

# Immunopathogenesis of Eosinophilic Esophagitis

Hans-Uwe Simon<sup>a</sup> Alex Straumann<sup>b</sup>

<sup>a</sup>Institute of Pharmacology, University of Bern, Bern, and <sup>b</sup>Swiss EoE Clinic and Research Group, Olten, Switzerland

## Key Words

Allergy · Cytokines · Eosinophilic esophagitis · Inflammation

## Abstract

**Background:** Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus associated with dysphagia in adults and refractory reflux syndromes in children.

**Methods:** Immunological and genetic approaches have been used to better understand the pathophysiology of the underlying inflammation. **Results and Conclusions:** Evidence has accumulated that EoE represents a T-helper (Th) 2-type inflammatory disease, in which allergens play a role in triggering the disease. The majority of the patients suffer from concurrent allergic rhinitis, asthma, and eczema, and have a history of atopy. The chronic inflammatory response in EoE is associated with tissue damage and remodeling, both of which lead to esophageal dysfunction and bolus impaction. The new insights into the pathophysiology have resulted in the development of the first pharmacological therapies of EoE.

© 2014 S. Karger AG, Basel

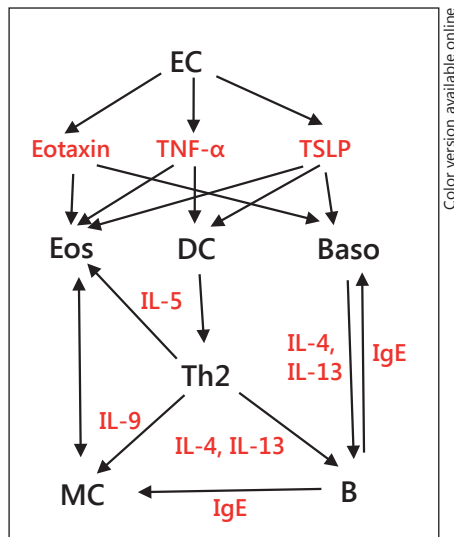
## Introduction

In a broad spectrum of inflammatory diseases, eosinophils are found among infiltrating cells [1, 2]. For example, in allergic diseases, such as atopic dermatitis [3],

bronchial asthma [4, 5], and rhinosinusitis [6], eosinophil numbers are increased. However, the pathogenic role of eosinophils in these diseases has not been defined yet. The functions of eosinophils have been related to the protection against helminth parasites [7], immunopathology [7, 8], remodeling processes, and immunoregulation [9]. Although the functional role of eosinophils often remains uncertain, their presence suggests that an immunologic mechanism contributes to the pathogenesis of given diseases. Since eosinophil infiltration of the esophageal tissue is a hallmark of eosinophilic esophagitis (EoE), immunological mechanisms have been investigated over the last decade by several groups. Here, we summarize published key findings that clearly point to the immune system as a central player in the pathogenesis of EoE.

## Cells and Cytokines

The esophageal epithelium of EoE patients contains not only eosinophils, but also IL-5-expressing T cells, B cells, and IgE-bearing mast cells that suggest EoE is an allergic disease [10] (fig. 1). A summary of quantitative analyses of infiltrating inflammatory cells in the esophageal epithelium has recently been published [11]. Moreover, it has also been demonstrated that the inflammatory response in EoE patients is restricted to the esophagus and does not involve the stomach and/or duodenum [10]. The Th2-type inflammatory profile of EoE was sub-



**Fig. 1.** Simplified scheme of the immunopathogenesis of EoE. EoE is believed to be triggered by aero- and food allergens. The epithelial cells (EC) of the esophagus that are activated by IL-13 (not shown) actively contribute to the inflammatory process. Thymic stromal lymphopoietin (TSLP) promotes dendritic cell (DC)-mediated Th2 differentiation and activates basophils (Baso) as well as eosinophils (Eos). TNF- $\alpha$  increases adhesion molecules on endothelial cells (not shown) and eotaxin-3 attracts Eos. IL-13 helps B cells to produce IgE. IL-9 activates mast cells (MC), which, like Baso, bind IgE by their high-affinity IgE receptor. IL-5 activates Eos and may delay their apoptosis. Eos and MC generate additional cytokines and participate in the immunoregulatory process (not shown). Eos also generate TGF- $\beta$ , which stimulates fibroblasts to produce extracellular matrix proteins (not shown). Eos may also damage EC by releasing cationic proteins and reactive oxygen species (not shown).

sequently confirmed in pediatric and adult EoE [12], and relevant allergens were identified for both pediatric and adult EoE [11, 13]. Moreover, a strong link between atopy and EoE was subsequently described in both pediatric and adult EoE patient groups [14, 15]. It should be noted, however, that intrinsic (non-IgE-mediated) forms exist in both pediatric and adult EoE in which no relevant allergens can be identified, neither by measuring IgE nor by performing skin prick tests.

