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OXFORD JLB JOURNAL OF LEUKOCYTE BIOLOGY

Journal of Leukocyte Biology, 2024, **116**, 349–356

https://doi.org/10.1093/jleuko/qiae043
Advance access publication 20 March 2024
Review Article

Animal models of eosinophilic esophagitis

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Abstract

Eosinophilic esophagitis is a chronic inflammatory disorder of the esophagus. Over the past 25 yr, great strides have been made toward understanding its pathogenesis, in part due to studies in several types of animal models. The vast majority of these models have been characterized in mice. In this review, we summarize the histopathological features of eosinophilic esophagitis recapitulated by these animal models, as well as discuss their strengths and weaknesses.

Keywords: animal models, basal cell hyperplasia, eosinophilic esophagitis, fibrosis

1. Introduction

In eosinophilic esophagitis (EoE), chronic, immune-mediated esophageal inflammation can cause esophageal dysfunction of serious consequence. Although its clinical presentation varies with patient age, EoE often presents as failure to thrive, food intolerance/refusal, abdominal pain, and vomiting in infants and children, and as dysphagia or food impaction in adolescents and adults. Endoscopically, EoE features include edema (loss of vascularization), exudates (white plaques), furrows (vertical ridges), rings (horizontal ridges), and stricture (esophageal narrowing). EoE is differentially diagnosed from other esophageal diseases with similar symptoms by the presence of ≥15 eosinophils per high-power field (hpf) on esophageal biopsy.[1] Besides esophageal eosinophilia, other histopathological EoE characteristics include eosinophilic microabscesses, basal cell hyperplasia, spongiosis (dilated intercellular spaces), rete peg/papillae elongation, and lamina propria (LP) fibrosis.[2] Although EoE's molecular pathogenesis remains incompletely understood, it involves interplay among esophageal epithelial and immune cells (Fig. 1). EoE is putatively triggered by food antigens, such as those found in eggs, fish, milk, nuts, soy, and wheat; however, emerging evidence also implicates aeroallergens, and particularly pollen, in EoE pathogenesis.[3] Briefly, these antigens cause epithelial cells to release alarmins such as thymic stromal lymphopoietin (TSLP) and interleukin (IL)-33,[4] which activate dendritic cells (among other immune cells) that stimulate T helper (Th) 2 cells. Th2 cells produce cytokines such as IL-4, IL-5, and IL-13, which activate JAK/STAT signaling, including STAT6-mediated eotaxin-3 transcription, in epithelial cells. Eotaxins and IL-5 recruit and activate eosinophils, respectively, as well as mast cells and basophils, to the esophagus. These granulocytes secrete cytokines such as tumor necrosis factor and transforming growth factor β (TGF-β). Collectively, this inflammatory milieu promotes fibroblast-to-myofibroblast transition in the LP, which leads to increased deposition of extracellular matrix components and ultimately subepithelial fibrosis.[1,5]

2. Mouse EoE models

The array of mouse EoE models described thus far involve genetic modification and/or rely on cytokine, chemical, or antigen exposure (Table 1). While all these models result in esophageal eosinophilia, not all feature eosinophilic infiltration beyond the LP and into the epithelium. Importantly, mouse eosinophils are more difficult to identify in hematoxylin and eosin–stained tissues than human eosinophils. As such, unambiguous detection of mouse eosinophils requires antibody-based approaches, such as immunohistochemistry for the eosinophil granule proteins eosinophil peroxidase and major basic protein (MBP), or flow cytometry for the canonical eosinophil surface marker Siglec-F. Among these antibody-based approaches, immunohistochemistry is better suited for in situ detection of eosinophils and their degranulation status, whereas flow cytometry may be more appropriate for absolute quantification.[40]

Additionally, mouse strain represents another important experimental consideration for in vivo EoE studies. Although there are exceptions, BALB/c and C57BL/6 mice tend to exhibit more pronounced Th2 and Th1 immune responses, respectively, particularly in parasitic infection, food allergy, and asthma models.[41–43] Similarly, experimental EoE phenotypes may differ in severity across strains,[44] which can confound interstrain comparisons.

