HHS Public Access

Author manuscript

J Allergy Clin Immunol. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

J Allergy Clin Immunol. 2016 November ; 138(5): 1381–1383. doi:10.1016/j.jaci.2016.09.001.

Linking impaired skin barrier function to esophageal allergic inflammation via IL-33

Jared Travers, BS, **Mark Rochman, PhD**, **Cora E. Miracle**, **Jared P. Cohen**, and **Marc E. Rothenberg, MD, PhD**

Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Keywords

Cytokines; food allergy; basophils; eosinophils; innate Immunity; barrier function

Eosinophilic esophagitis (EoE) is an emerging chronic allergic inflammatory disorder that selectively affects the esophagus and is characterized clinically by symptoms of esophageal dysfunction, including vomiting and dysphagia.[1] Molecularly, EoE is characterized by a T_H2 immune response based on increased expression of the cytokines IL-4, IL-5, and IL-13.[2] IL-13 promotes immune cell infiltration by inducing production of chemokines, such as CCL26 (eotaxin-3),[3] and by impairing epithelial barrier function through reduced expression of the epithelial adhesion molecule desmoglein 1[4] and overexpression of the protease calpain 14,[5] which is encoded by the *CAPN14* gene at chromosome 2p23 and is a major susceptibility genetic locus for EoE.[6,7] Patients with EoE often present with comorbid conditions, including asthma and atopic dermatitis,[1] which also involve dysregulated T_H2 responses and impaired barrier function. The similarity of the pathogeneses of these disorders is evidenced by the significant degree of shared genetic associations that exists among patients with these allergic disorders, including the overabundance of genetic variants in the thymic stromal lymphopoietin *(TSLP)*[8,9] and filaggrin (*FLG)* loci.[10]

There is a critical need to elucidate the factors that initiate and propagate the T_H2 responses present in patients with EoE. The disease is considered to be driven by food antigens because strict elimination diets cause complete remission of the disease[11] and experimental EoE can be induced in mice through allergen exposure.[12] Currently, the route of sensitization to these food antigens is not clear. It is notable that many patients with EoE are sensitized to aeroallergens[13] and that there are seasonal variations in the clinical symptoms of patients with EoE.[14] Additionally, experimental murine studies indicate that EoE-like disease can be induced by allergen challenge after epicutaneous[15] or respiratory[12] sensitization. However, after sensitization occurs, it remains unclear how the T_H2 immune

Corresponding author: Marc E. Rothenberg, MD, PhD, Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, MLC 7028, Cincinnati, OH 45229-3039. Marc.Rothenberg@cchmc.org.

Disclosure of potential conflict of interest: M. E. Rothenberg receives grant support from the National Institutes of Health; consulting fees from Receptos Immune Pharmaceuticals, NKT Therapeutics, and PulmOne Therapeutics; patents with Miraca Life Science; royalties from Teva Pharmaceuticals; and stock options from PulmOne, NKT Therapeutics, and Immune Pharmaceuticals. The rest of the authors declare that they have no relevant conflicts of interest.

response is initiated and propagated upon re-exposure to food antigens, although this likely includes activation of innate immune cells, including antigen-presenting cells, by epithelium-derived, T_H2-promoting innate cytokines. Notably, esophageal TSLP is expressed at increased levels in patients with EoE[16,17] and activates dendritic cells[18] and basophils[19] to induce T_H2 polarization of $CD4^1$ T cells. Additionally, Noti et al[16] showed a critical role for TSLP in the pathogenesis of EoE using an experimental mouse model that induces eosinophilic infiltration and T_H2 cytokine production in the esophagus after epicutaneous sensitization and repeated intragastric challenge with the food antigen ovalbumin. Genetic deficiency in TSLP or its receptor prevented induction of disease in this model, and administering TSLP-neutralizing antibodies after establishing esophageal eosinophilia reversed the features of the disease. Preliminary evidence was presented that basophils were the critical target of TSLP because depleting basophils phenocopied loss of TSLP, although the definitive experiment of adoptive transfer of wild-type and TSLP receptor–deficient basophils was not performed.

