

Advances in eosinophilic diseases in 2018



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Interest in eosinophil biology and eosinophilic diseases is increasing, as reflected in a doubling of the number of annual articles focused on this topic published in the *Journal of Allergy and Clinical Immunology* over the past decade. Although the majority of these publications relate to eosinophilic asthma, a growing proportion of them focus on breakthroughs in the diagnosis, treatment, and pathogenesis of other eosinophilic disorders, most notably eosinophilic esophagitis. This review highlights advances in our understanding of eosinophilia and eosinophilic disorders (excluding asthma) published in the *Journal* in 2018. (*J Allergy Clin Immunol* 2019;144:1490-4.)

Key words: Apoptosis, asthma, eosinophils, esophagitis, gastrointestinal and hypereosinophilic

With the availability of new therapies, including targeted biologics, interest in the eosinophil and eosinophil-related disorders has continued to increase. This is reflected in the literature, with 107 publications in the *Journal of Allergy and Clinical Immunology* (JACI) in 2018 searching PubMed using the MeSH term “eosinophil OR eosinophilia OR eosinophilic OR hypereosinophilia OR hypereosinophilic” compared with 88 in 2015 and 64 in 2010. Although the majority of these publications relate to eosinophilic asthma, a growing proportion focus on breakthroughs in the diagnosis, treatment, and pathogenesis of other eosinophilic disorders, most notably eosinophilic

esophagitis (EoE). This review highlights advances in our understanding of eosinophilia and eosinophilic disorders (excluding asthma) published in the JACI in 2018. We hope that the reader will find this summary a useful supplement to reading the original articles.

EOSINOPHILS AND ALLERGIC INFLAMMATION

The field of allergic inflammation is becoming increasingly complex with the description of novel pathways and mediators. The JACI advances in 2018 examined both the factors leading to tissue eosinophilia and the effect of eosinophils on the inflammatory process itself. In a novel study examining the role of the prostaglandin pathway in chronic rhinosinusitis (CRS), Choi et al¹ deleted the autophagy-related gene *Atg7* in the myeloid lineage of mice challenged with a mixture of *Aspergillus* species protease and ovalbumin to induce CRS.¹ They not only observed an increase in eosinophilic inflammation in the *Atg7*-deficient mice but also associated dysregulation of the prostaglandin D₂ pathway. Macrophage autophagy and IL-1 played a major role in this process, highlighting a potential new therapeutic approach for CRS. A second study by Venkateshaiah et al² addressing the promotion of eosinophilic inflammation provided evidence supporting a role for IL-18 in eosinophil expression of CD101 and CD274, 2 markers that have been associated with an inflammatory eosinophil phenotype in mice.

With respect to the role of eosinophils in the inflammatory response and its sequelae, eosinophils and their degranulation products have been shown to interact with fibroblasts to promote fibrogenesis both *in vitro* and *in vivo* in animal models. Using primary human lung fibroblasts cultured with conditioned medium from eosinophils from allergic patients, Bernau et al³ demonstrated that the eosinophil-fibroblast interaction also produces mediators involved in neutrophil recruitment to the inflammatory milieu. Further illustrating the complex interactions between fibroblasts, fibrosis, and eosinophils, Doan et al⁴ showed that the asthma-associated extracellular matrix glycoprotein tenascin-C promotes hematopoietic progenitors and suppresses IL-5–driven maturation of murine lung eosinophils in a reversible manner. They confirm their findings in tenascin-deficient mice, showing that they have an increased progenitor pool that expands in an accelerated way *ex vivo*.

EoE

Focusing on EoE, Aceves et al⁵ aimed to understand the ability of caregiver report to predict patients' self-reported symptoms and the relationship of patient-reported outcomes with histology. Through a multisite study associated with the Consortium of Eosinophilic Gastrointestinal Disease Researchers,⁶ parents of children with EoE were shown to accurately report their children's disease symptoms and quality of life. Interestingly,

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This work was supported in part by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH; to A.D.K.) and by NIH grant U19 AI070235, NIH R01 AI124355, and R37 A1045898, the Campaign Urging Research for Eosinophilic Disease (CURED) Foundation, and the Sunshine Charitable Foundation and its supporters, Denise A. Bunning and David G. Bunning (to M.E.R.).

