78,79). Based on the importance of IL-13 in allergic diseases and the high concordance between asthma and EoE in humans, we delivered IL-13 to the lung by intratracheal administration (Figure 2). Our experimentation established that pulmonary inflammation, triggered by IL-13, is associated with the development of EoE. In humans IL-13 induced lung and esophageal eosinophilia was reduced by pretreatment with human neutralizing IL-13 (CAT-354) antibody (80). Use of experimental models in mice has established that Th2 signaling is required for induction of experimental EoE (41) and this will be further proven by our findings that STAT6 gene-deficient mice are protected from allergen- and IL-13-induced experimental EoE (81, 82). The emerging clinical and experimental data support a central role for IL-5 and IL-13 in EoE pathogenesis (71,81). Furthermore, a clinical report indicated that stimulation with food and environmental aeroallergens induced Th2 cytokine (IL-5 and IL-13) production by peripheral blood mononuclear cells in adult EoE patients (83). Collectively, these findings demonstrate that not only external allergic triggers but also intrinsic Th2 cytokines and eosinophil effector function are critical in EoE pathogenesis. The intimate connection between the lung and the esophagus was previously shown in experimental models of EoE; however, recent findings indicate that allergen-induced EoE is independent of the lung inflammation (84). Following intranasal allergen challenge, esophageal eosinophilic inflammation is induced in CD4 gene-deficient mice without inducing eosinophilic lung inflammation (84), although lung and esophageal inflammation is a T cell dependent process (84). This indicates a different mechanism is operational in the induction of esophageal and lung eosinophilic inflammation that requires further research to provide a better understanding of the mechanistic pathway of the induction of EoE and its relation to other allergic diseases.

Pathophysiological abnormalities develop in EoE

Recently, we and others showed that eosinophil recruitment to the esophagus induces esophageal remodeling, specifically in the lamina propria in the pediatric EoE population (10,11). An impressive collagen accumulation in the epithelial and subepithelial mucosa, increased vascularity, basal cell hyperplasia and vascular activation along with increased expression of TGF- β , VCAM-1, SMAD2/3, MUC5AC and IL-5 genes was observed in esophageal biopsies of EoE patients (10). The induced gene expression of TGF- β and its signaling molecule SMAD2/3 in the esophagus of human and experimental EoE indicates that the TGF- β pathway may play a critical role in the development of esophageal pathophysiological abnormalities including the formation of esophageal rings and strictures in EoE patients. By using mouse models of EoE, we demonstrated that local IL-5 expression-induced esophageal eosinophilia is critical in the development of esophageal remodeling (11). Fibroblast proliferation is observed in the esophageal biopsies of EoE patients, and previously it has been reported that eosinophil-fibroblast interactions generate subepithelial fibrosis in tissue in inflammatory states. Our recent observation that local expression of IL-5

is critical for esophageal remodeling is in accordance with a previous report showing that IL-5 induces fibroblast to myofibroblast transdifferentiation and the expression of α -smooth muscle actin and ?? extracellular matrix (85). Although a few recent reports indicate that esophageal remodeling and fibrosis occurs in EoE, the mechanism of the induction of esophageal fibrogenesis remains unclear. In order to define the changes in esophageal epithelial cells, fibroblast proliferation, differentiation, extracellular matrix accumulation and smooth muscle hyperplasia in EoE more experimental studies are needed.

