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A DOUBLE-EDGED SWORD: EOSINOPHILS AND THE PATHOGENESIS OF ALLERGIC AND AUTOIMMUNE DISEASES

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Abstract

Traditionally, eosinophils are regarded as terminally differentiated cells that play an essential role in host defense against helminths. However, the role of eosinophils has been redefined based on recent advances in transcriptomics and single-cell RNA sequencing (scRNA-seq) between 2015 and 2026. Eosinophils are regarded as pleiotropic immunomodulatory architects that play an essential role in both homeostatic regulation and tissue destruction in disease. The discovery of eosinophils, comprising resident homeostatic (iEos) and inflammatory (rEos) cells, has resolved the long-standing paradox of their functional heterogeneity. The essential regulators of eosinophils include the transcription factor GATA-1, which is involved in eosinophil lineage commitment, and the IL-5/JAK1/STAT5 axis, which is involved in terminal differentiation and survival. Eosinophils play an essential role in the pathogenesis of diseases through their effector functions, which include the release of four main cationic proteins, MBP-1, ECP, EPO, and EDN, and eosinophil extracellular traps (EETs). Severe Eosinophilic Asthma affects about half of patients with severe asthma, and Eosinophilic Esophagitis (EOE) is an emerging condition that has increased many fold in incidence since the mid-2000s, leading to dysphagia and fibrosis in the esophagus. Autoimmune Disorders, like Eosinophilic Granulomatosis with Polyangiitis (EGPA) and Bullous Pemphigoid (BP), are characterized by eosinophils, leading to organ-specific destructive pathology and vasculitis. The biotherapeutic revolution in the management of eosinophilic disorders, targeting IL-5 (mepolizumab, reslizumab), IL-5Rα (benralizumab), and IL-4Rα (dupilumab), has been significant. Precision medicine, based on combined biomarkers like ECP, EDN, and their ratios like rEos/iEos, is being developed to tackle the about one third non-responder rates seen with current therapies. Eosinophil biology represents a complex interplay between helpful immune regulation and unhelpful tissue damage. Future therapeutic success will be based on precision medicine approaches to tailor therapy to particular disease endotypes and the particular molecular signature of particular subpopulations of eosinophils.

INTRODUCTION

Eosinophils are granulocytic leukocytes of the myeloid lineage, characterized by their bilobed nucleus and large, eosin-stained secondary granules packed with highly cationic effector proteins. These cells represent approximately 1–5% of circulating leukocytes in healthy adults, with absolute blood counts normally maintained between 100 and 500 cells/μL under homeostatic conditions (Kita, 2011, cited in Rosenberg et al., 2013). For much of the 20th century, it was proposed that eosinophils played a unique immunological role: by generating terminal effectors in the host's defense against helminthic invasions. This antiparasitic function, mediated by Fc receptor-triggered degranulation of cytotoxic granule proteins on antibody-coated parasite surfaces, constituted the fundamental frame of reference within which research on eosinophils was largely conducted until the mid-2000s, when this reductionist view became undeniable when advances in transcriptomics, proteomics, and the development of biological therapies in the period 2015-2026 revealed the leukocyte to have extraordinary immunological versatility, with functions that include tissue homeostasis, adaptive immune regulation, allergic inflammation, and autoimmune destruction (Rosenberg et al., 2013; Griseri et al., 2020).

The shift from a purely effector-focused to a pluralistic view of eosinophil biology is greatly accelerated by the publication of important single-cell RNA sequencing (scRNA-seq) studies between 2019 and 2024. This research distinguished at least two transcriptionally and functionally distinct eosinophil subsets: eosinophils recruited for inflammation (rEos) and resident homeostatic eosinophils (iEos). Their unique gene expression signature has helped solve long-standing paradoxes in eosinophil biology, such as why complete eosinophil depletion does not always, and sometimes even worsens, clinical outcome (Zhu et al., 2023; Griseri et al., 2020). The discovery of homeostatic eosinophils as required residents in the GI lamina propria, whose functions are supportive of IgA, the microbiome, and metabolism, established that eosinophil biology indeed contains an orthogonal dimension that is completely separate and distinct from the inflammatory response paradigm (Chu et al., 2014; Jung and Rothenberg, 2017).