Increased numbers of dendritic cells and IgE-secreting plasma cells have also been described in the esophageal epithelium of EoE patients [16]. Besides the infiltrating leukocytes, the esophageal epithelial cells appear to contribute to the inflammatory response. For instance, the epithelial cells highly express TNF- $\alpha$  [10] and eotaxin-3 [17] which likely represent key factors largely responsible for the recruitment of eosinophils to the esophagus.

Moreover, esophageal epithelial cells of EoE patients have been reported to produce thymic stromal lymphopoietin [18], a cytokine favoring Th2 differentiation [19]. Recent studies point to the possibility that the role of regulatory T cells may differ between pediatric and adult EoE. While increased numbers of regulatory T cells were seen in pediatric cases, adult EoE patients were found to have a relative lack of FoxP3-positive T cells [20]. Taken together, the main allergen-induced immunological mechanisms leading to eosinophilic inflammation and allergen-specific IgE synthesis seem to be very similar to other allergic diseases (fig. 1).

These correlative studies in EoE patients were largely confirmed by mechanistic studies performed in experimental mouse models of EoE. For instance, T cell-deficient, but not B cell-deficient, mice seem to be unable to develop EoE [21]. Moreover, experimental EoE was inducible by allergens [22] and IL-13 [23], and IL-5 and eotaxin were found to be crucial for disease development [23]. A recent study suggests that exaggerated basophil responses triggered by thymic stromal lymphopoietin contribute to EoE pathogenesis [24]. Taken together, the data in experimental mouse systems support the view that EoE likely represents an allergic disease in which T cells and eosinophils play key pathogenic roles (fig. 1).

## Tissue Damage and Remodeling

Remodeling of the esophagus is a hallmark of EoE, and both histological and molecular features of this process have been described [25–28]. Extracellular matrix proteins were found to be deposited in significant amounts in EoE patients [25–27]. Interestingly, the deposition of extracellular matrix proteins, including its associated subepithelial fibrosis, was reversible in EoE patients receiving topical corticosteroid therapy [25, 27]. TGF- $\beta$ 1, a key cytokine for epithelial growth, fibrosis, and tissue remodeling, has been identified with EoE [25–27]. Tissue remodeling suggests the existence of previous tissue damage. Indeed, TUNEL-positive epithelial cells indicative for cell death were particularly found in close proximity to eosinophil infiltrations [26], and tissue remodeling correlated with eosinophil degranulation [27].

The latter observations point to a possible role of the eosinophil in the immunopathology of the esophagus in EoE patients. Immunohistochemical studies have revealed evidence for eosinophil degranulation in the esophageal epithelium [26, 27, 29]. The granule proteins major basic protein, eosinophil cationic protein, and eo-

sinophil peroxidase have cytotoxic effects, which explains (at least partially) the death of epithelial cells associated with EoE. Eosinophil-mediated epithelial damage can also be explained by toxic hydrogen peroxide and halide acids generated by eosinophil peroxidase as well as reactive oxygen species produced as a consequence of NADPH oxidase activation. Clearly, besides their role as effector cells, eosinophils may contribute to EoE pathogenesis by their capacity to participate in immunoregulatory [9] and tissue remodeling processes [26]. Whether eosinophils generate extracellular DNA traps [30–32] in EoE patients remains an open question.

## Conclusions

EoE is a chronic Th2-type inflammatory disease. It has become increasingly clear that there is a significant allergic predisposition in the EoE population, with the major-

ity of the patients having concurrent allergic rhinitis, asthma, eczema, and/or a history of atopy [11]. Based on its pathogenesis, it is likely that EoE represents a new manifestation of atopy.

## Acknowledgement

Work in the laboratory of H.-U.S. is supported by the Swiss National Science Foundation and Allergie-Stiftung Ulrich Müller-Gierok, Bern, Switzerland.

## Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of the article.