Diagnosis and therapies for EoE

EoE is a newly recognized disease and is an emerging entity throughout developing and developed countries including the US (5,6,12-16,19,22,86,87). Therefore, understanding of the causes, natural history, diagnosis and management is important for future therapeutic interventions for EoE. The diagnosis of EoE is generally made by performing an esophageal biopsy, with evidence of eosinophils infiltrating the esophageal mucosa. Once EoE is diagnosed, an allergist will typically perform extensive allergy testing looking for evidence of food and environmental allergen sensitization. Currently, therapy for esophageal inflammation is based on antigen elimination trials, anti-inflammatory approaches, and physical dilatation when strictures are present. The latter approach, which has been the strategy reported for adults, temporarily reduces symptoms of dysphagia; however, it involves the significant risk of rupture and hemorrhage, needs to be repeated regularly, and does not reduce the underlying inflammation (88). An antigen elimination approach in sensitized individuals (e.g. aeroallergen avoidance and food elimination diets) is typically unsatisfactory or practically difficult (when patients are sensitized to many allergens), probably because the current allergen sensitization tests (skin prick and patch tests, as well as allergen-specific plasma IgE levels) are not optimal for detecting sensitization. A diet consisting exclusively of an elemental (amino acid based) formula frequently improves symptoms and normalizes esophageal pathology (89-91). However, this approach is often not tolerated (especially in older individuals), frequently requires a feeding tube, and can be expensive. Systemic steroids are used for acute exacerbations, while topical glucocorticoids are used to provide long-term control (92,93). Glucocorticoid treatment shows significant effect in reducing esophageal eosinophilia. Newer glucocorticoids with decreased systemic effect may improve the care of EoE patients. Although some treatments are effective in EoE, the molecular mechanisms involved in the remission have still not been established. Humanized antibody therapy designed to block IL-5 and IL-13 is currently in testing and has demonstrated great promise. Recent reports indicate that anti-IL-5 therapy has a significant effect on EoE in patients and CAT-354, an IL-13 blocking antibody has been shown to prevent lung and esophageal eosinophilia in mice (68,80). The anti-IL-5 therapeutic trials have been conducted in a small number of patients and more extensive studies are needed. The development of an experimental model of EoE is the most useful tool to dissect the molecular mechanisms involved in remission or resistance to therapy. The current knowledge suggests that targeting IL-5, IL-13 and eotaxin-3 may be promising therapeutic strategies for the treatment of EoE.

Conclusion

EoE is linked to allergic responses to food or aeroallergens, but cases have also been reported in which patients have EE without detectable food allergies by patch or prick skin testing. This indicates that EE could also be associated with immune dysregulation and these tests might not reflect hypersensitivity driven by discrete antigens. The pathogenesis of EE is still not clear, but a growing body of evidence has established that this condition represents a T cell mediated immune response involving a number of pro-inflammatory mediators and chemoattractants known to regulate eosinophilic accumulation in the esophagus, such as IL-4, IL-5, IL-13 and eotaxin-1, -2 and -3. Our recent findings indicate that the most highly expressed gene in EoE

patients is eotaxin-3, whereas, eotaxin-1 and -2 are modestly increased. In addition, esophageal eosinophilia correlates with eotaxin-3 mRNA and protein levels in esophageal biopsies of EoE patients. It has been recently reported that the esophageal epithelium from esophageal biopsies of EE patients expresses eotaxin-3 and exposure of esophageal epithelial cells to IL-13 induces eotaxin-3. These data indicate that IL-5, IL-13 and eotaxin-3 are the major mediators that regulate eosinophil numbers in the esophagus. Determining the mechanism(s) through which human esophageal cell-derived factors ultimately induce the functional abnormalities observed, and to which antigens EoE patients are sensitized that lead to the manifestation of symptoms is of significant interest. Esophageal dysmotility is a recognized complication of GERD, but has not yet been studied in EoE. Therefore, experimental models need to be designed to identify and evaluate the key factors in the inflammatory pathways of EoE that are directly responsible for altered smooth muscle contractility and eventually clinical symptoms. These studies will lead to a better understanding of the mechanisms of the development of EoE and likely provide further treatment options.