There has been much recent interest in investigating whether another epithelium-derived, T_H2-promoting innate cytokine, IL-33, could serve as an additional signal to initiate and propagate the T_H2 response in patients with EoE. IL-33 is an alarmin that is present during homeostasis in the nuclei of epithelial cells[20,21] and is released during necrosis or cellular damage.[22] Upon extracellular release, it can activate a wide variety of immune cells that express its receptor, ST2, including type 2 innate lymphoid cells,[23] $CD4^1$ T cells,[24] eosinophils,[25] mast cells,[26] and basophils.[26] IL-33 and ST2 are required for induction of allergic asthma in murine models.[27,28] Two recent studies have shown that esophageal biopsy specimens from patients with EoE express higher levels of IL-33 protein than those from control subjects.[17,29] Additionally, there is association between genetic variants in the *IL33* locus and disease risk.[6] Finally, Judd et al[29] showed that intraperitoneal injection of recombinant IL-33 induces esophageal eosinophilia, epithelial hyperplasia, and production of T_H2-associated cytokines.

In this issue of the *Journal*, Venturelli et al[30] provide evidence of a requirement for IL-33 in the pathogenesis of experimental murine EoE-like disease. Eosinophil infiltration and T_H2-associated cytokine production were induced in the esophagus by means of repeated intranasal challenge with ovalbumin after epicutaneous sensitization by disrupting the skin epithelial barrier through tape-stripping or genetic deficiency of *FLG*. Disrupting the skin epithelial barrier was required because allergic sensitization did not occur in wild-type mice without tape-stripping of the skin. IL-33 was a critical mediator in this model because esophageal symptoms were not present in mice either genetically deficient in *ST2* or given ST2-neutralizing antibodies. Furthermore, genetic deficiency in both *FLG* and *ST2* prevented esophageal symptoms. Basophil depletion prevented disease induction, and esophageal symptoms were restored on adoptive transfer of wild-type, but not *ST2*-deficient, basophils. This observation supports that basophils were the target of IL-33, at least in part. Collectively, the data show that IL-33–ST2 interactions in basophils and impaired skin epithelial barrier integrity mediate induction of EoE-like disease induced by epicutaneous allergen sensitization (summarized in Fig 1).

The work presented in this article builds on the aforementioned work by Noti et al[16] showing the requirement of basophils and TSLP for induction of EoE-like disease in mice, which used a different model of allergen challenge (intragastric vs intranasal). Although this work provides strong evidence for the importance of basophils in 2 different experimental mouse models, concerns remain with regard to translating these findings to human disease. Although Noti et al[16] show accumulation of basophils in human biopsy specimens, this finding has not been independently confirmed by others, including Venturelli et al.[30] In contrast, esophageal biopsy specimens from patients with active EoE are notable for infiltration of mast cells and eosinophils,[31] which are both potently activated by IL-33. Therefore, it is likely that IL-33 activating these cells also contributes to the human disease. Additionally, the experimental antigen exposure is of supraphysiologic doses of a single antigen with one route of sensitization, whereas the human disease likely involves multiple allergens at more physiologic exposure doses and with several routes of sensitization. Finally, the mechanism through which skin sensitization leads to esophageal priming, whether involving basophils or not, remains unclear.

In summary, this study identifies that epicutaneous sensitization promotes induction of EoE-like disease in mice through a mechanism that involves IL-33/ST2–mediated activation of basophils. This study further supports the view that deficiency of *FLG* predisposes patients to EoE and suggests that blocking the IL-33–ST2 axis and protecting or enhancing the skin barrier would be of therapeutic value for treating EoE. It will also be of interest to apply these results directly to the esophagus because esophageal epithelial barrier function in patients with EoE is impaired, likely through IL-13–mediated dysregulation of calpain 14[5,6] and desmoglein 1.[4]

Acknowledgments

Supported by National Institutes of Health grants R37 AI045898, R01 AI124355, and U19 AI070235; the Campaign Urging Research for Eosinophilic Disease (CURED); the Buckeye Foundation; and the Sunshine Charitable Foundation and its supporters, Denise A. Bunning and David G. Bunning

We thank Shawna Hottinger for editorial assistance.