Current research in eosinophils is at the crossroads of precision immunology and clinical translation. In the last seven years, between 2015 and 2026, six biologics that target eosinophils either directly or indirectly have been approved, namely, mepolizumab (2015), reslizumab (2016), benralizumab (2017), dupilumab (2022 for eosinophilic esophagitis), tezepelumab (2021), and lirenteliumab (phase 3, 2023-2025). The clinical spectrum of eosinophils has also been extended to include autoimmune diseases, particularly eosinophilic granulomatosis and polyangiitis (EGPA) and bullous pemphigoid (BP) (Wechsler et al., 2017; Menzies-Gow et al., 2021). This revolution in eosinophil therapeutics validated the eosinophil-centric pathogenic hypothesis for certain endotypes of disease, and at the same time, underscored the biological heterogeneity underlying partial response and nonresponse, only precision medicine can fully address (Canonica et al., 2021).

The classic model of eosinophils as terminally differentiated effector cells recruited to inflamed tissues, degranulated, and eliminated has been thoroughly revised with data collected mainly between 2015 and 2026. The modern eosinophil is now recognized as a pleiotropic immunomodulatory cell capable of presenting antigens to T lymphocytes through constitutive expression of MHC class II and costimulatory molecules (CD80, CD86), which secrete cytokines and chemokines involved in the amplification of inflammation and immunosuppression, interact with ILC2 and mast cells, sensitize sensory nerves by secreting nerve growth factor (NGF), facilitate tissue repair, and regulate metabolism in adipose tissue (Jacobsen et al., 2012, Kolbeck et al., 2010; This multiplicity functional requires a conceptual framework in which the fate of eosinophil effectors is understood as context-dependent (determined by tissue microenvironment, cytokine milieu, surface receptor expression, and activation history) rather than fixed by lineage commitment.

Among the most important reconceptualizations of the past decade is the recognition of the constitutive role of eosinophils in the gastrointestinal lamina propria, thymus, and adipose tissue under nonallergic physiological conditions, where they exert homeostatic rather than inflammatory functions. Chu et al. (2014) showed that intestinal eosinophils, through APRIL and BAFF secretion, are essential for IgA plasma cell survival and mucosal IgA production, an observation confirmed by the approximately 60–70% reduction in intestinal IgA-secreting plasma cells in eosinophilia-deficient (ΔdblGATA) mice. Subsequent studies confirmed that these tissue-resident eosinophils express a transcriptional phenotype (high CD62L, high Siglec-8, high BCL-2, and low expression of granular proteins) that is qualitatively different from circulating inflammatory eosinophils and is inconsistent with the classical degranulation paradigm (Griseri et al., 2020; Zhu et al., 2020).

Transcriptomic characterizations of single-cell eosinophils, published between 2019 and 2024, provide the most precise molecular-level evidence of functional heterogeneity. Zhu et al. (2023), using single-cell RNA sequencing (scRNA-seq) in eosinophils from human nasal polyps, identified two distinct transcriptome clusters corresponding to inflammatory states (rEos: high expression of MBP1, ECP, EPO, and EDN; enrichment in degranulation genes) and homeostatic states (iEos: high expression of IL-10, TGF-β1, BCL-2, and lipid metabolism genes). The rEos/iEos ratio correlates with the severity of muscle inflammation and, importantly, with the response to steroids. Parallel findings in murine models of asthma, EE, and colitis suggest that the iEos-rEos transition is reversible and driven by specific cytokine inputs (IL-5 and IL-33 promote rEos polarization; TSLP and IL-4 maintain iEos identity), providing potential targets for selective therapeutic interventions of these subsets that maintain homeostatic eosinophil populations (Griseri et al., 2020; Jung and Rothenberg, 2017).