Acknowledgements

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References

1. Mishra A, Hogan SP, Lee JJ, Foster PS, Rothenberg ME. Fundamental signals that regulate eosinophil homing to the gastrointestinal tract. *J Clin Invest* 1999;103:1719–1727. [PubMed: 10377178]
2. DeBrosse CW, Case JW, Putnam PE, Collins MH, Rothenberg ME. Quantity and distribution of eosinophils in the gastrointestinal tract of children. *Pediatr Dev Pathol* 2006;9:210–218. [PubMed: 16944979]
3. White RJ, Zhang Y, Morris GP, Paterson WG. Esophagitis-related esophageal shortening in opossum is associated with longitudinal muscle hyperresponsiveness. *Am J Physiol Gastrointest Liver Physiol* 2001;280:G463–469. [PubMed: 11171629]
4. Paterson WG. Role of mast cell-derived mediators in acid-induced shortening of the esophagus. *Am J Physiol* 1998;274:G385–388. [PubMed: 9486193]
5. Cantu P, Velio P, Prada A, Penagini R. Ringed oesophagus and idiopathic eosinophilic oesophagitis in adults: an association in two cases. *Dig Liver Dis* 2005;37:129–134. [PubMed: 15733527]
6. Croese J, Fairley SK, Masson JW, Chong AK, Whitaker DA, Kanowski PA, Walker NI. Clinical and endoscopic features of eosinophilic esophagitis in adults. *Gastrointest Endosc* 2003;58:516–522. [PubMed: 14520283]
7. Mann NS, Leung JW. Pathogenesis of esophageal rings in eosinophilic esophagitis. *Med Hypotheses* 2005;64:520–523. [PubMed: 15617859]
8. Zimmerman SL, Levine MS, Rubesin SE, Mitre MC, Furth EE, Laufer I, Katzka DA. Idiopathic eosinophilic esophagitis in adults: the ringed esophagus. *Radiology* 2005;236:159–165. [PubMed: 15983073]
9. Ruigomez A, Alberto Garcia Rodriguez L, Wallander MA, Johansson S, Eklund S. Esophageal stricture: incidence, treatment patterns, and recurrence rate. *Am J Gastroenterol* 2006;101:2685–2692. [PubMed: 17227515]
10. Aceves SS, Newbury RO, Dohil R, Bastian JF, Broide DH. Esophageal remodeling in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2007;119:206–212. [PubMed: 17208603]
11. Mishra A, Wang M, Pemmaraju VR, Collins MH, Fulkerson PC, Abonia JP, Blanchard C, Putnam PE, Rothenberg ME. Esophageal Remodeling Develops as a Consequence of Tissue Specific IL-5-Induced Eosinophilia. *Gastroenterology* 2008;134:204–214. [PubMed: 18166354]
12. Cury EK, Schraibman V, Faintuch S. Eosinophilic infiltration of the esophagus: gastroesophageal reflux versus eosinophilic esophagitis in children--discussion on daily practice. *J Pediatr Surg* 2004;39:e4–7. [PubMed: 14966764]
13. Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci* 1993;38:109–116. [PubMed: 8420741]

14. Fujiwara H, Morita A, Kobayashi H, Hamano K, Fujiwara Y, Hirai K, Yano M, Naka T, Saeki Y. Infiltrating eosinophils and eotaxin: their association with idiopathic eosinophilic esophagitis. *Ann Allergy Asthma Immunol* 2002;89:429–432. [PubMed: 12392390]
15. Munitiz V, Martinez de Haro LF, Ortiz A, Pons JA, Bermejo J, Serrano A, Molina J, Parrilla P. Primary eosinophilic esophagitis. *Dis Esophagus* 2003;16:165–168. [PubMed: 12823222]
16. Lucendo AJ, Carrion G, Navarro M, Pascual JM, Gonzalez P, Castillo P, Erdozain JC. Eosinophilic esophagitis in adults: an emerging disease. *Dig Dis Sci* 2004;49:1884–1888. [PubMed: 15628721]
17. Straumann A, Spichtin HP, Bucher KA, Heer P, Simon HU. Eosinophilic esophagitis: red on microscopy, white on endoscopy. *Digestion* 2004;70:109–116. [PubMed: 15383737]
18. Straumann A. What is your diagnosis? Primary eosinophilic esophagitis. *Schweiz Rundsch Med Prax* 2004;93:795–796.
19. Orenstein SR, Shalaby TM, Di Lorenzo C, Putnam PE, Sigurdsson L, Kocoshis SA. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. *Am J Gastroenterol* 2000;95:1422–1430. [PubMed: 10894574]
20. Furuta GT. Eosinophils in the esophagus: acid is not the only cause. *J Pediatr Gastroenterol Nutr* 1998;26:468–471. [PubMed: 9552148]
21. Fox VL, Nurko S, Furuta GT. Eosinophilic esophagitis: It's not just kid's stuff. *Gastrointest Endosc* 2002;56:260–270. [PubMed: 12145607]
22. Rothenberg ME, Mishra A, Collins MH, Putnam PE. Pathogenesis and clinical features of eosinophilic esophagitis. *J Allergy Clin Immunol* 2001;108:891–894. [PubMed: 11742263]
23. Dahms BB. Reflux esophagitis: sequelae and differential diagnosis in infants and children including eosinophilic esophagitis. *Pediatr Dev Pathol* 2004;7:5–16. [PubMed: 15255030]
24. Walsh SV, Antonioli DA, Goldman H, Fox VL, Bousvaros A, Leichtner AM, Furuta GT. Allergic esophagitis in children: a clinicopathological entity. *Am J Surg Pathol* 1999;23:390–396. [PubMed: 10199468]
25. Liacouras CA, Ruchelli E. Eosinophilic esophagitis. *Curr Opin Pediatr* 2004;16:560–566. [PubMed: 15367851]
26. Sant'Anna AM, Rolland S, Fournet JC, Yazbeck S, Drouin E. Eosinophilic Esophagitis in Children: Symptoms, Histology and pH Probe Results. *J Pediatr Gastroenterol Nutr* 2004;39:373–377. [PubMed: 15448427]
27. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004;351:940–941. [PubMed: 15329438]
28. Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology* 2003;125:1660–1669. [PubMed: 14724818]
29. Vasilopoulos S, Murphy P, Auerbach A, Massey BT, Shaker R, Stewart E, Komorowski RA, Hogan WJ. The small-caliber esophagus: an unappreciated cause of dysphagia for solids in patients with eosinophilic esophagitis. *Gastrointest Endosc* 2002;55:99–106. [PubMed: 11756928]
30. Potter JW, Saeian K, Staff D, Massey BT, Komorowski RA, Shaker R, Hogan WJ. Eosinophilic esophagitis in adults: an emerging problem with unique esophageal features. *Gastrointest Endosc* 2004;59:355–361. [PubMed: 14997131]
31. Ruchelli E, Wenner W, Voytek T, Brown K, Liacouras C. Severity of esophageal eosinophilia predicts response to conventional gastroesophageal reflux therapy. *Pediatr Dev Pathol* 1999;2:15–18. [PubMed: 9841701]
32. Rothenberg ME. Eosinophilia. *N Engl J Med* 1998;338:1592–1600. [PubMed: 9603798]
33. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;133:1342–1363. [PubMed: 17919504]
34. Tottrup A, Fredens K, Funch-Jensen P, Aggestrup S, Dahl R. Eosinophil infiltration in primary esophageal achalasia. A possible pathogenic role. *Dig Dis Sci* 1989;34:1894–1899. [PubMed: 2689111]