2.1 Antigen models

The ubiquitous fungus *Aspergillus fumigatus* predominantly causes invasive fungal lung disease in immunocompromised

Received: October 30, 2023. **Revised:** February 6, 2024. **Accepted:** February 9, 2024. **Corrected and Typeset:** March 20, 2024

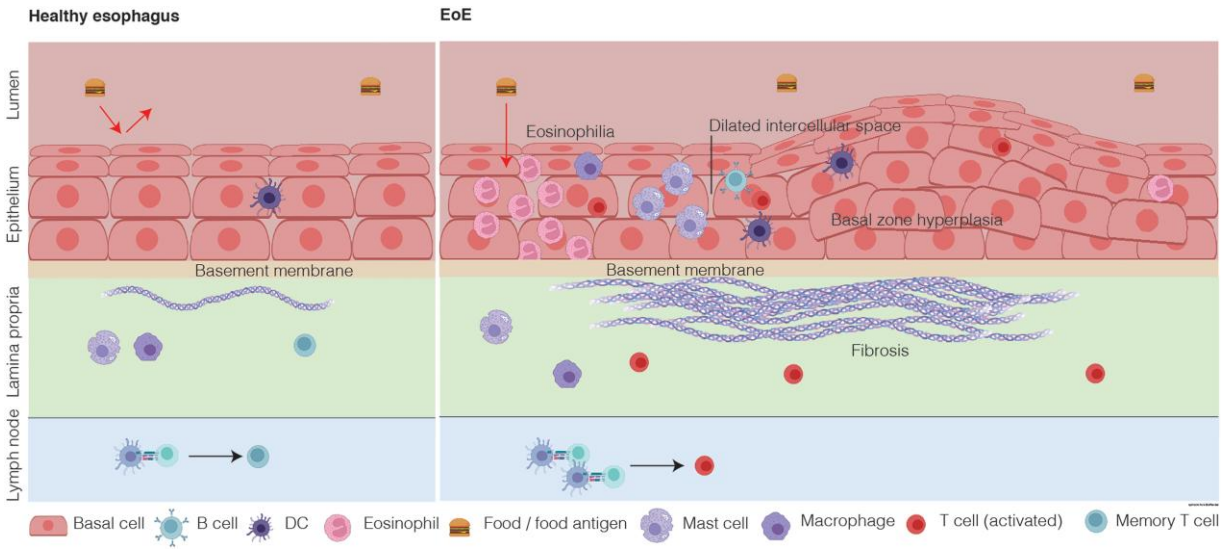

Fig. 1. Key features of EoE. Eosinophils are recruited to the esophageal epithelium, which is normally devoid of eosinophils, from the blood by chemokines resulting in eosinophilia and secretion of proinflammatory and profibrotic cytokines. Mast cells, which under homeostatic conditions largely reside in the esophageal lamina propria, are recruited to the epithelium, where they undergo increased degranulation. Dendritic cells (DCs) predominantly in the lymph nodes as well as in the mucosa present food antigens to T cells, which activates and polarizes them to Th1 and Th2 subtypes. Macrophages and esophageal epithelial cells may also function as antigen-presenting cells. Epithelial cells undergo increased proliferation resulting in basal cell hyperplasia. Moreover, chronic inflammation results in increased collagen deposition, which ultimately leads to fibrosis.

individuals; however, *A. fumigatus* can also cause allergic hypersensitivity reactions.[45] Given the well-established correlation between allergy and peripheral blood eosinophilia, Mishra et al.[6] hypothesized that repeated *A. fumigatus* exposure would elicit EoE-like phenotypes in mice. Indeed, intranasal *A. fumigatus* treatments increased eosinophil numbers in the esophagus, bronchoalveolar lavage fluid (BALF), and blood of immunocompetent mice. In this model, intranasal *A. fumigatus* delivery putatively induces experimental EoE through incidental esophageal antigen exposure, as only anesthetized, but not nonanesthetized, *A. fumigatus*–treated mice developed pulmonary and esophageal eosinophilia. Moreover, ~33% of this *A. fumigatus* was later detected in the gastrointestinal tract.[6] In further support of this proposed mechanism, a subsequent study reported the presence of fluorophore-conjugated *A. fumigatus*, detected by flow cytometry, in both the lungs and esophagus of intranasally *A. fumigatus*–treated mice.[7]