## References

- Simon D, Simon HU: Eosinophilic disorders. *J Allergy Clin Immunol* 2007;119:1291–1300.
- Simon HU: Allergic inflammation: focus on eosinophils. *Allergy* 2013;68:823–824.
- Novak N, Simon D: Atopic dermatitis – from new pathophysiologic insights to individualized therapy. *Allergy* 2011;66:830–839.
- Hoskins A, Roberts JL 2nd, Milne G, Choi L, Dworski R: Natural-source d- $\alpha$ -tocopheryl acetate inhibits oxidant stress and modulates atopic asthma in humans in vivo. *Allergy* 2012;67:676–682.
- Agache I, Akdis C, Jutel M, Virchow JC: Untangling asthma phenotypes and endotypes. *Allergy* 2012;67:835–846.
- Pezato R, Swierczynska-Krepa M, Nizankowska-Mogilnicka E, Derycke L, Bachert C, Pérez-Novo CA: Role of imbalance of eicosanoid pathways and staphylococcal superantigens in chronic rhinosinusitis. *Allergy* 2012;67:1347–1356.
- Klion AD, Nutman TB: The role of eosinophils in host defense against helminth parasites. *J Allergy Clin Immunol* 2004;113:30–37.
- Frigas E, Motojima S, Gleich GJ: The eosinophilic injury to the mucosa of the airways in the pathogenesis of bronchial asthma. *Eur Respir J* 1991;13:S123–S135.
- Roth N, Städtler S, Lemann M, Hösli S, Simon HU, Simon D: Distinct eosinophil cytokine expression patterns in skin diseases – the possible existence of functionally different eosinophil subpopulations. *Allergy* 2011;66:1477–1486.
- Straumann A, Bauer M, Fischer B, Blaser K, Simon HU: Idiopathic eosinophilic esophagitis is associated with a T-helper 2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001;108:954–961.
- Straumann A, Aceves SS, Blanchard C, Collins MH, Furuta GT, Hirano I, Schoepfer AM, Simon D, Simon HU: Pediatric and adult eosinophilic esophagitis: similarities and differences. *Allergy* 2012;67:477–490.
- Bullock JZ, Villanueva JM, Blanchard C, Filipovich AH, Putnam PE, Collins MH, et al: Interplay of adaptive Th2 immunity with eotaxin-3/c-C chemokine receptor 3 in eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2007;45:22–31.
- Simon D, Straumann A, Dahinden C, Simon HU: Frequent sensitization to *Candida albicans* and profilins in adult eosinophilic esophagitis. *Allergy* 2013;68:945–948.
- 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;119:731–738.
- Simon D, Marti HP, Heer P, Simon HU, Braathen LR, Straumann A: Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases. *J Allergy Clin Immunol* 2005;115:1090–1092.
- Lucendo AJ, Navarro M, Comas C, Pascual JM, Burgos E, Santamaria L, et al: Immunophenotypic characterization and quantification of the epithelial inflammatory infiltrate in eosinophilic esophagitis through stereology: an analysis of the cellular mechanisms of the disease and the immunologic capacity of the esophagus. *Am J Surg Pathol* 2007;31:598–606.
- Blanchard C, Wang N, Stringer KF, Mishra A, Fulkerson PC, Abonia JP, et al: Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* 2006;116:536–547.
- 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.
- Ziegler SF, Artis D: Sensing the outside world: TSLP regulates barrier immunity. *Nat Immunol* 2010;11:289–293.
- Stuck MC, Straumann A, Simon HU: Relative lack of T regulatory cells in adult eosinophilic esophagitis – no normalization after corticosteroid therapy. *Allergy* 2011;66:705–707.
- 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.
- 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.
- 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.
- 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;19:1005–1013.

- 25 Aceves SS, Newbury RO, Chen D, Mueller J, Dohil R, Hoffman H, et al: Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. *Allergy* 2010;65:109–116.
- 26 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 randomized, placebo-controlled, double-blind trial. *Gut* 2010;59:21–30.
- 27 Straumann A, Conus S, Degen L, Felder S, Kummer M, Engel H, et al: Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology* 2010;139:1526–1537.
- 28 Mueller S, Aigner T, Neureiter D, Stolte M: Eosinophil infiltration and degranulation in oesophageal mucosa from adult patients with eosinophilic oesophagitis: a retrospective and comparative study on pathological biopsy. *J Clin Pathol* 2006;59:1175–1180.
- 29 Chehade M, Sampson HA, Morotti RA, Magid MS: Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2007;45:319–328.
- 30 Yousefi S, Gold JA, Andina N, Lee JJ, Kelly AM, Kozlowski E, et al: Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense. *Nat Med* 2008;14:949–953.
- 31 Simon D, Hoesli S, Roth N, Staedler S, Yousefi S, Simon HU: Eosinophil extracellular DNA traps in skin diseases. *J Allergy Clin Immunol* 2011;127:194–199.
- 32 Dworski R, Simon HU, Hoskins A, Yousefi S: Eosinophil and neutrophil extracellular DNA traps in human allergic asthmatic airways. *J Allergy Clin Immunol* 2011;127:1260–1266.