35. Justinich CJ, Ricci A Jr, Kalafus DA, Treem WR, Hyams JS, Kreutzer DL. Activated eosinophils in esophagitis in children: a transmission electron microscopic study. *J Pediatr Gastroenterol Nutr* 1997;25:194–198. [PubMed: 9252907]
36. Liacouras CA, Wenner WJ, Brown K, Ruchelli E. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;26:380–385. [PubMed: 9552132]
37. Vasilopoulos S, Shaker R. Defiant dysphagia: small-caliber esophagus and refractory benign esophageal strictures. *Curr Gastroenterol Rep* 2001;3:225–230. [PubMed: 11353559]
38. Spergel JM. Eosinophilic esophagitis in adults and children: evidence for a food allergy component in many patients. *Curr Opin Allergy Clin Immunol* 2007;7:274–278. [PubMed: 17489048]
39. Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol* 2005;95:336–343. [PubMed: 16279563]
40. Rothenberg SJ, Kondrashov V, Manalo M, Manton WI, Khan F, Todd AC, Johnson C. Seasonal variation in bone lead contribution to blood lead during pregnancy. *Environ Res* 2001;85:191–194. [PubMed: 11237506]
41. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001;107:83–90. [PubMed: 11134183]
42. Gleich GJ, Adolphson CR. The eosinophilic leukocyte: structure and function. *Adv Immunol* 1986;39:177–253. [PubMed: 3538819]
43. Gleich GJ, Frigas E, Loegering DA, Wassom DL, Steinmuller D. Cytotoxic properties of the eosinophil major basic protein. *J Immunol* 1979;123:2925–2927. [PubMed: 501097]
44. Slifman NR, Loegering DA, McKean DJ, Gleich GJ. Ribonuclease activity associated with human eosinophil-derived neurotoxin and eosinophil cationic protein. *Journal of Immunology* 1986;137:2913–2917.
45. Jacoby DB, Gleich GJ, Fryer AD. Human eosinophil major basic protein is an endogenous allosteric antagonist at the inhibitory muscarinic M2 receptor. *Journal of Clinical Investigation* 1993;91:1314–1318. [PubMed: 8473484]
46. 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;157:1981–1991. [PubMed: 6854212]
47. Kirsch R, Bokhary R, Marcon MA, Cutz E. Activated mucosal mast cells differentiate eosinophilic (allergic) esophagitis from gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 2007;44:20–26. [PubMed: 17204948]
48. Blanchard C, Wang N, Stringer KF, Mishra A, Fulkerson PC, Abonia JP, Jameson SC, Kirby C, Konikoff MR, Collins MH, Cohen MB, Akers R, Hogan SP, Assa'ad AH, Putnam PE, Aronow BJ, Rothenberg ME. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* 2006;116:536–547. [PubMed: 16453027]
49. Tung HN, Schulze-Delrieu K, Shirazi S. Infiltration of hypertrophic esophageal smooth muscle by mast cells and basophils. *J Submicrosc Cytol Pathol* 1993;25:93–102. [PubMed: 8462073]
50. Sommerhoff CP. Mast cell tryptases and airway remodeling. *Am J Respir Crit Care Med* 2001;164:S52–58. [PubMed: 11734467]
51. Lewis RA, Austen KF, Soberman RJ. Leukotrienes and other products of the 5-lipoxygenase pathway. Biochemistry and relation to pathobiology in human diseases. *New England Journal of Medicine* 1990;323:645–655. [PubMed: 2166915]
52. Straumann A, Kristl J, Conus S, Vassina E, Spichtin HP, Beglinger C, Simon HU. Cytokine expression in healthy and inflamed mucosa: probing the role of eosinophils in the digestive tract. *Inflamm Bowel Dis* 2005;11:720–726. [PubMed: 16043986]
53. Gao JL, Sen AI, Kitauro M, Yoshie O, Rothenberg ME, Murphy PM, Luster AD. Identification of a mouse eosinophil receptor for the CC chemokine eotaxin. *Biochemical & Biophysical Research Communications* 1996;223:679–684. [PubMed: 8687456]
54. Elsner J, Hochstetter R, Kimmig D, Kapp A. Human eotaxin represents a potent activator of the respiratory burst of human eosinophils. *European Journal of Immunology* 1996;26:1919–1925. [PubMed: 8765040]

