

Pro/Con Review

Eosinophilic Esophagitis: A Primary Disease of the Esophageal Mucosa

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Eosinophilic esophagitis (EoE) is an inflammatory chronic antigen-driven disorder affecting both children and adults and is defined by a significant T helper lymphocyte type 2 (Th2) inflammation limited to the esophagus, with associated esophageal dysfunction, and for some, a risk of irreversible fibrosis if their disease is untreated.^{1,2} EoE is diagnosed if an esophageal biopsy shows an eosinophilic infiltration greater than 15 eosinophils per high power field (eos/hpf) noted after other causes of esophageal eosinophilia have been ruled out.² Like many other atopic diseases, EoE has been more often diagnosed in western countries, with a yearly incidence now similar to that of inflammatory bowel diseases such as Crohn's disease.³⁻⁸

Since the first report of a series of cases by Kelly et al,⁹ there have been tremendous progresses in understanding the pathophysiological mechanisms underlying EoE progression.¹⁰ This progress has led to establishing globally accepted therapies for EoE, such as diet restriction and/or topical swallowed steroid therapies, which essentially control esophageal histopathology. As we treat more patients and we learn more about the disease, many questions have begun to arise. Among these questions: is EoE a local or systemic disease? We will review the current evidence that favors either of these hypotheses. Indeed, understanding if EoE is a local or systemic disease may lead to more effective treatments and management strategies, and eventually a cure.

PRO: EoE IS A LOCALIZED DISEASE PROCESS

Several lines of evidence point to the fact that indeed EoE is a localized process limited to the esophagus: (1) EoE by definition is a disease limited to the esophagus; (2) the diagnosis and the follow-up are done only by studying the tissue biopsies; (3) topical treatments such as steroids are highly effective; (4) genes implicated in EoE pathogenesis are expressed in the epithelial cells of the esophagus, and a dysfunctional epithelium is currently speculated to be key in local Th2-driven inflammation.

EoE is by definition a disease characterized by an inflammation limited to the esophagus, and there are abundant scientific and clinical basis underlying this definition. Indeed, when looking several cell types across the gastrointestinal tract in patients with EoE, there is a well-established increase in eosinophils, natural killer T (NKT) cells, Th2 cells, mast cells, and basophils within the esophagus alone, which is not noted for either the stomach or the duodenum.¹¹

In the last decade, there has been extensive molecular characterization of the genes expressed in the local esophageal tissues. These data have shown that the expression of genes in EoE provides a unique molecular signature examining 92 genes, which differentiates EoE from other diseases that can cause eosinophilic infiltration of the esophagus such as gastroesophageal reflux disease (GERD) and to a lesser extent proton-pump inhibitor responsive esophageal eosinophilia (PPI-REE).^{12,13} EoE was readily differentiated from both normal controls without evidence of esophageal disease and patients with GERD when utilizing an upper limit maximum of 14 eos/hpf for GERD. In this case, the limited amount of esophageal pathology and eosinophilia driven by GERD is unable to mimic the EoE transcriptome. On the other hand, only a single gene within the transcriptome (potassium voltage-gated channel subfamily j member 2, *KCNJ2*) differentiates between EoE and PPI-REE.

Although there are numerous cellular and molecular markers that can differentiate active EoE from inactive EoE, as well as from other eosinophilic gastrointestinal disorders, when esophageal biopsies are used, no markers are currently reliable for use on blood or other patient samples. Only poor to fair correlation with EoE disease activity is noted for peripheral blood eosinophilia, peripheral blood eosinophil progenitors, eosinophil-derived neurotoxin, and eotaxin-3 in the blood.¹⁴⁻¹⁶ Similarly, Caldwell et al¹³ showed, in contrast to EoE, that eosinophilic gastritis is a systemic disorder involving profound blood and gastrointestinal tract eosinophilia, Th2 immunity, and a conserved gastric transcriptome markedly distinct from the EoE transcriptome.