The regulatory capacity of eosinophils extends to their role in modulating adaptive immune responses. Eosinophils that process and present antigens can induce both Th2 and regulatory T cell (Treg) responses, depending on the costimulatory context and cytokines present at the time of antigen presentation. Eosinophil-derived TGF-β1 is a well-known factor in fibrotic remodeling (pathological) and the concomitant induction of peripheral (regulatory) Tregs; this dual function highlights the tissue-dependent nature of eosinophil immunomodulation (Jacobsen et al., 2012; Salter et al., 2021). Understanding which signals direct eosinophils toward regulatory or destructive effector responses represents one of the most important unresolved questions from a clinical perspective in modern eosinophil biology.

Clinical burden and epidemiological context

The epidemiological landscape of eosinophil-associated disease has changed dramatically in the last decade since 2015, with the increasing incidence of multiple conditions, broadening of disease definitions based on precise characterization of biomarkers, and increasing recognition of the multisystem burden imposed by chronic eosinophilic inflammation. Severe eosinophilic asthma, defined by the Global Initiative for Asthma (GINA, 2024) as asthma that is not controlled despite treatment with high-dose inhaled corticosteroids/long-acting beta-2 agonists (ICS/LABA), with a blood eosinophil count ≥ 150–300 cells/μL or sputum eosinophilia ≥ 3%, accounts for approximately 50% of severe asthma cases worldwide and produces proportional healthcare costs, significant emergency department use, and significant morbidity associated with chronic dependence on oral corticosteroids, including osteoporosis, diabetes, adrenal insufficiency, cardiovascular disease, and cataracts (Canonica et al.,, and cataracts (Canonica et al.,,) 2021, GINA, 2024). The annual economic burden of severe asthma in high-income countries exceeds US$80 billion if direct medical costs and productivity losses are added together (Canonica et al., 2021).

Eosinophilic esophagitis experienced a significant epidemiological increase between 2015 and 2026. Its incidence in North America and Northern Europe is now estimated at 40 to 90 cases per 100,000 person-years, representing a 10- to 15-fold

increase compared with baseline populations since the mid-2000s. The point prevalence approaches 1 case per 2,000 people in affected regions, which, according to Dellon and Hirano (2018), corresponds to a truly emerging disease and not just an artifact related to changing diagnostic recognition. Dysphagia, food blockages, esophageal strictures, and the resulting dietary restrictions have significant consequences for quality of life and nutrition, especially in children and young people, the most affected populations (Dellon and Hirano, 2018; Furuta and Katzka, 2015).

Atopic dermatitis affects between 10% and 20% of children and 2% and 4% of adults worldwide. Moderate to severe forms are associated with eosinophilia in the blood and tissues, a key factor in skin barrier dysfunction, neurogenic inflammation, and chronic itching, which is the main symptom (Kapur et al., 2018). An analysis of data from the 2022 Global Burden of Disease study ranked atopic dermatitis as the leading cause of death among skin diseases worldwide, with a higher number of disability-adjusted life years (DALYs) lost than psoriasis. These include sleep disorders, psychiatric co-morbidities, and productivity losses associated with these moderate to severe forms. Bullous pemphigoid, whose increase has been reported with demographic aging, the use of DPP-4 inhibitors, and immunotherapies with immune checkpoint inhibitors, has a 15–30% 1-year mortality rate in elderly patients, mainly due to the toxicity of immunosuppressive therapies, fully justifying the use of eosinophil-targeted therapy (Schmidt and Zillikens, 2013). Eosinophilic granulomatosis with polyangiitis (EGPA), although rare (prevalence of 10–14 cases per million), leads to severe multiorgan morbidity, including cardiomyopathy (16–40% of patients), multiple mononeuropathy, and glomerulonephritis, with cardiac involvement determining the prognosis (Vaglio et al., 2013).