In *A. fumigatus*–treated mice, most esophageal eosinophils were localized to the LP; however, a few were interspersed throughout the epithelium. Moreover, esophagi from *A. fumigatus*–treated mice contained numerous extracellular eosinophilic granules, as evidenced by MBP immunohistochemistry as well as electron microscopy. Additionally, *A. fumigatus* treatment increased esophageal epithelial proliferation. Global IL-5 or eotaxin-1 deficiency fully or partially rescued, respectively, *A. fumigatus*–induced eosinophilia. Moreover, global IL-5 deficiency decreased esophageal epithelial proliferation to baseline levels in *A. fumigatus*–treated mice.[6] In addition to the phenotypes described previously, several other studies have reported esophageal epithelial, LP, and muscularis thickening, as well as severe pulmonary inflammation, in intranasally *A. fumigatus*–treated mice.[8–12] However, experimental EoE in intranasally *A. fumigatus*–treated mice occurred independently of several known mediators of EoE, namely IL-4, IL-13, and STAT6.[10] Rather, roles for IL-18, mast cells, macrophages, MID1, NLRP3/caspase-1 inflammasome, TRAIL, and TSLP have been demonstrated in the intranasal *A. fumigatus* EoE model.[9,11,13]

Another study from the Rothenberg group examined the efficacy of epicutaneous, rather than intranasal, sensitization to *A. fumigatus* vs ovalbumin (OVA) antigen in experimental EoE. Repeated epicutaneous sensitization with *A. fumigatus* or OVA alone provoked atopic dermatitis; however, addition of a single *A. fumigatus* or OVA intranasal challenge triggered both pulmonary and esophageal eosinophilia. Importantly, despite the increased prevalence of atopic dermatitis among EoE patients, the potential role of epicutaneous antigen sensitization in human EoE pathophysiology remains unknown. Like in the intranasal *A. fumigatus* model, MBP^+ esophageal eosinophils were largely confined to the LP and rarely found within the epithelium of OVA-treated mice. Unlike in the intranasal *A. fumigatus* model, however, these phenotypes were IL-4, IL-5, IL-13, and STAT6 dependent.[14]

Subsequent iterations of the OVA model have tested modifications to the sensitization and/or challenge protocols in terms of time frame, method, frequency, and dose. The most widely used OVA protocol entails intraperitoneal OVA sensitization (with aluminum hydroxide used as adjuvant) followed by intraesophageal OVA challenge. Using this model, several groups have observed increases in esophageal MBP^+ eosinophils (predominantly in the LP), LP collagen and fibronectin deposition, basal zone hyperplasia, and angiogenesis in OVA-treated mice, as compared with vehicle-treated mice.[16–18] Moreover, these phenotypes were partially eosinophil dependent, as they were rescued by pretreatment with an antibody against the canonical eosinophil marker Siglec-F.[16]

Another variation of the OVA protocol involves subcutaneous OVA sensitization followed by intraesophageal OVA challenge, which elicited similar esophageal changes, namely recruitment of EPX^+ cells and collagen deposition in the esophageal LP.[19,20] A third variation of the OVA protocol involves epicutaneous OVA sensitization followed by intranasal OVA challenge. In this model, basophil depletion in OVA-treated mice prevented esophageal eosinophilia in an IL-33 receptor (IL1RL1/ST2)–dependent manner. Specifically, reconstitution of basophil-depleted mice with wild-type (WT), but not $St2^{-/-}$, basophils restored esophageal eosinophil numbers. In further support of the role of the IL-33/ST2 axis in EoE, esophageal biopsies from EoE patients displayed greater IL1RL1/ST2 expression than those from healthy control subjects.[15]

Table 1. Summary of mouse models of EoE.