Current treatments also focus on the importance of a localized disease. Indeed, topical swallowed steroids are the mainstream therapy of EoE with high rate of therapeutic success ranging between 70% and 80% based on the most recent studies.^{17,18}

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Abbreviations used

CAPN14- Calpain 14

CTD- Connective tissue disorder

DSG1- Desmoglein-1

EDS- Ehlers-Danlos syndrome

EGID- Eosinophilic gastrointestinal disease

EoE- Eosinophilic esophagitis

FLG- Filaggrin

GERD- Gastroesophageal reflux disease

GWAS- Genome-wide array studies

hpf- High power field

LDS- Loews-Dietz syndrome

MFS- Marfan syndrome

NKT- Natural killer T cells

NS- Netherton syndrome

PHTS- Phosphatase and tensin homolog hamartoma tumor syndrome

PPI-REE- Proton-pump inhibitor responsive esophageal eosinophilia

SPINK5- Serine protease inhibitor Kazal type 5

Th2- T helper lymphocyte type 2

TSLP- Thymic stromal lymphopoietin

Swallowed inhaled corticosteroids are considered as first-line therapies for initial and maintenance management of EoE as they have low bioavailability due to first pass metabolism and less systemic side effects compared with oral steroids absorption.^{19,20} Swallowed viscous budesonide has been shown to have significant contact with the esophageal epithelium suggesting that those steroids act indeed topically and not indirectly due to their systemic absorption.²¹

Similarly, food allergens have been shown to be the most common trigger in both adults and children with EoE, without causing any other systemic symptoms.²²⁻²⁶ There has been a globally demonstrated success of the treatment of EoE with food avoidance, with rates close to 100% with elemental diets (amino acid formulas) and up to 80% for elimination diet,^{23,25-28} and despite this antigen-driven effect, the mechanism underlying this response remains under intense investigation. It has been widely speculated that foods cause a T-cell-mediated reaction in genetically predisposed individuals due to a dysfunctional epithelium that promotes a Th2 effector local reaction to foods.²⁹ In support of this notion, it has been reported that filaggrin (*FLG*) loss of function mutation 2282del4, which is known to determine an increase of epithelial permeability, is significantly overrepresented in EoE compared with control individuals (6.1% vs 1.3%, respectively).³⁰ Single genes and genome-wide array studies (GWAS) have identified the thymic stromal lymphopoietin (*TSLP*) gene, at 5q22, the calpain 14 (*CAPN14*) on chr2p23.1, and the *c11orf30/EMSY* gene on chr11q13.5 3 as candidate genes in the pathogenesis of EoE. Interestingly, like *FLG* and eotaxin 3, *TSLP* and *CAPN14* are epithelial genes and *CAPN14* is specifically expressed by esophageal cells.²⁹ Eotaxin 3 and *TSLP* are mediators known to promote local eosinophilic and Th2 inflammation. On the other hand, *FLG* and most likely *CAPN14* dysregulation favor increased permeabilization of the esophageal epithelium. Indeed, inhibition of *FLG*, which is downregulated by Th2 cytokines, is known to favor peanut sensitization in children with atopic dermatitis, most likely by favoring the access of the antigen to an immune system predisposed to produce a Th2 instead of

tolerogenic response to foods. *CAPN14* is a protease that appears to be highly and selectively expressed in the esophagus,^{31,32} and upregulated by Th2 cytokines (ie, IL-13³³ and IL-4³⁴). Although the specific biological function of *CAPN14* is currently unknown, it is easy to speculate that an increase in expression of *CAPN14*, like the one of other members of the proteases belonging to the calpain family, may favor increased epithelial permeability by damaging tight junction proteins.^{33,35,36} All together, these data point to the fact that food allergens in genetically predisposed individuals may be able to penetrate damaged epithelium expressing less *FLG* and more *CAPN14* for example, and in the presence of high level of *TSLP* and eotaxin 3 promote a strong local eosinophilic Th2 inflammation.

CON: EoE IS A SYSTEMIC DISEASE

Evidence that EoE is a systemic disease comes from 3 particular findings: (1) EoE has a strong genetic component affecting not just localized tissue; (2) there is evidence of peripheral eosinophilia in EoE and the systemic administration of anti-IL-5 reduces both the esophageal and the peripheral eosinophilia; and (3) the direct gastric administration of known problematic foods can elicit an active EoE state.