55. Ponath PD, Qin S, Post TW, Wang J, Wu L, Gerard NP, Newman W, Gerard C, Mackay CR. Molecular cloning and characterization of a human eotaxin receptor expressed selectively on eosinophils. *Journal of Experimental Medicine* 1996;183:2437–2448. [PubMed: 8676064]
56. Daugherty BL, Siciliano SJ, DeMartino JA, Malkowitz L, Sirotina A, Springer MS. Cloning, expression, and characterization of the human eosinophil eotaxin receptor. *Journal of Experimental Medicine* 1996;183:2349–2354. [PubMed: 8642344]
57. Post TW, Bozic CR, Rothenberg ME, Luster AD, Gerard N, Gerard C. Molecular characterization of two murine eosinophil beta chemokine receptors. *Journal of Immunology* 1995;155:5299–5305.
58. Alkhatib G, Combadiere C, Broder CC, Feng Y, Kennedy PE, Murphy PM, Berger EA. CC CKR5 - a RANTES, MIP-1-alpha, MIP-1-beta receptor as a fusion cofactor for macrophage-tropic HIV-1. *Science* 1996;272:1955–1958. [PubMed: 8658171]
59. Combadiere C, Ahuja SK, Murphy PM. Cloning and functional expression of a human eosinophil CC chemokine receptor. *Journal of Biological Chemistry* 1995;270:16491–16494. [PubMed: 7622448]
60. Forssmann U, Uguccioni M, Loetscher P, Dahinden CA, Langen H, Thelen M, Baggiolini M. Eotaxin-2, a novel CC chemokine that is selective for the chemokine receptor CCR3, and acts like eotaxin on human eosinophil and basophil leukocytes. *J Exp Med* 1997;185:2171–2176. [PubMed: 9182688]
61. Kitaura M, Suzuki N, Imai T, Takagi S, Suzuki R, Nakajima T, Hirai K, Nomiyama H, Yoshie O. Molecular cloning of a novel human CC chemokine (Eotaxin-3) that is a functional ligand of CC chemokine receptor 3. *J Biol Chem* 1999;274:27975–27980. [PubMed: 10488147]
62. Blanchard C, Mingler MK, Vicario M, Abonia JP, Wu YY, Lu TX, Collins MH, Putnam PE, Wells SI, Rothenberg ME. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol* 2007;120:1292–1300. [PubMed: 18073124]
63. Sanderson CJ. Interleukin-5, eosinophils, and disease. *Blood* 1992;79:3101–3109. [PubMed: 1596561]
64. Collins PD, Marleau S, Griffiths-Johnson DA, Jose PJ, Williams TJ. Cooperation between interleukin-5 and the chemokine eotaxin to induce eosinophil accumulation in vivo. *Journal of Experimental Medicine* 1995;182:1169–1174. [PubMed: 7561691]
65. Rothenberg SJ, Manalo M, Jiang J, Cuellar R, Reyes S, Sanchez M, Diaz M, Khan F, Aguilar A, Reynoso B, Juaregui M, Acosta S, Johnson C. Blood lead level and blood pressure during pregnancy in South Central Los Angeles. *Arch Environ Health* 1999;54:382–389. [PubMed: 10634227]
66. Straumann A, Bauer M, Fischer B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001;108:954–961. [PubMed: 11742273]
67. Mishra A, Hogan SP, Brandt EB, Wagner N, Crossman MW, Foster PS, Rothenberg ME. Enterocyte expression of the eotaxin and interleukin-5 transgenes induces compartmentalized dysregulation of eosinophil trafficking. *J Biol Chem* 2002;277:4406–4412. [PubMed: 11733500]
68. Stein ML, Collins MH, Villanueva JM, Kushner JP, Putnam PE, Buckmeier BK, Filipovich AH, Assa'ad AH, Rothenberg ME. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol* 2006;118:1312–1319. [PubMed: 17157662]
69. Paul CC, Tolbert M, Mahrer S, Singh A, Grace MJ, Baumann MA. Cooperative effects of interleukin-3 (IL-3), IL-5, and granulocyte- macrophage colony-stimulating factor: a new myeloid cell line inducible to eosinophils. *Blood* 1993;81:1193–1199. [PubMed: 8443379]
70. Hogan SP, Mishra A, Brandt EB, Royalty MP, Pope SM, Zimmermann N, Foster PS, Rothenberg ME. A pathological function for eotaxin and eosinophils in eosinophilic gastrointestinal inflammation. *Nat Immunol* 2001;2:353–360. [PubMed: 11276207]
71. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. IL-5 promotes eosinophil trafficking to the esophagus. *J Immunol* 2002;168:2464–2469. [PubMed: 11859139]
72. Barata LT, Ying S, Grant JA, Humbert M, Barkans J, Meng Q, Durham SR, Kay AB. Allergen-induced recruitment of Fc epsilon RI+ eosinophils in human atopic skin. *Eur J Immunol* 1997;27:1236–1241. [PubMed: 9174616]