Model				Phenotype				Mediator	Ref.
Type	**Basis**	**Strain**	**Details**	**Eos**	**BCH**	**Fibrosis**	**Other**	**Dependent on**	
Antigen	*Aspergillus fumigatus*	BALB/c	Intranasal S → Intranasal C	LP, E	✓	✓	Degranulation	Eotaxin-1, IL-5, IL-18, MID1, TRAIL, TSLP	6–13
		BALB/c	Epicutaneous S → Intranasal C	LP, E				IL-4, IL-5, IL-13, STAT6	14
	Ovalbumin	BALB/c	Epicutaneous S → Intranasal C	LP, E				Basophils, IL-4, IL-5, IL-13, IL1RL1/ST2, STAT6	14,15
		BALB/c	Intraperitoneal S → Intraesophageal C	LP, E	✓	✓	Angiogenesis	Eosinophils	16–18
		BALB/c	Subcutaneous S → Intraesophageal C	LP, E		✓			19,20
		BALB/c	Epicutaneous S → Intragastric C	LP, E	✓		Impaction, degranulation	Basophils, TSLP	21
	Cockroach/dust mite	BALB/c	Intranasal S → Intranasal C	LP				CCR3, eotaxin-1/2, IL-5	22
	Corn/peanut	BALB/c	Intraperitoneal S → Intranasal or Intragastric C	LP, E			Degranulation	CD1d, eoxtaxin-1/2	23
	Peanut	BALB/c	Intranasal S → Intranasal C	LP	✓	✓	Impaction	Eosinophils	24
Chemical	Oxazolone	C57BL/6	Epicutaneous S → Intraesophageal C	LP, E	✓	✓		IL-13, IL-13Rα1	25
Genetic	IL-5	BALB/c	*CD2-Il5*	LP				Eotaxin-1	26,27
		BALB/c	*Fabpi-Il5*	LP					27
	IL-5 + Oxazolone	C57BL/6	*EBV-ED-L2-Il5* Epicutaneous S → Intraesophageal C	LP, E	✓	✓	Degranulation, steroid-responsive		28
	IL-13	C57BL/6	*Krt5-rtTA; tetO-Il13*	✓	✓				29
		FVB/n	*Cc10-rtTA; tetO-Il13*	LP, E	✓	✓		Eotaxin-1	30,31
	IL-18	C57BL/6	*Cc10-rtTA; tetO-Il18*	LP, E		✓			32
	IL-33	C57BL/6	*EBV-ED-L2-Il33*	LP, E	✓	✓			33
		C57BL/6	*EBV-ED-L2-rtTA; tetO-Il33*	LP, E	✓				34
	NIK	C57BL/6	$Nik^{-/-}$	LP, E	✓	✓	Degranulation	$CD4^+$ T cells	35,36
	TGF–β1	129S	$Tgfb1^{M318R/+}$	LP, E	✓		Dilation, impaction, degranulation		37
Exogenous	IL-13	BALB/c	Intratracheal or intranasal T	LP, E	✓			Eotaxin-1, IL-5, STAT6	38
	IL-18	BALB/c	Intranasal T	✓				CD1d, IL-5	32
	IL-33	C57BL/6	Intraperitoneal T	LP, E	✓			IL-13	39

Abbreviations: BCH = basal cell hyperplasia; C = challenge; Eos = esophageal eosinophilia; E = epithelium; LP = lamina propria; S = sensitization; T = treatment.

In a modification to these OVA protocols, Noti et al.[21] demonstrated that simultaneous, epicutaneous application of the vitamin D analog calcipotriol (MC903) and OVA, followed by 2 intragastric OVA challenges, dramatically increased eosinophil numbers and basal cell hyperplasia in the esophagus, as compared with either MC903 or OVA sensitization alone. Unlike in other OVA models, combinatorial OVA and MC903 sensitization promoted infiltration of Siglec-F$^+$ eosinophils into the esophageal epithelium, in addition to the LP. Further ultrastructural analysis revealed evidence of eosinophilic degranulation. Moreover, when these researchers subjected mice to multiple intragastric OVA challenges (7 total) to recapitulate chronic inflammation, approximately 30% of the mice exhibited evidence of food impaction, a particularly devastating consequence of EoE. Both these acute and chronic EoE-like phenotypes were basophil and TSLP dependent, yet IgE independent,[21] in agreement with clinical trials that have revealed little benefit of anti-IgE therapy for EoE patients.[46–49] In further clinical support of these results, esophageal biopsies from pediatric patients with active EoE (defined as ≥15 eosinophils/hpf) possessed greater numbers of basophils as well as higher TSLP expression than those from pediatric patients with inactive EoE (defined as <15 eosinophils/hpf and prior history of active EoE) or healthy control subjects.[21] Moreover, when these patients were further stratified by TSLP genotype, those homozygous or heterozygous for a gain-of-function polymorphism associated with EoE risk[50] displayed higher basophil frequencies in their peripheral blood mononuclear cells, as compared with those without the polymorphism.[21]