Disclosure of potential conflict of interest: M. E. Rothenberg is a consultant for PulmOne, Spoon Guru, ClostraBio, Celgene, Astra Zeneca, and Allakos and has an equity interest in the first 3 listed; receives royalties from reslizumab (Teva Pharmaceuticals), PEESV2 (Mapi Research Trust), and UpToDate; and is an inventor of patents owned by Cincinnati Children's Hospital Medical Center. A. D. Klion declares that she has no relevant conflicts of interest.

Received for publication October 3, 2019; revised October 14, 2019; accepted for publication October 17, 2019.

Available online October 23, 2019.

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0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2019.10.010>

self- and parent-reported symptoms correlated with proximal esophageal histology but not distal histology. These findings show the reliable value of parenteral reporting of symptoms and lend support for such monitoring in clinical trials in children.

One of the key advances in the EoE field is the recognition that proton pump inhibitors can fully treat EoE, at least in some patients, leading to a change in the diagnostic criteria for EoE, which no longer focus on failure to respond to proton pump inhibitor therapy.⁷ This radical change in thinking about EoE and proton pump inhibitor therapy was propelled by Wen et al,⁸ who demonstrated that the esophageal transcriptome was comparable between patients with EoE regardless of their responsiveness to proton pump inhibitors. Furthermore, Wen et al⁸ showed that proton pump inhibitors were able to fully reverse the EoE transcriptome, including genes associated with allergic inflammation (type 2 immunity) and impaired barrier genes. More recently, Nguyen et al⁹ demonstrated that the histology of the esophagus was also similar between patients with EoE and those with proton pump inhibitor-responsive esophageal eosinophilia. In addition, Wright et al¹⁰ preliminarily reported similarities between esophageal overexpression of GATA-3 and T-bet in patients with EoE and proton pump inhibitor-responsive esophageal eosinophilia.^{9,10}

Zeng et al¹¹ aimed to understand the response of the esophagi of patients with EoE to acid; the team focused on the acid-protective mechanisms centered around carrier family 9, subfamily A, member 3 (*SLC9A3*), and its ability to regulate intracellular pH, as well as formation of dilated intercellular spaces (DISs), because this is a process germane to the esophageal barrier impairment seen in patients with EoE. *SLC9A3* was the most dysregulated esophageal gene central to regulating intracellular pH, and its increased expression positively correlated with disease severity, as defined by the number of eosinophils/high-power field and the presence of DISs. Interestingly, IL-13 treatment of esophageal epithelial cells induced *SLC9A3* expression and Na⁺-dependent proton secretion. Importantly, blockade of *SLC9A3* transport abrogated IL-13-induced DIS formation. These data elucidate the fine tuning that the esophagus undergoes to deal with acid exposure and present a mechanism that accounts for the barrier loss in patients with EoE, at least in part, as recently reviewed.¹² The interplay of acid and *SLC9A3* with the anti-protease/protease imbalance that underscores EoE^{13,14} will likely be an active area of research inquiry.

A number of new genetic risk factors have been identified for EoE.^{15,16} Many of these risk factors are present in genes encoded for by esophageal epithelial cells, and evidence is emerging that the critical disease pathogenesis is related to epithelial cell dysfunction and loss of epithelial cell differentiation.¹³ A key dilemma remains because these genetic associations might be driven by the underlying atopic disease also present in EoE cohorts. As such, Martin et al¹⁷ aimed to disentangle the genetic components related to EoE versus those related to atopy. Using a large-scale candidate gene approach and different control groups (atopic and nonatopic), the investigators were able to show a contribution for the IL-4/kinesin family member 3A (*IL4/KIF3A*) gene, but this was driven by the atopy component. In contrast, the EoE component was associated with genetic variants in the genes *TSLP*, *CAPN14*, and *ST2*, encoding for thymic stromal lymphopoietin, calpain-14, and the IL-33 receptor, respectively. Notably, there was gene-gene interaction between variants in the *TSLP* and *IL4* genes.

The recent development of esophageal organoids¹⁸ provides a novel experimental framework to eventually decipher the mechanisms of these gene-gene interactions. The role of other recently identified EoE susceptibility loci, such as 16p13 (likely related to the *CLEC16A* gene),¹⁶ will be an important line of future research.