Precision Medicine Requirements

The era of biotherapies, which began for eosinophilic disease with the first market approval of mepolizumab in 2015, has transformed clinical management, highlighting the biological heterogeneity that limits universal therapeutic efficacy. Anti-IL-5 biotherapies reduce the rate of severe asthma exacerbations by approximately 50% and allow for a reduction in the dose of oral corticosteroids by approximately 50% to 65% in patients who respond to treatment (Pavord et al., 2012; Nair et al., 2017). Blockade of IL-4Rα/IL-13Rα1 receptors with dupilumab induces histological remission (≤ 6 eosinophils/high-resolution field) in approximately 60% of patients with eosinophilic esophagitis (Dellon et al., 2022). Mepolizumab induces remission in approximately 28% of patients with eosinophilic granulomatosis and polyangiitis (EGPA) at week 52, compared with 3% with standard therapy (Wechsler et al., 2017). These clinically important findings are likely to modify clinical practice and validate eosinophil-centric pathogenic hypotheses for defined disease endotypes.

However, the non-response and partial response rates of 20 to 40% observed for all approved biotherapies suggest that the biological endpoint (eosinophil count above a certain threshold) is an insufficient predictor of the underlying pathological mechanism (Brussels et al., 2013; Canonica et al., 2021). Precision medicine approaches including composite biomarker signatures (blood eosinophil count + FeNO + IgE + periostin), eosinophil subpopulation profiles (rEos vs iEos ratios by CD62L/Siglec-8 flow cytometry), multi-omic disease endotyping, and machine learning-based response prediction models have outperformed single biomarker approaches in retrospective analyses of large clinical trial data and are undergoing prospective validation (Menzies-Gow et al., 2021; Zhu et al., 2023). To fulfill the promise of eosinophil-targeted precision medicine, we will need to proactively integrate multi-omics stratification into prospective trial designs, foster interdisciplinary collaboration involving allergology, rheumatology, gastroenterology, and dermatology, and invest in the biomarker infrastructure needed to routinely individualize therapeutic selection in clinical practice.

Biology and Mechanisms of Eosinophil Activation

Eosinophil differentiation into CD34 + hematopoietic pluripotent stem cells (HSCs) occurs according to a hierarchical myeloid differentiation program, in which lineage commitment to the eosinophil progenitor (EoP) stage is regulated by a network of transcription factors centered on the GATA-1 binding protein. Current knowledge, refined by mass cytometry and single-cell RNA sequencing (scRNA-seq) studies published between 2019 and 2024, recognizes at least four functionally distinct progenitor stages in eosinophil ontogeny: common myeloid progenitor (CMP); granulocytic-monocytic progenitor (GMP); eosinophil/basophil progenitor (EoP/BaP); and committed eosinophil progenitor (cEoP), the latter can now be seen in peripheral blood as a circulating progenitor population (Lin $^{-}$ CD34 $^{+}$ IL-5Rα $^{+}$) with direct clinical relevance as an early biomarker of type 2 inflammatory activation (Salter et al., 2021).

GATA-1 remains a key non-redundant regulator of eosinophil adhesion, as clearly demonstrated by the selective and complete ablation of eosinophil development in murine models by ΔdblGATA knock-in. Between 2015 and 2026, chromatin immunoprecipitation sequencing (ChIP-seq) analyzed mapped GATA-1 binding sites across the eosinophil genome, identifying lineage-specific enhancer regions that control transcription of MBP1, EPO, ECP, and CCR3 genes, accessible to eosinophil progenitors but epigenetically repressed in other myeloid lineages (Salter et al., 2021; Griseri et al., 2020). GATA-2 interacts with GATA-1 during progenitor migration and shares regulatory binding sites with many eosinophil-specific enhancers. CCAAT/enhancer-binding protein epsilon (C/EBPε) controls the synthesis of terminal granule proteins; and PU.1, whose progressive downregulation is required for eosinophil commitment, acts as an antagonistic transcription factor whose sustained activity diverts progenitors to monocytic fates (Griseri et al., 2020).