An alternative viewpoint of the GWAS studies that show *TSLP* and *EMSY*^{33,36-38} as risk factors for EoE is that these genes represent systemic alterations. Both of these genes are not isolated to the esophagus, but are expressed throughout the body. In murine models of EoE, *TSLP* knockout prevents the expression of EoE feature. In humans, *TSLP* is located on chromosome 5q22.1 next to the atopic cytokine (IL-4, IL-5, IL-13, IL-3) cluster of chromosome 5q31, and is a potent promoter of Th2 inflammation by priming dendritic cells to support the development of antigen Th2 differentiated cells, by inducing Th2 cytokine production (IL4, IL13) by T cells, basophils, mast cells, NKT cells, and eosinophils while hindering the production and/or maintenance of FOXP3+ Tregs.³⁹⁻⁴² These changes are systemic in nature and not localized to the esophagus. Given the likely systemic effect of *TSLP* gene variations, it is not surprising that patients with EoE are highly atopic and nearly 80% have either asthma, allergic rhinitis, or IgE-mediated food allergy.^{2,43-45} Relative to the general population, the incidence of these atopic disorders is significantly increased suggesting that EoE is not an expression of a disease limited to the esophagus alone, but rather a local manifestation of a systemic immune dysregulation involving several organs.

Similarly, beyond these common atopic disorders, there is also the presence of other disparate clinical disorders often associated with epithelial dysfunction that confer an increased risk of EoE. This includes connective tissue disorders (CTDs) with extra-esophageal findings such as Marfan syndrome (MFS), Loews-Dietz syndrome (LDS), and the Ehlers-Danlos syndrome (EDS), or epithelial disorders such as Netherton syndrome (NS) and *FLG* mutation. The presence of CTDs increases the risk of EoE by approximately 8-fold, and we estimate that 5% to 15% of EoE population has an underlying connective tissue disorder as represented by MFS, LDS, and EDS.^{46,47} These CTDs have been demonstrated to have defects impacting the TGF β pathway with fibrillin-1 mutations in MFS being associated with poor sequestration of TGF β ,⁴⁸ TGF β 1 and β 2 receptor defects in LDS being associated with an activating mutation of within the pathway along with a high incidence of food allergy and

TABLE I. Disorders related to EoE

Clinical disorder	Gene(s)	Risk or incidence of related to gene	References
Connective tissue disorders			
Marfans	<i>FBN1</i>	8-fold combined for these disorders	46,47
Loeys-Dietz syndrome	<i>TGFBR1</i>	<i>TGFBR</i> receptors are associated with EoE 60% (6/10)	
Ehlers-Danlos syndrome	<i>TGFBR2</i>		
NS	<i>SPINK5</i>	44% (4/9)	57,58
Eczematous dermatitis	<i>DSG1</i>	<i>DSG1</i> 33% (1/3)	61-63
	<i>FLG</i>	<i>FLG</i> with increased risk of EoE	
Cystic fibrosis	<i>CFTR</i>	EoE has been identified in 3 patients with CF	69
Phosphatase and tensin homolog hamartoma tumor syndrome	<i>PTEN</i>	75% (6/8) with 275-fold increased risk of EoE	64

Abbreviations used: *DSG1*, Desmoglein-1; *EoE*, eosinophilic esophagitis; *FBN1*, TGF β pathway with fibrillin-1; *FLG*, filaggrin; *NS*, Netherton syndrome; *PTEN*, phosphatase and tensin homolog; *SPINK5*, serine protease inhibitor Kazal type 5; *TGFBR*, TGF β receptor.

eosinophilic gastrointestinal disease (EGID),^{47,49} and collagen III A1 being associated with increased plasma TGF- β , and excess circulating levels of vascular cell adhesion protein 1.⁵⁰ Within EoE itself, excess TGF- β 1 has also been identified, with immunohistochemical localization noted to eosinophils and mast cells within esophageal lamina propria and esophageal smooth muscle cells, respectively.^{19,51-53} This excess TGF- β 1 could lead to esophageal fibrosis and smooth muscle contraction that could potentially be related to the mechanical esophageal dysfunction present in EoE.^{19,54-56}

NS represents a systemic disorder with erythematous and scaly skin with notable epidermal eosinophilia, gross elevations in IgE, and known defects in serine protease inhibitor Kazal type 5 (*SPINK5*).⁵⁷⁻⁵⁹ This is of particular interest for EoE, as *SPINK5* can reduce desmoglein-1 (*DSG1*) expression as seen in EoE.⁶⁰ An early report identified EoE in a single patient with NS of a case series, whereas several other of these patients with NS had sensitization to a variety of foods, dietary eliminations, and gastrointestinal complaints.⁵⁷ Although a single case report would not be definitive, NS may also represent a disorder with an apparent increased risk of EoE, as another recent provisional study identified 4 of 9 patients with NS with concomitant EoE.⁵⁸ *DSG1* deficiency has also been separately associated with a severe disease process of severe dermatitis, allergies, and metabolic wasting (severe dermatitis, multiple allergies, and metabolic wasting [SAM] syndrome) in which 1 of 3 patients was also noted to carry a diagnosis of EoE.⁶¹ Similarly, defects in *FLG* have been associated with severe eczema, and *FLG* loss-of-function mutations have been identified as a risk variant for EoE, albeit without a clear alteration in *FLG* expression noted between patients with atopic and nonatopic EoE.^{62,63}