In addition to genetic causes, EoE susceptibility has a strong environmental component, as revealed by twin studies.¹⁹ Jensen et al²⁰ reported that early-life environmental exposures are key determinants. Among these factors, maternal fever during pregnancy, preterm labor, cesarean section, and fever in the early-life period are positive risk factors. Among all positive risk factors, exposure to proton pump inhibitors has the strongest risk, which is consistent with recent findings showing that use of these drugs is also a risk factor for food allergy.²¹ Notably, the presence of a pet dog in the first year of life was protective for the development of EoE.

Combining these collective genetic and environmental findings, another recent article examined gene-environment interactions and their effect on EoE susceptibility.²² The investigators produced evidence for an interplay of genetic variants in the *CAPN14* gene and early-life environment factors (breast-feeding and admission to the neonatal intensive care unit). In particular, breast-feeding in those with the susceptibility gene variant in *CAPN14* reduced the risk of EoE.

Krishnan et al²³ examined the relationship between EoE and congenital esophageal atresia. After finding a large increased risk for EoE in patients with surgically repaired esophageal atresia (364-fold enrichment), the investigators probed the related disease pathogenesis by subjecting the esophageal tissue to molecular profiling with the EoE Diagnostic Panel, a set of 94 transcripts associated with EoE. The EoE diagnostic panel revealed a major overlap between EoE and esophageal atresia with 25% sharing of the transcriptome, including genes involved in epithelial barrier function and type 2-associated inflammatory responses. This dysregulated baseline epithelial barrier and type 2-associated genes in esophageal atresia might explain the greater EoE prevalence in patients with esophageal atresia. In addition to its clinical implications (eg, being aware of EoE development in patients with repaired esophageal atresia), further understanding the related disease pathogenesis might open up new avenues for the treatment of both diseases.

A number of advances in the diagnosis and treatment of EoE have been described recently.²⁴ Focusing on the diagnosis, a machine learning algorithm based on esophageal transcript expression has been described.²⁵ Furthermore, levels of eosinophil progenitors in the blood show evidence of diagnostic potential for EoE.²⁶ Focusing on treatment, although it has been recognized that proton pump inhibitors can be therapeutic (rather than simply diagnostic), diet therapy is being fine-tuned from simple 6-food elimination diets to less restrictive diets.²⁷ Investigators from Spain reported a multisite prospective study in which patients with EoE underwent a 6-week 2-food-group elimination diet consisting of removal of milk and gluten-containing cereals.²⁸ After finding an approximate 40% response rate defined by histology, the investigators proposed that a step-up approach from less restrictive diets might be the best approach to treating adults and pediatric patients with EoE. The important role of milk as an eliciting food in patients with EoE might be related to the strong anti-milk IgG₄ response, as well as the strong type