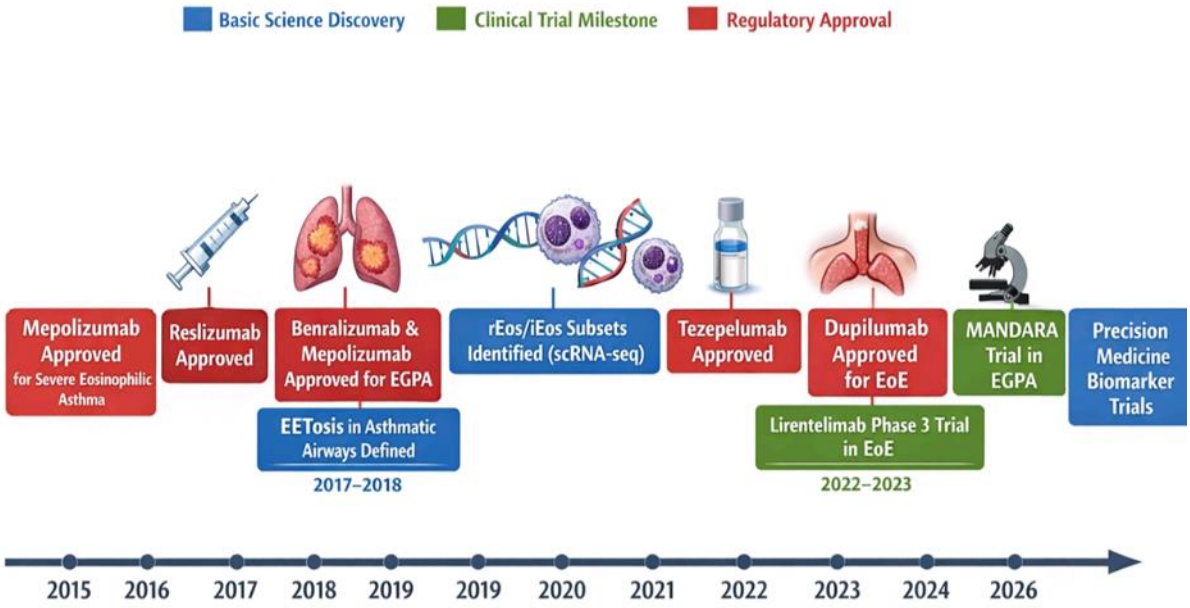

Figure 1. Timeline of key stages of eosinophil biology and its clinical application

Interleukin-5 (IL-5), which signals through the heterodimeric IL-5Rα/βc receptor via the JAK1/JAK2→STAT5 and PI3K/AKT cascades, remains a highly lineage-selective eosinophil cytokine: it promotes terminal differentiation of compromised EoP, prolongs the survival of mature eosinophils by suppressing apoptosis, induces surface expression of CCR3 and FcεRII for tissue recruitment and further activation, and mobilizes eosinophil depots from the bone marrow to the

peripheral blood during type 2 inflammatory responses (Molfino et al., 2012, as reviewed in Canonica et al., 2012). 2021). The IL-5Rα survival signal downstream of JAK1/STAT5 is a direct molecular target of the ADCC mechanism of benralizumab: binding of the anti-IL-5Rα antibody recruits NK cells and macrophages expressing FcγRIIIa, induces eosinophil apoptosis, and achieves a >90% depletion of peripheral blood eosinophils within 24 to 48 hours after the first dose, much faster and more complete than the approximately 80% depletion achieved by neutralization of IL-5 with mepolizumab or reslizumab (Kolbeck et al., 2010; Bleecker et al., 2016).

The major development in the period 2019–2024 is the discovery of circulating eosinophil precursors (c-EoP) as an early, rather than late, biomarker of eosinophil activation. Salter et al. (2021) demonstrated, in a prospective cohort of 78 asthmatic patients and 22 healthy control subjects that the frequency of c-EoP in peripheral blood correlated with the evolution of blood eosinophil levels during asthma exacerbations, which is significantly higher than the blood eosinophil level measured at the same time. An additional finding from scRNA-seq studies of intestinal biopsies identified a mucosal eosinophil progenitor (m-EoP) that locally reconstitutes homeostatic gastrointestinal eosinophils from tissue progenitors, which may explain the persistence of intestinal eosinophilia in other patients who achieve systemic IL-5 blockade and establish local progenitor dynamics as a relevant therapeutic target in eosinophilic gastrointestinal diseases (Zhu et al., 2023).