References

1. Davis BP, Rothenberg ME. Mechanisms of disease of eosinophilic esophagitis. Annu Rev Pathol. 2016; 11:365–93. [PubMed: 26925500]
2. 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. [PubMed: 18073124]
3. Blanchard C, Wang N, Stringer KF, Mishra A, Fulkerson PC, Abonia JP, et al. Eo-taxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagi-tis. J Clin Invest. 2006; 116:536–47. [PubMed: 16453027]
4. 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. [PubMed: 24220297]
5. Davis BP, Stucke EM, Khorki ME, Litosh VA, Rymer JK, Rochman M, et al. Eosinophilic esophagitis-linked calpain 14 is an IL-13-induced protease that mediates esophageal epithelial barrier impairment. JCI Insight. 2016; 1:e86355. [PubMed: 27158675]

6. 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. [PubMed: 25017104]
7. 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. [PubMed: 25407941]
8. 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. [PubMed: 20208534]
9. 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; 126:160–5.e3. [PubMed: 20620568]
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. [PubMed: 20208004]
11. Davis BP, Rothenberg ME. Emerging concepts of dietary therapy for pediatric and adult eosinophilic esophagitis. Exp Rev Clin Immunol. 2013; 9:285–7.
12. Mishra A, Schlotman J, Wang M, Rothenberg ME. Critical role for adaptive T cell immunity in experimental eosinophilic esophagitis in mice. J Leuk Biol. 2007; 81:916–24.
13. Aceves SS. Food and aeroallergens in eosinophilic esophagitis: role of the allergist in patient management. Curr Opin Gastroenterol. 2014; 30:391–5. [PubMed: 24867155]
14. Almansa C, Krishna M, Buchner AM, Ghabril MS, Talley N, Devault KR, et al. Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. Am J Gastroenterol. 2009; 104:828–33. [PubMed: 19240704]
15. Akei HS, Mishra A, Blanchard C, Rothenberg ME. Epicutaneous antigen exposure primes for experimental eosinophilic esophagitis in mice. Gastroenterology. 2005; 129:985–94. [PubMed: 16143136]
16. Noti M, Wojno ED, Kim BS, Siracusa MC, Giacomin PR, Nair MG, et al. Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. Nat Med. 2013; 19:1005–13. [PubMed: 23872715]
17. Simon D, Radonjic-Hosli S, Straumann A, Yousefi S, Simon HU. Active eosinophilic esophagitis is characterized by epithelial barrier defects and eosinophil extracellular trap formation. Allergy. 2015; 70:443–52. [PubMed: 25620273]
18. Ziegler SF, Roan F, Bell BD, Stoklasek TA, Kitajima M, Han H. The biology of thymic stromal lymphopoietin (TSLP). Adv Pharmacol. 2013; 66:129–55. [PubMed: 23433457]
19. Siracusa MC, Saenz SA, Hill DA, Kim BS, Headley MB, Doering TA, et al. TSLP promotes interleukin-3-independent basophil haematopoiesis and type 2 inflammation. Nature. 2011; 477:229–33. [PubMed: 21841801]
20. Carriere V, Roussel L, Ortega N, Lacorre DA, Americh L, Aguilar L, et al. IL-33, the IL-1-like cytokine ligand for ST2 receptor, is a chromatin-associated nuclear factor in vivo. Proc Natl Acad Sci U S A. 2007; 104:282–7. [PubMed: 17185418]
21. Moussion C, Ortega N, Girard JP. The IL-1-like cytokine IL-33 is constitutively expressed in the nucleus of endothelial cells and epithelial cells in vivo: a novel 'alarmin'? PLoS One. 2008; 3:e3331. [PubMed: 18836528]
22. Zhao W, Hu Z. The enigmatic processing and secretion of interleukin-33. Cell Mol Immunol. 2010; 7:260–2. [PubMed: 20305685]
23. Neill DR, Wong SH, Bellosi A, Flynn RJ, Daly M, Langford TK, et al. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. Nature. 2010; 464:1367–70. [PubMed: 20200518]
24. Peine M, Marek RM, Lohning M. IL-33 in T cell differentiation, function, and immune homeostasis. Trends Immunol. 2016; 37:321–33. [PubMed: 27055914]
25. Bouffi C, Rochman M, Zust CB, Stucke EM, Kartashov A, Fulkerson PC, et al. IL-33 markedly activates murine eosinophils by an NF-kappaB-dependent mechanism differentially dependent upon an IL-4-driven autoinflammatory loop. J Immunol. 2013; 191:4317–25. [PubMed: 24043894]

26. Saluja R, Ketelaar ME, Hawro T, Church MK, Maurer M, Nawijn MC. The role of the IL-33/IL-1RL1 axis in mast cell and basophil activation in allergic disorders. Mol Immunol. 2015; 63:80–5. [PubMed: 25017307]