In addition to *A. fumigatus* and OVA, various other allergens have been tested for their ability to induce mouse experimental EoE. For instance, repeated treatment with cockroach or dust mite, but not cat or dog, allergen extract increased eosinophil numbers in the BALF, blood, and esophagus. In the esophagus, MBP$^+$ eosinophils were almost exclusively detected within the LP of cockroach or dust mite extract–treated mice. This esophageal eosinophilia was rescued by global IL-5, eotaxin-1/2, or CCR3 deficiency. However, this study did not further assess EoE-associated histopathology.[22]

Similarly, intraperitoneal sensitization followed by intranasal or intragastric challenge to peanut, and, to a lesser extent, corn extract increased eosinophil numbers in the BALF and esophagus. In the esophagus, MBP$^+$ eosinophils were observed both throughout the LP and within the epithelium, and particularly in the basal epithelial layer, of peanut or corn extract–treated mice. Additionally, these esophageal eosinophils exhibited evidence of degranulation, namely, extracellular MBP$^+$ granules. Pulmonary and esophageal eosinophilia in this model could be rescued by global eotaxin-1/2 or CD1d deficiency.[7,23]

Another group replicated these findings in an intranasal peanut extract sensitization/challenge model. Beyond esophageal LP eosinophilia, their model recapitulated other features of EoE-related esophageal remodeling, namely increased fibronectin deposition, food impaction, and basal cell hyperplasia. Moreover, eosinophil depletion via administration of an anti-Siglec-F antibody-encoding adeno-associated virus ameliorated these phenotypes.[24]

2.2 Chemical models

More recent work has established oxazolone (OXA) as a potent inducer of EoE-like phenotypes in mice. Specifically, epicutaneous OXA sensitization followed by intraesophageal OXA challenge recruited numerous MBP$^+$ eosinophils to the esophageal epithelium and LP, with concomitant increases in epithelial and LP thickness attributed to basal cell hyperplasia and collagen deposition, respectively. Moreover, transcriptomic analysis revealed numerous transcripts similarly enriched in both OXA-treated mice and human EoE patients, including many involved in immune response and cell proliferation. Whole-body or esophageal epithelial-specific IL13Rα1 deficiency, as well as antibody-mediated IL-13 neutralization, completely abrogated EoE-like phenotypes after OXA treatment.[25]

2.3 Genetic models

The eosinophilic effects of transgenic (Tg) IL-5 overexpression, under control of the human lymphocyte promoter CD2, were first described in 1990. CD2-Il5 Tg mice exhibited greater numbers of eosinophils in the blood, bone marrow (BM), lungs, mesenteric lymph nodes, peritoneal exudate, small intestinal LP and Peyer's patches, and spleen as compared with WT mice.[26] Although this initial study did not examine the esophagus, Mishra et al.[27] later reported that CD2-Il5 Tg mice developed esophageal eosinophilia in a partially eotaxin-1–dependent manner. IL-5 overexpression under control of the rat intestine promoter Fabpi or IL-5 treatment elicited a similar phenotype, i.e. recruitment of MBP$^+$ eosinophils to the esophageal LP, near the basal cell layer.[27] More recently, this group discovered that intravenous IL-18 administration exacerbated esophageal intraepithelial eosinophilia as well as eosinophilic degranulation in the CD2-Il5 Tg model.[13] Notably, these early IL-5–driven models failed to reproduce other histopathological hallmarks of EoE (e.g. hyperplasia, fibrosis) besides esophageal eosinophilia.