The directed migration of eosinophils from peripheral blood to inflamed tissues is orchestrated by a sequential cascade of adhesion and chemotaxis: capture by E/P-selectin and PSGL-1; strong adhesion by integrin β2 (CD18/CD11b, Mac-1), ICAM-1, and VCAM-1 (both strongly activated by IL-4 and IL-13 on endothelial cells); and directed migration, mediated by the chemokine receptor CC3 (CCR3), along tissue eotaxin gradients. CCR3, highly expressed on the surface of mature eosinophils with approximately 25,000 receptors per cell and completely absent from other myeloid cell populations, is the major chemotactic receptor and explains the tissue tropism of eosinophils in type 2 inflammatory disease (Johansson and Mosher, 2013). Direct therapeutic targeting of CCR3 has been explored but has not yet resulted in approved agents, possibly due to the redundancy of non-CCR3 chemotactic signals that maintain established tissue eosinophilia.

The three CCR3 ligands differ significantly in their tissue distribution and cytokine regulation, which explains the organ-specific eosinophilic inflammation profiles observed in different diseases. The expression of CCL26 (eotaxin-3) is induced in the esophageal epithelium extremely strongly by IL-13 (8- to 15-fold greater than that of CCL11), establishing a direct molecular mechanism of eosinophilic tropism of the esophagus in eosinophilic esophagitis (EoE) and justifying the therapeutic use of anti-IL-13 in this disease (Dellon & Hirano, 2018; Hirano et al., 2020). CCL11 (eotaxin-1) is abundant in the lower respiratory tract, dermis, and nasal mucosa, consistent with the accumulation of eosinophils observed in asthma, atopic dermatitis, and allergic rhinitis. Its gene expression in bronchial epithelial cells is regulated by a GATA-3-dependent mechanism that links Th2 transcription factor activity to local eosinophil recruitment in a coordinated manner directly at the tissue level (Johansson and Mosher, 2013). CCL24 (eotaxin-2) is widely distributed in the gastrointestinal lamina propria and contributes both to the maintenance of eosinophil homeostasis under physiological conditions and to their pathological recruitment during eosinophilic gastroenteritis.

Recent studies (2020–2024) identified key chemotactic and homing signals unrelated to eotaxin that complement CCR3-mediated eosinophil recruitment and may explain the incomplete depletion of eosinophils in tissues observed with anti-IL-5 strategies. Periostin, a cellular matrix protein secreted by esophageal epithelium and lung fibroblasts under TGF-β1 and IL-13 stimulation, directly promotes eosinophil adhesion and tissue homing by interacting with the αvβ3 integrin. Thus, it acts as a non-chemokinetic homing signal to tissues that

maintains eosinophil infiltration independent of IL-5-induced recruitment (Hirano et al., 2020). IL-33, acting through the eosinophil receptor ST2, induces CCR3 expression on the cell surface and increases chemotactic sensitivity to eotaxins, thereby positioning the IL-33/ST2 axis as an upstream amplifier of CCR3-mediated recruitment. This mechanism is particularly important during asthma exacerbations induced by respiratory viral infections and environmental pollutants (Tay et al., 2021). In eosinophilic autoimmune diseases, complement-derived C5a, generated by immune complex deposition, provides a CCR3-independent chemotactic signal capable of maintaining eosinophil recruitment to tissues even in the event of IL-5 neutralization (Schmidt and Zillikens, 2013).

Granular proteins and cytotoxic mechanisms

The effector capabilities of eosinophils are centered on four major cationic proteins stored in secondary granules: major basic protein 1 (MBP-1), eosinophil cationic protein (ECP/RNase 3), eosinophil-derived neurotoxin (EDN/RNase 2), and eosinophil peroxidase (EPO). These proteins share a highly cationic biochemistry (isoelectric point 8.9 to 11.0), which allows electrostatic interaction with anionic phospholipid membranes, an interaction that is the molecular basis for their cytotoxicity through membrane disruption. Their tissue concentrations, combined with sites of eosinophil degranulation, systematically exceed the threshold for damage to mammalian host cells, which explains the tissue damage caused by eosinophils in allergic and autoimmune diseases (Venge et al., 2010, Canonica et al., 2021).