Finally, other rare systemic genetic diseases have been reported to be associated with EoE and may provide insight into the EoE pathogenesis as well as potentiality of being a systemic disease. Patients with phosphatase and tensin homolog hamartoma tumor syndrome (PHTS) are noted to have an increased risk of EGID in a small case series, with a 272-fold increased risk of EGID being noted in the PHTS patient population.⁶⁴ Of those patients with comorbid PHTS and EGID, 75% (6/8) were noted to have esophageal eosinophilia often with concomitant eosinophilic gastritis, as well as a history of food allergies.

Although each of these systemic disorders is associated with increased risk of EoE, they represent only a relatively small subset of patients with EoE (see summary, Table I). Regardless, along

with the increased risk of an atopic disorder and IgE-mediated food allergy in EoE, the presence of these systemic disorders supports a notion of not only esophageal disease but also a clinically relevant process extending beyond the esophagus that needs to be addressed for patients with unique forms of EoE.

In support of this, patients with EoE have been noted to have increased peripheral blood eosinophilia, excess peripheral blood eosinophil progenitors as well as increased serum levels of eosinophil derived neurotoxinin.¹⁴⁻¹⁶ Such systemic eosinophilia and the esophageal one completely resolve both in pediatric and adult patients on systemic administration of antieosinophilic antibody like anti-IL-5.^{53,65} These data suggest that patients with EoE may have a systemic activation and increased levels of eosinophils despite having only local end organ manifestation.

Additional evidence that EoE may indeed be a systemic disease comes from insight into food allergy pathogenesis in an animal model of EoE. When the vitamin D analog, MC903, is administered far away from the esophagus (the mouse's ear), along with ovalbumin skin sensitization, there is esophageal eosinophilia that is dependent on *TSLP* and basophils.⁶⁶ Beyond vitamin D, cow's milk could potentially provide other bioactive substances such as TGF β that survive and are increased by the pasteurization process.^{67,68} Indeed, cow's milk-derived TGF β 1 remains bioactive in human cell lines⁶⁸ and shares 95% identity with human-derived TGF β 1. Regardless, as a source of a variety of bioactive substances, cow's milk could provide a unique milieu that potentially primes the esophagus to support pathologic EoE via vitamin D in a manner like that seen in animal models.⁶⁶ Finally, exposure to the antigen that bypasses the esophagus can also lead to disease. We have patients with nasogastric tubes that bypass the esophagus, yet develop EoE. When the food is switched to nonallergic formula, their EoE resolves. This indicates that EoE is a nonlocalized disease that can be driven by systemic exposure from beyond the esophagus. Therefore, food allergy in EoE, albeit being a local inflammatory process, maybe due to a more systemic process that implicates a systemic sensitization resulting in a local manifestation where a dysfunctional epithelium become permissive for disease development.

CONCLUSIONS

There is evidence that EoE is both a localized disease and systemic disease. The tissue inflammation is localized to the esophagus and treatment is focused on removing the inflammatory cells and cytokines from the esophagus. Genetic evidence

points to both localized genes (*CAPN14*) and systemic genes (*TSLP*, *EMSY*) that play key roles in the development of disease. Patients with EoE have evidence of systemic inflammation as demonstrated by increased peripheral activated eosinophils even if they have apparently localized esophageal tissue injury. Overall, after reviewing all the evidence, we can conclude that EoE is a systemic disease with a wide array of genetic risk factors with localized inflammation that leads to localized symptoms. That EoE may represent a systemic disease is supported by the fact that patients with EoE have many comorbidities. Given that it becomes apparent that EoE and some of its comorbidities may have similar genetic/environmental triggers, a treatment that targets a single disease may be insufficient, whereas targeting the global predisposition to develop those diseases, especially in patients carrying the genetic mutations, will greatly improve the quality of life of these patients and limit the adverse consequences of our current treatment methodologies.