To address these limitations, another iteration of the IL-5–driven model fuses elements of both genetic and chemical models: Tg IL-5 overexpression under control of the squamous cell–specific EBV-ED-L2 promoter, combined with epicutaneous OXA sensitization followed by intragastric OXA challenge. Like CD2-Il5 Tg and Fabpi-Il5 Tg mice, EBV-ED-L2-Il5 Tg mice possessed greater numbers of eosinophils in the blood, BM, esophagus, and spleen at baseline, as compared with WT mice. Moreover, OXA-treated EBV-ED-L2-Il5 Tg mice displayed other histopathological manifestations of EoE, namely numerous MBP$^+$ intraepithelial and LP eosinophils, basal cell hyperplasia, eosinophilic microabscesses and degranulation, epithelial inflammation, and LP thickening. Additionally, esophageal eosinophils isolated from OXA-treated EBV-ED-L2-Il5 Tg mice more closely resembled mature, tissue-resident granulocytes (i.e. expressed higher levels of cell-surface CCR3 and Ly6C) than those isolated from vehicle-treated mice. Last, intraperitoneal administration of the corticosteroid dexamethasone ameliorated these phenotypes.[28]

Besides IL-5, transgenic overexpression of other cytokines, namely IL-13, IL-18, and IL-33, also induces experimental EoE. For instance, doxycycline-induced IL-13 overexpression under control of the basal progenitor–specific Krt5 promoter recruited eosinophils to the esophagus, promoted basal cell proliferation, and inhibited basal cell differentiation.[29] Similarly, doxycycline-induced IL-13 overexpression under control of the airway epithelial cell-specific Cc10 promoter led to accumulation of MBP$^+$ eosinophils as well as thickening throughout the esophageal epithelium and LP.[30] Moreover, ciprofloxacin-mediated inhibition of the minichromosome maintenance helicase, which is essential for DNA replication, prevented basal cell hyperplasia and intercellular edema in this model.[31]

Similarly, doxycycline-induced, Cc10-driven IL-18 overexpression recruited eosinophils to the esophageal epithelium and LP as well as promoted collagen deposition in the esophageal epithelium, LP, and muscularis mucosa.[32] As with IL-13 and IL-18

overexpression, squamous cell–specific IL-33 overexpression (EBV-ED-L2 driven) elicited eosinophil and Th2 cell infiltration into the esophagus, as well as esophageal fibrosis and hyperplasia.[33] Similar results were observed in a doxycycline-inducible model.[34]

In addition to these cytokine models, 2 other genetic EoE mouse models have been described: $Nik^{-/-}$ and $Tgfb1^{M318R/+}$. NF-κB–inducing kinase (NIK) (MAP3K14) is essential for noncanonical NF-κB signaling, which has been reported to be dysregulated in EoE patients.[35,51] $Nik^{-/-}$ mice spontaneously develop severe, multiorgan eosinophilia and inflammation, particularly in the liver, lung, skin, and spleen, by 12 wk of age. Notably, these phenotypes were $CD4^+$ T cell dependent, as intercross of $Nik^{-/-}$ mice with either $Rag1^{-/-}$ mice, which lack T and B cells, or $MhcII^{-/-}$ mice, which lack $CD4^+$ T cells, completely abolished systemic hypereosinophilic disease.[36] A subsequent study revealed numerous EoE-like esophageal phenotypes in $Nik^{-/-}$ mice, namely marked infiltration of MBP^+ eosinophils into the LP as well as the epithelium (with occasional microabscess formation), increased deposition of collagen into the LP, eosinophilic degranulation, and basal cell hyperplasia. Moreover, $Nik^{-/-}$ esophagus exhibited greater expression of the Th2 cytokines Il4 and l13; the Th1 cytokines Il1b, Ifng, and Tnf; and the alarmin Tslp as compared with $Nik^{+/+}$ esophagus.[35]

$Tgfb1^{M318R}$ is a germline, homozygous lethal mutation that abolishes TGF-β1's kinase activity. $Tgfb1^{M318R/+}$ mice spontaneously developed numerous gross and histopathological characteristics of EoE by 6 mo of age, namely esophageal dilation, food impaction, basal cell hyperplasia, elongated rete pegs, and MBP^+ intraepithelial and LP eosinophils, often degranulated and/or in microabscesses. Moreover, $Tgfb1^{M318R/+}$ esophagi contained more eosinophils, myeloid antigen-presenting cells, mast cells, type 2 innate lymphoid cells, and T cells than WT esophagi. Additionally, this group compared the transcriptomes of $Tgfb1^{M318R/+}$ esophagi and human EoE biopsies representative of the 3 different EoE endotypes: EoEe1, EoEe2, and EoEe3. EoEe1 is associated with steroid sensitivity, normal esophageal appearance on endoscopy, and atopy. "Inflammatory" EoEe2 is typically steroid refractory and pediatric onset, whereas "fibrostenotic" EoEe3 is generally adult onset.[52] These analyses revealed that the $Tgfb1^{M318R/+}$ esophageal transcriptional profile correlated best with that of EoEe2. Interestingly, these phenotypes were not lymphocyte dependent, as neither RAG2 deficiency nor WT BM transplantation prevented experimental EoE development in $Tgfb1^{M318R/+}$ mice.[37]