73. Akdis M, Akdis CA, Weigl L, Disch R, Blaser K. Skin-homing, CLA+ memory T cells are activated in atopic dermatitis and regulate IgE by an IL-13-dominated cytokine pattern: IgG4 counter-regulation by CLA- memory T cells. *J Immunol* 1997;159:4611–4619. [PubMed: 9379063]
74. Katagiri K, Itami S, Hatano Y, Yamaguchi T, Takayasu S. In vivo expression of IL-4, IL-5, IL-13 and IFN-gamma mRNAs in peripheral blood mononuclear cells and effect of cyclosporin A in a patient with Kimura's disease. *Br J Dermatol* 1997;137:972–977. [PubMed: 9470918]
75. Pawankar RU, Okuda M, Hasegawa S, Suzuki K, Yssel H, Okubo K, Okumura K, Ra C. Interleukin-13 expression in the nasal mucosa of perennial allergic rhinitis. *Am J Respir Crit Care Med* 1995;152:2059–2067. [PubMed: 8520776]
76. Pawankar R, Okuda M, Yssel H, Okumura K, Ra C. Nasal mast cells in perennial allergic rhinitis exhibit increased expression of the Fc epsilonRI, CD40L, IL-4, and IL-13, and can induce IgE synthesis in B cells. *J Clin Invest* 1997;99:1492–1499. [PubMed: 9119992]
77. al Ghamdi K, Ghaffar O, Small P, Frenkiel S, Hamid Q. IL-4 and IL-13 expression in chronic sinusitis: relationship with cellular infiltrate and effect of topical corticosteroid treatment. *J Otolaryngol* 1997;26:160–166. [PubMed: 9176799]
78. Elias JA, Zhu Z, Chupp G, Homer RJ. Airway remodeling in asthma. *J Clin Invest* 1999;104:1001–1006. [PubMed: 10525034]
79. Kim CH, Qu CK, Hangoc G, Cooper S, Anzai N, Feng GS, Broxmeyer HE. Abnormal Chemokine-induced Responses of Immature and Mature Hematopoietic Cells from Mice Implicate the Protein Tyrosine Phosphatase SHP-1 in Chemokine Responses. *J Exp Med* 1999;190:681–690. [PubMed: 10477552]
80. Blanchard C, Mishra A, Saito-Akei H, Monk P, Anderson I, Rothenberg ME. Inhibition of human interleukin-13-induced respiratory and oesophageal inflammation by anti-human-interleukin-13 antibody (CAT-354). *Clin Exp Allergy* 2005;35:1096–1103. [PubMed: 16120093]
81. Mishra A, Rothenberg ME. Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1, and STAT6-dependent mechanism. *Gastroenterology* 2003;125:1419–1427. [PubMed: 14598258]
82. Akei HS, Mishra A, Blanchard C, Rothenberg ME. Epicutaneous antigen exposure primes for experimental eosinophilic esophagitis in mice. *Gastroenterology* 2005;129:985–994. [PubMed: 16143136]
83. Yamazaki K, Murray JA, Arora AS, Alexander JA, Smyrk TC, Butterfield JH, Kita H. Allergen-specific in vitro cytokine production in adult patients with eosinophilic esophagitis. *Dig Dis Sci* 2006;51:1934–1941. [PubMed: 17009121]
84. Mishra A, Schlotman J, Wang M, Rothenberg ME. Critical role for adaptive T cell immunity in experimental eosinophilic esophagitis in mice. *J Leukoc Biol* 2007;81:916–924. [PubMed: 17194734]
85. Phipps S, Ying S, Kay AB. The relationship of infiltrating eosinophils to markers of repair and resolution (myofibroblasts, TGF- and tenascin) in allergen-induced late phase reactions in human skin. *J Allergy Clin Immunol* 2002;109:S169.
86. Straumann A. Eosinophilic esophagitis: a novel entity? *Schweiz Rundsch Med Prax* 2006;95:191–195.
87. Furuta GT. Clinicopathologic features of esophagitis in children. *Gastrointest Endosc Clin N Am* 2001;11:683–715. vii. [PubMed: 11689362]
88. Nostrant TT. Esophageal Dilation / Dilators. *Curr Treat Options Gastroenterol* 2005;8:85–95. [PubMed: 15625037]
89. Liacouras CA, Spergel JM, Ruchelli E, Verma R, Mascarenhas M, Semeao E, Flick J, Kelly J, Brown-Whitehorn T, Mamula P, Markowitz JE. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005;3:1198–1206. [PubMed: 16361045]
90. Markowitz JE, Liacouras CA. Eosinophilic esophagitis. *Gastroenterol Clin North Am* 2003;32:949–966. [PubMed: 14562583]
91. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 1995;109:1503–1512. [PubMed: 7557132]