SUMMARY

EoE is a clinical pathological disease limited to the esophagus. Current treatments focus on controlling local inflammation with limited systemic side effects. However, the extraesophageal features, its frequent association with other systemic diseases, suggest that despite an apparent local manifestation of an immunologic disorder, EoE could actually be a systemic disorder. Finding a singular strategy to control these systemic processes with multiple end organ manifestations rather than multiple separate treatments would be ideal.

REFERENCES

- Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;133:1342-63.
- Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3-20.e6.
- Prasad GA, Alexander JA, Schleck CD, Zinsmeister AR, Smyrk TC, Elias RM, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol* 2009;7:1055-61.
- Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004;351:940-1.
- Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol* 2005;115:418-9.
- Hruz P, Straumann A, Bussmann C, Heer P, Simon HU, Zwahlen M, et al. Escalating incidence of eosinophilic esophagitis: a 20-year prospective, population-based study in Olten County, Switzerland. *J Allergy Clin Immunol* 2011;128:1349-1350.e5.
- Cherian S, Smith NM, Forbes DA. Rapidly increasing prevalence of eosinophilic esophagitis in Western Australia. *Arch Dis Child* 2006;91:1000-4.
- van Rhijn BD, Verheij J, Smout AJ, Bredenoord AJ. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. *Neurogastroenterol Motil* 2013;25:47-52.e5.
- 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;109:1503-12.
- Merves J, Muir A, Modayur Chandramouleeswaran P, Cianferoni A, Wang ML, Spergel JM. Eosinophilic esophagitis. *Ann Allergy Asthma Immunol* 2014;112:397-403.
- 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;108:954-61.
- Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. *J Allergy Clin Immunol* 2015;135:187-97.
- Caldwell JM, Collins MH, Stucke EM, Putnam PE, Franciosi JP, Kushner JP, et al. Histologic eosinophilic gastritis is a systemic disorder associated with blood and extragastric eosinophilia, TH2 immunity, and a unique gastric transcriptome. *J Allergy Clin Immunol* 2014;134:1114-24.
- Konikoff MR, Blanchard C, Kirby C, Buckmeier BK, Cohen MB, Heubi JE, et al. Potential of blood eosinophils, eosinophil-derived neurotoxin, and eotaxin-3 as biomarkers of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;4:1328-36.
- Dellon ES, Rusin S, Gebhart JH, Covey S, Higgins LL, Beitia R, et al. Utility of a noninvasive serum biomarker panel for diagnosis and monitoring of eosinophilic esophagitis: a prospective study. *Am J Gastroenterol* 2015;110:821-7.
- Morris DW, Stucke EM, Martin LJ, Abonia JP, Mukkada VA, Putnam PE, et al. Eosinophil progenitor levels are increased in patients with active pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2016;138:915-918.e5.
- Aceves SS, Bastian JF, Newbury RO, Dohil R. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. *Am J Gastroenterol* 2007;102:2271-9, quiz 80.
- Butz BK, Wen T, Gleich GJ, Furuta GT, Spergel J, King E, et al. Efficacy, dose reduction, and resistance to high-dose fluticasone in patients with eosinophilic esophagitis. *Gastroenterology* 2014;147:324-333.e5.
- Aceves SS, Chen D, Newbury RO, Dohil R, Bastian JF, Broide DH. Mast cells infiltrate the esophageal smooth muscle in patients with eosinophilic esophagitis, express TGF-beta1, and increase esophageal smooth muscle contraction. *J Allergy Clin Immunol* 2010;126:1198-1204.e4.
- Conus S, Straumann A, Bettler E, Simon HU. Mepolizumab does not alter levels of eosinophils, T cells, and mast cells in the duodenal mucosa in eosinophilic esophagitis. *J Allergy Clin Immunol* 2010;126:175-7.
- Dellon ES, Sheikh A, Speck O, Woodward K, Whitlow AB, Hores JM, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. *Gastroenterology* 2012;143:321-324.e1.
- Doerfler B, Bryce P, Hirano I, Gonsalves N. Practical approach to implementing dietary therapy in adults with eosinophilic esophagitis: the Chicago experience. *Dis Esophagus* 2015;28:42-58.
- Gonsalves N. Food allergies and eosinophilic gastrointestinal illness. *Gastroenterol Clin North Am* 2007;36:75-91. vi.
- Gonsalves N, Kagalwalla AF. Dietary treatment of eosinophilic esophagitis. *Gastroenterol Clin North Am* 2014;43:375-83.
- Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;4:1097-102.
- Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol* 2012;130:461-467.e5.
- Lucendo AJ, Arias A, Gonzalez-Cervera J, Yague-Compadre JL, Guagnozzi D, Angueira T, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol* 2013;131:797-804.
- Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA, et al. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol* 2013;108:679-92. quiz 93.
- Cianferoni A, Spergel JM, Muir A. Recent advances in the pathological understanding of eosinophilic esophagitis. *Expert Rev Gastroenterol Hepatol* 2015;9:1501-10.
- Blanchard C, Stucke EM, Burwinkel K, Caldwell JM, Collins MH, Ahrens A, et al. Coordinate interaction between IL-13 and epithelial differentiation cluster genes in eosinophilic esophagitis. *J Immunol* 2010;184:4033-41.
- Consortium GT. The Genotype-Tissue Expression (GTEx) project. *Nat Genet* 2013;45:580-5.
- Uhlen M, Oksvold P, Fagerberg L, Lundberg E, Jonasson K, Forsberg M, et al. Towards a knowledge-based Human Protein Atlas. *Nat Biotechnol* 2010;28:1248-50.
- Kottyan LC, Davis BP, Sherrill JD, Liu K, Rochman M, Kaufman K, et al. Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease. *Nat Genet* 2014;46:895-900.
- Ueta M, Sotozono C, Kinoshita S. Expression of interleukin-4 receptor alpha in human corneal epithelial cells. *Jpn J Ophthalmol* 2011;55:405-10.
- Dear TN, Boehm T. Identification and characterization of two novel calpain large subunit genes. *Gene* 2001;274:245-52.
- Sleiman PM, Wang ML, Cianferoni A, Aceves S, Gonsalves N, Nadeau K, et al. GWAS identifies four novel eosinophilic esophagitis loci. *Nat Commun* 2014;5:5593.