2.4 Exogenous models

Besides antigen or chemical exposure and genetic modification, exogenous cytokine treatment has also been utilized for EoE models. For example, intratracheal or intranasal IL-13 administration induced esophageal and pulmonary eosinophilia in a dose-dependent manner, as well as esophageal basal cell hyperplasia. In the esophagus, MBP^+ eosinophils were predominantly observed in the LP, and rarely in the epithelium. These phenotypes were fully rescued by global STAT6 or IL-5 deficiency and partially rescued by global eotaxin-1 deficiency.[10,38] Similarly, intranasal IL-18 administration triggered dose-dependent eosinophil and mast cell esophageal infiltration, which could be rescued by global IL-5 or CD1d deficiency. However, this study did not report any associated esophageal remodeling.[32] Last, intraperitoneal IL-33 administration elicited numerous EoE-associated esophageal pathologies, including basal cell hyperplasia, eosinophil and leukocyte infiltration into the epithelium and LP, loss of cell polarity, muscle hypoplasia, and transmural inflammation. Notably, global IL-13 deficiency partially ameliorated the effects of IL-33 treatment.[39]

3. Other animal EoE models

Although the vast majority of EoE models were developed in mice, EoE models have also been developed in guinea pigs and swine. The major advantage of EoE modeling in larger animals is the ability to perform serial upper endoscopy, which is technically infeasible in mice with currently available equipment. Guinea pigs subjected to intraperitoneal OVA sensitization followed by intranasal OVA challenge displayed esophageal eosinophilia but no other epithelial structural changes.[53–56] The swine model uses the food antigen hen egg white protein (HEWP), of which OVA is a major component. Swine subjected to intraperitoneal HEWP sensitization followed by oral HEWP challenge developed esophageal basal cell hyperplasia, eosinophilia, fibrosis, and microabscesses. Furthermore, HEWP-treated swine exhibited endoscopic characteristics of EoE, including white exudates and linear furrows.[57,58]

4. Concluding remarks

Numerous experimental EoE models have been developed over the last 3 decades, largely for use in mice. While all these models induce esophageal eosinophilia to varying extents, not all recapitulate other histopathological and gross features of EoE-associated tissue remodeling. For instance, most, but not all, experimental EoE protocols give rise to basal cell hyperplasia. Even fewer give rise to fibrosis, whose functional consequences remain largely uninvestigated in vivo. Although they are well described and widely used, antigen models tend to yield less robust and more strain-dependent phenotypes than chemical, exogenous, or genetic models. While less characterized, the chemical and exogenous models benefit from simpler experimental design, and, in the case of the exogenous models, the shortest experimental protocols. Despite their relative complexity, many of the genetic models offer unparalleled temporal- and tissue-specific control of transgene expression, as evidenced by the preponderance of such models at the 12th Biennial Symposium of the International Eosinophil Society. Future research efforts should strive to refine the current models, as well as develop additional models that better recapitulate EoE pathogenesis—particularly its chronic consequences.

Author Contributions

J.M.P. drafted and revised the manuscript. J.J. designed the figure. J.J., M.A.B., and Y.A.C. edited the manuscript. J.M.P., J.J., M.A.B., and Y.A.C. reviewed and approved the final version.

Funding

Y.A.C. is supported by a U.S. Department of Veterans Affairs Award (IK2BX004648). J.J. is supported by an Academy Ter Meulen Grant from the Royal Netherlands Academy of Arts and Sciences as well as a Cultural Foundation Grant from the Prince Bernhard Cultural Foundation. M.A.B. is supported by the Vanderbilt Supporting Careers in Research for Interventional Physicians and Surgeons Scholar Fund.

Conflict of interest statement. None declared.

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