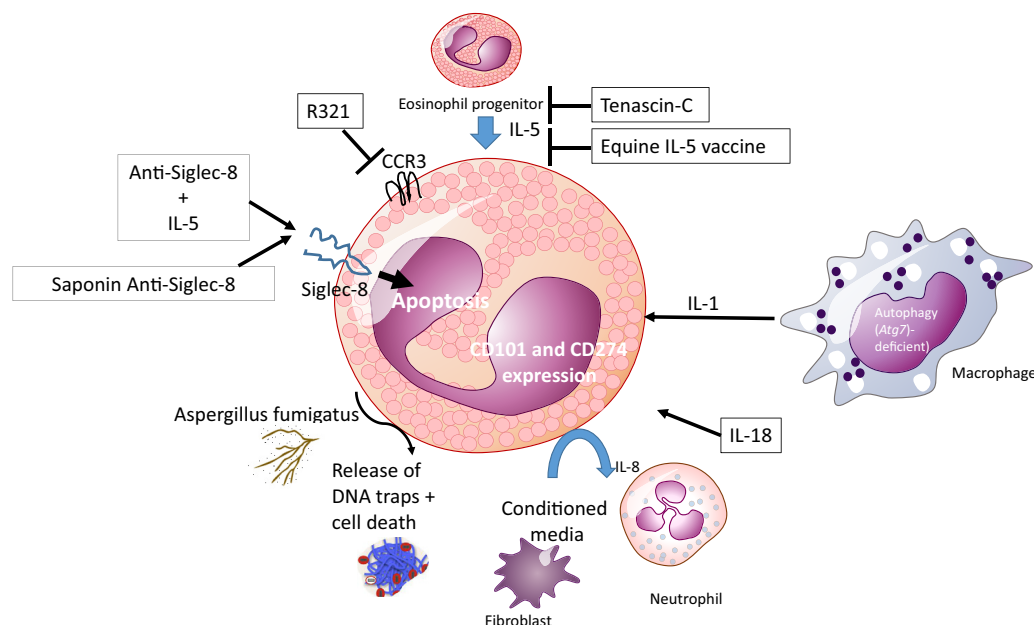


FIG 1. Schematic summary of the regulation and role of eosinophils. The figure depicts eosinophil progenitors developing into eosinophils, followed by cellular interactions with myeloid cells and fibroblasts. Regulatory, control, and effector mechanisms are shown. Partially adapted from Ueki et al (Eosinophil extracellular trap cell death–derived DNA traps: Their presence in secretions and functional attributes. *J Allergy Clin Immunol* 2016;137:258-267).

2– and regulatory T cell–dependent immunity that are characteristic of EoE.²⁹⁻³¹

CRS WITH NASAL POLYPOSIS

Recent advances in the JACI focused on eosinophilic diseases have also included CRS with nasal polyposis. In addition to eosinophils, the nasal tissue also contains abundant mast cells. Wang et al³² have reported that the aryl hydrocarbon receptor is selectively expressed by polyp mast cells. Aryl hydrocarbon receptor is a transcription factor that acts as an environmental sensor, translocating from the cytoplasm to the nucleus on engaging with its ligands, which include the tryptophan metabolite indoleamine 2,3-dioxygenase 1, tryptophan 2,3-dioxygenase. Wang et al³² showed that KYN has the capacity to activate mast cells, including their release of reactive oxygen species. These findings elucidate a novel mechanism of mast cell activation in patients with eosinophilic CRS with nasal polyposis.

EOSINOPHILS AND HOST RESPONSE

Over the past several years, there has been increasing interest in the role of eosinophils in the host response to a wide variety of microorganisms, including bacteria and fungi. Using confocal microscopy, Muniz et al³³ demonstrated the presence of *Aspergillus fumigatus* hyphae, abundant eosinophils, and eosinophil-derived extracellular DNA traps in bronchial mucus plugs from patients with allergic bronchopulmonary aspergillosis. *In vitro* studies confirmed that *A fumigatus* can induce isolated eosinophils to form extracellular DNA traps in a nonoxidative process that involves the Syk tyrosine kinase pathway and leads to eosinophil cell death without effects on fungal viability. These findings provide important new insights into the role of eosinophils in the pathogenesis of allergic bronchopulmonary aspergillosis.

NOVEL APPROACHES TO THERAPY

Currently available therapies that specifically target eosinophils are largely limited to those that bind IL-5 (mepolizumab and reslizumab) or IL-5 receptor (benralizumab). Although selective inhibition of chemokine-induced eosinophil activation and migration to the tissues has been demonstrated convincingly in mice, translation of these findings to human subjects has been problematic. To this end, Grozdanovic et al³⁴ described a novel peptide nanoparticle antagonist of CCR3 (R321) that appears to overcome many of the prior hurdles. Specifically, R321 binds both murine and human CCR3 and blocks G protein signaling through the receptor without affecting receptor internalization and degradation, which are important in preventing the development of drug tolerance. In addition to blocking chemotaxis of human eosinophils *in vitro*, R321 administered intravenously to mice significantly reduced eosinophil recruitment to the lung after allergen challenge. Whether this agent will prove more effective than prior CCR3 inhibitors in the treatment of human eosinophilic disorders remains to be seen.

Sialic acid-binding immunoglobulin-like lectin 8 (Siglec-8) is best known as an inhibitory receptor that promotes eosinophil apoptosis and inhibits mast cell activation, and antibodies to Siglec-8 are currently in development for the treatment of eosinophilic disorders.³⁵ Prior data showed that Siglec-8 induces apoptosis in IL-5–primed eosinophils in a manner dependent on mitochondrial damage and release of reactive oxygen species, suggesting that it might function as an activating receptor. Using purified human peripheral blood eosinophils, Carroll et al³⁶ demonstrate that Siglec-8 engagement leads to CD11b/CD18-dependent adhesion after IL-5 priming. This integrin-mediated adhesion is necessary for NADPH oxidase activation, reactive oxygen species generation, and eosinophil apoptosis, confirming that Siglec-8 acts uniquely as an activating receptor on IL-5–primed eosinophils and