37. Sherrill JD, Gao PS, Stucke EM, Blanchard C, Collins MH, Putnam PE, et al. Variants of thymic stromal lymphopoietin and its receptor associate with eosinophilic esophagitis. *J Allergy Clin Immunol* 2010;126:160-165.e3.
38. Rothenberg ME, Spergel JM, Sherrill JD, Annaiah K, Martin LJ, Cianferoni A, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. *Nat Genet* 2010;42:289-91.
39. Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol* 2002;3:673-80.
40. Ito T, Wang YH, Duramad O, Hori T, Delespesse GJ, Watanabe N, et al. TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand. *J Exp Med* 2005;202:1213-23.
41. Duan W, Mehta AK, Magalhaes JG, Ziegler SF, Dong C, Philpott DJ, et al. Innate signals from Nod2 block respiratory tolerance and program T(H)2-driven allergic inflammation. *J Allergy Clin Immunol* 2010;126:1284-1293.e10.
42. Lei L, Zhang Y, Yao W, Kaplan MH, Zhou B. Thymic stromal lymphopoietin interferes with airway tolerance by suppressing the generation of antigen-specific regulatory T cells. *J Immunol* 2011;186:2254-61.
43. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, Franciosi J, Shuker M, Verma R, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr* 2009;48:30-6.
44. Assa'ad AH, Putnam PE, Collins MH, Akers RM, Jameson SC, Kirby CL, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. *J Allergy Clin Immunol* 2007;119:731-8.
45. Roy-Ghanta S, Larosa DF, Katzka DA. Atopic characteristics of adult patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2008;6:531-5.
46. Abonia JP, Wen T, Stucke EM, Grotjan T, Griffith MS, Kemme KA, et al. High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders. *J Allergy Clin Immunol* 2013;132:378-86.
47. Frischmeyer-Guerrero PA, Guerrero AL, Oswald G, Chichester K, Myers L, Halushka MK, et al. TGFbeta receptor mutations impose a strong predisposition for human allergic disease. *Sci Transl Med* 2013;5:195ra94.
48. Matt P, Schoenhoff F, Habashi J, Holm T, Van Erp C, Loch D, et al. Circulating transforming growth factor-beta in Marfan syndrome. *Circulation* 2009;120:526-32.
49. Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. *N Engl J Med* 2006;355:788-98.
50. Morissette R, Schoenhoff F, Xu Z, Shilane DA, Griswold BF, Chen W, et al. Transforming growth factor-beta and inflammation in vascular (type IV) Ehlers-Danlos syndrome. *Circ Cardiovasc Genet* 2014;7:80-8.
51. Aceves SS, Newbury RO, Dohil R, Bastian JF, Broide DH. Esophageal remodeling in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2007;119:206-12.
52. Mishra A, Wang M, Pemmaraju VR, Collins MH, Fulkerson PC, Abonia JP, et al. Esophageal remodeling develops as a consequence of tissue specific IL-5-induced eosinophilia. *Gastroenterology* 2008;134:204-14.
53. Straumann A, Conus S, Grzonka P, Kita H, Kephart G, Bussmann C, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut* 2010;59:21-30.