92. Faubion WA Jr, Perrault J, Burgart LJ, Zein NN, Clawson M, Freese DK. Treatment of eosinophilic esophagitis with inhaled corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;27:90–93. [PubMed: 9669733]
93. Arora AS, Perrault J, Smyrk TC. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. *Mayo Clin Proc* 2003;78:830–835. [PubMed: 12839078]

Figure 1. Diagrammatic representation of allergen induced accumulation of inflammatory cells in the lung and esophagus

Food or aeroallergen exposure promotes eosinophilia and mastocytosis in the allergic lung and esophagus. Interestingly, induced eosinophilia or mastocytosis is not observed in the stomach or small intestine. Allergen-induced Th2 cytokine (IL-5 and IL-13) induction is implicated in the induction of tissue eosinophilia.

Figure 2. Paradigm of allergen-induced esophageal accumulation of eosinophils, mast cells and tissue remodeling in EE

Antigen presenting cells (APCs) process the allergen and present antigen to the T cells. These T cells home to the esophagus via blood circulation and upon activation release eosinophil specific cytokines (IL-5 and IL-13), which induce chemokines (eotaxin-3) in the esophageal epithelium that attract eosinophils into the esophagus. Additionally, in response to allergens, B cells and mast cells numbers also increase in the esophagus. B cells synthesize IgE locally or systemically that may activate mast cells, as IgE is detected on the surface of mast cells in EE patients. The activated eosinophil and mast cells are a rich source of TGF- β that may play a critical role in the disease pathogenesis, including esophageal remodeling.