27. Lee HY, Rhee CK, Kang JY, Byun JH, Choi JY, Kim SJ, et al. Blockade of IL-33/ST2 ameliorates airway inflammation in a murine model of allergic asthma. Exp Lung Res. 2014; 40:66–76. [PubMed: 24446582]

28. Zoltowska AM, Lei Y, Fuchs B, Rask C, Adner M, Nilsson GP. The interleukin-33 receptor ST2 is important for the development of peripheral airway hyperresponsiveness and inflammation in a house dust mite mouse model of asthma. Clin Exp Allergy. 2016; 46:479–90. [PubMed: 26609909]

29. Judd LM, Heine RG, Menheniott TR, Buzzelli J, O'Brien-Simpson N, Pavlic D, et al. Elevated IL-33 expression is associated with pediatric eosinophilic esophagitis, and exogenous IL-33 promotes eosinophilic esophagitis development in mice. Am J Physiol Gastrointest Liver Physiol. 2016; 310:G13–25. [PubMed: 26514775]

30. Venturelli N, Lexmond WS, Ohsaki A, Nurko S, Karasuyama H, Fiebiger E, et al. Allergic skin sensitization promotes eosinophilic esophagitis through the IL-33-basophil axis in mice. J Allergy Clin Immunol. 2016; 138:1367–80. [PubMed: 27233150]

31. 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-b1, and increase esophageal smooth muscle contraction. J Allergy Clin Immunol. 2010; 126:1198–204.e4. [PubMed: 21047675]

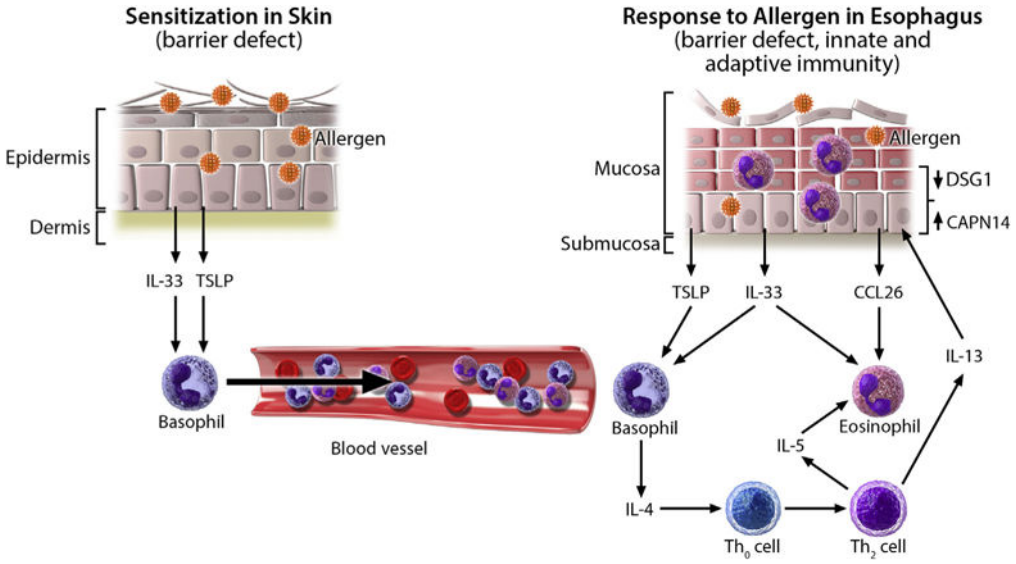

FIG 1.

Proposed model for the development of allergic inflammation in patients with EoE. Impaired skin barrier integrity, such as that caused by injury or *FLG* mutations, allows for increased allergen penetration through the epithelium, causing allergic sensitization and release of IL-33 and TSLP from the epithelium. Secondary to activation by these cytokines, there is increased trafficking of basophils through the bloodstream to the esophagus. Later, direct exposure of allergens to the esophageal epithelium leads to the release of TSLP and IL-33, which induce IL-4 production from basophils and subsequent release of IL-5 and IL-13 from T_H2 cells. IL-13 causes esophageal epithelial barrier impairment and increased allergen exposure by decreasing desmoglein 1 *(DSG1)* and increasing calpain 14 *(CAPN14)* expression. Additionally, IL-13 induces CCL26 production from the epithelium, which, in combination with IL-5, causes eosinophil infiltration into the esophagus.