54. Abonia JP, Franciosi JP, Rothenberg ME. TGF-beta1: mediator of a feedback loop in eosinophilic esophagitis—or should we really say mastocytic esophagitis? *J Allergy Clin Immunol* 2010;126:1205-7.
55. Chakir J, Shannon J, Molet S, Fukakusa M, Elias J, Laviolette M, et al. Airway remodeling-associated mediators in moderate to severe asthma: effect of steroids on TGF-beta, IL-11, IL-17, and type I and type III collagen expression. *J Allergy Clin Immunol* 2003;111:1293-8.
56. Branton MH, Kopp JB. TGF-beta and fibrosis. *Microbes Infect* 1999;1:1349-65.
57. Hannula-Jouppi K, Laasanen SL, Heikkilä H, Tuomiranta M, Tuomi ML, Hilvo S, et al. IgE allergen component-based profiling and atopic manifestations in patients with Netherton syndrome. *J Allergy Clin Immunol* 2014;134:985-8.
58. Paluel-Marmont C, Bellon N, Barbet P, Leclerc-Mercier S, Hadj-Rabia S, Dupont C. Eosinophilic esophagitis and colonic mucosal eosinophilia in Netherton syndrome [e-pub ahead of print]. *J Allergy Clin Immunol* 2016. <http://dx.doi.org/10.1016/j.jaci.2016.10.045>.
59. Smith DL, Smith JG, Wong SW, deShazo RD. Netherton's syndrome: a syndrome of elevated IgE and characteristic skin and hair findings. *J Allergy Clin Immunol* 1995;95(Pt 1):116-23.
60. Sherrill JD, Kc K, Wu D, Djukic Z, Caldwell JM, Stucke EM, et al. Desmoglein-1 regulates esophageal epithelial barrier function and immune responses in eosinophilic esophagitis. *Mucosal Immunol* 2014;7:718-29.
61. Samuelov L, Sarig O, Harmon RM, Rapaport D, Ishida-Yamamoto A, Isakov O, et al. Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting. *Nat Genet* 2013;45:1244-8.
62. Blanchard C, Mingler MK, Vicario M, Abonia JP, Wu YY, Lu TX, et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol* 2007;120:1292-300.
63. Sherrill JD, Rothenberg ME. Genetic dissection of eosinophilic esophagitis provides insight into disease pathogenesis and treatment strategies. *J Allergy Clin Immunol* 2011;128:23-32.
64. Henderson CJ, Ngeow J, Collins MH, Martin LJ, Putnam PE, Abonia JP, et al. Increased prevalence of eosinophilic gastrointestinal disorders in pediatric PTEN hamartoma tumor syndromes. *J Pediatr Gastroenterol Nutr* 2014;58:553-60.
65. Spergel JM, Rothenberg ME, Collins MH, Furuta GT, Markowitz JE, Fuchs G III, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2012;129:456-63. 463.e1-3.
66. Noti M, Wojno ED, Kim BS, Siracusa MC, Giacomini PR, Nair MG, et al. Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. *Nat Med* 2013;19:1005-13.
67. Ewaschuk JB, Unger S, O'Connor DL, Stone D, Harvey S, Clandinin MT, et al. Effect of pasteurization on selected immune components of donated human breast milk. *J Perinatol* 2011;31:593-8.
68. Rogers ML, Goddard C, Regester GO, Ballard FJ, Belford DA. Transforming growth factor beta in bovine milk: concentration, stability and molecular mass forms. *J Endocrinol* 1996;151:77-86.
69. Goralski JL, Lercher DM, Davis SD, Dellon ES. Eosinophilic esophagitis in cystic fibrosis: a case series and review of the literature. *J Cyst Fibros* 2013;12:9-14.