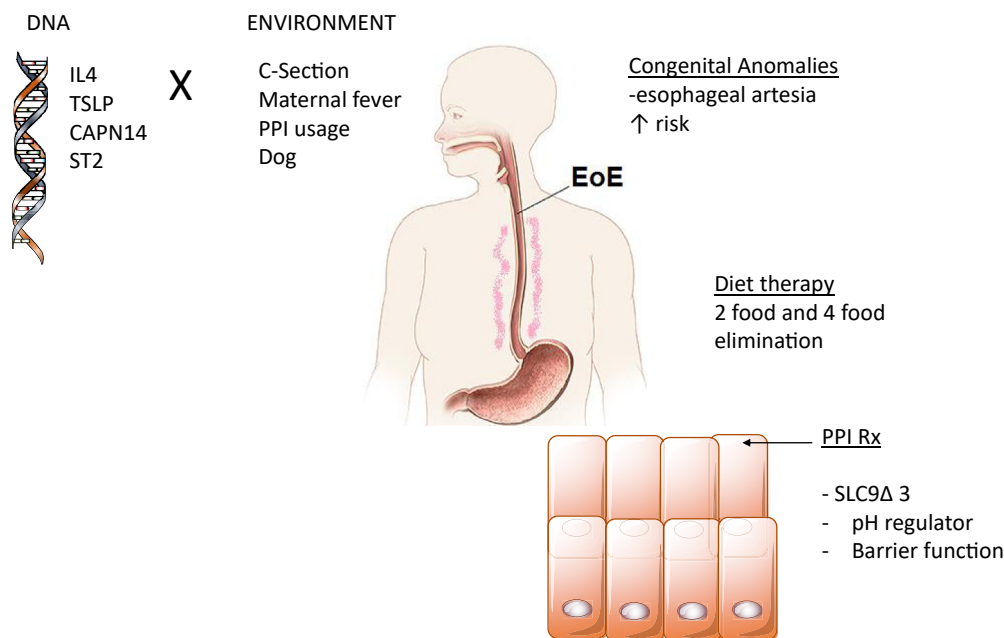


FIG 2. Breakthroughs in understanding and treating EoE. The genetic, environmental, and congenital factors that contribute to EoE susceptibility and their interaction are depicted. Therapy-related breakthroughs are shown. *PPI Rx*, Proton pump inhibitor prescription.

providing an explanation for the enhanced ability of antibodies to Siglec-8 to induce eosinophil apoptosis after IL-5 priming. In a second study exploring new technologies in drug development for eosinophilic disorders, Carroll et al³⁶ examined the potential use of Siglec-8 as a selective delivery system for toxins or other agents to eosinophils, basophils, and mast cells. After demonstrating that ligation of Siglec-8 on the cell surface led to endocytosis of the receptor to the lysosomal compartment through a mechanism distinct from that involved in shuttling of the receptor to the cell surface, the authors used saponin-conjugated antibody to Siglec-8 to effectively kill unprimed eosinophils and mast cell leukemia cells, both of which are typically resistant to the proapoptotic effects of antibody to Siglec-8.

One of the challenges in the treatment of eosinophilic disorders is the chronicity of disease and need for long-term (sometimes life-long) therapy.³⁷ To address this issue, Fettelesch-Gabriel et al³⁸ developed a therapeutic vaccine against equine IL-5 (eIL-5) to treat insect-bite hypersensitivity in horses, a chronic inflammatory form of seasonal equine allergic dermatitis associated with blood and lesional tissue eosinophilia. Horses immunized with eIL-5 coupled to virus-like particles from cucumber mosaic virus containing the tetanus toxoid universal T-cell epitope developed antibodies to eIL-5 after 2 injections that were associated with decreased blood eosinophilia and lesion size compared with those seen in control animals. The response was sustained through a second season after a single booster immunization. Of note, helminth parasite loads in the vaccinated animals were no different than in the control animals. Although long-term complications, such as autoimmunity development, were not addressed in this study, the potential application of a similar strategy in human disease is intriguing.

CONCLUSION

We hope that the readers will agree that 2018 was an exciting year for publications related to eosinophils. These studies

published in the JACI are summarized in the presented figures. Fig 1 highlights recent advances in understanding the regulation and role of eosinophils, whereas Fig 2 focuses on application of these breakthroughs in understanding diseases and developing better therapies for EoE.

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