ECP (RNase 3) causes membrane perforation through a perforin-like pore-forming mechanism, independent of its ribonuclease activity. It induces necrosis of target cells by disrupting organelles and activating mucosal mast cells through direct, TLR2-independent membrane interaction. Measurement of serum ECP using the validated ImmunoCAP system remains one of the best validated biomarkers of eosinophil activation in clinical practice: a 2019 prospective study by Bozek et al. (2019) showed that a serum ECP level ≥ 20 µg/L during asthma follow-up predicted unscheduled access to healthcare within 90 days with a sensitivity of 74% and a specificity of 68%, highlighting its value for therapeutic monitoring. In EE, the intensity of ECP immunostaining in tissues correlates with histological disease activity score (EoEHSS) regardless of peak eosinophil count in post-hoc analyses of pivotal studies with dupilumab (Dellon et al., 2022).

MBP-1, which represents more than 50% of the granule protein mass and is concentrated in the crystalloid core, induces cytotoxicity at concentrations ≥ 10 µM by forming pores in the phospholipid bilayer and, at sublytic concentrations, induces mast cell degranulation and histamine release from basophils through a lipid raft-dependent mechanism, potently alters junctional proteins (occludin, claudin-1, ZO-1) in the airway and esophageal epithelium, and directly induces airway smooth muscle hyperreactivity, thereby amplifying bronchoconstriction independently of ongoing neural reflexes (Venge et al., 2005; Johansson et al. 2020).

EPO generates hypobromous acid (HOBr) through bromide oxidation, which causes lipid peroxidation, protein carbonylation, and latent activation of MMP-9 in the extracellular matrix. The mechanistic study by Shim et al. (2019) showed that EPO-based reactive oxidants directly oxidize type I collagen in the esophageal lamina propria, leading to the generation of carbonyl cross-links that enhance fibrous stiffness and diminish extensibility of the lamina propria. This positions EPO as playing a key role in the mechanistic link between acute episodes of eosinophil activation and irreversible esophageal remodeling in eosinophilic esophagitis (EoE).EDN acts as a TLR2 agonist, activating dendritic cell maturation and secretion of Th2 polarizing cytokines (IL-6, IL-12p40) through MyD88-dependent signaling, a function demonstrated by Yang et al. (2008) and confirmed in human tissues treated with EE by Khoury et al. (2020), who revealed colocalization of EDN-TLR2 with sites of eosinophil degranulation in the inflamed esophageal submucosa.

Eosinophil extracellular traps (EETs).

Eosinophil extracellular traps (EETs) are protein structures composed of DNA granules that are released from eosinophils through a process called EETosis. This process is mechanistically characterized as either vital (non-lytic) or lytic, depending on the stimulation conditions. Vital EETosis preserves cellular integrity for subsequent effector functions (Ueki et al., 2013). EETs consist of a core structure of mitochondrial or nuclear DNA decorated with MBP, ECP, EPO, and histones in concentrations sufficient for direct cytotoxicity, thereby forming a spatially concentrated effector matrix with inflammatory foci. Biological triggers for EET formation include IL-5 activation, cross-linking of IgG/IgE immune complexes with Fc receptors, complement C5a, LPS (via TLR4), and IL-33 (via ST2). These broad stimuli allow TSEs to respond in allergic and type 2 autoimmune inflammatory contexts.

Clinical evidence for the pathological significance of TSEs in human disease has strengthened significantly between 2017 and 2024. Tay et al. (2021) demonstrated, in a prospective cohort of 146 adults with asthma of varying severity, that the concentration of extracellular DNA in sputum (a quantitative marker of TSEs) was significantly correlated with the annual rate of decline in FEV1 ($r = -0.52$, $p < 0.001$). of blood and sputum eosinophil counts. These results establish TSE biology as a dimension of eosinophil pathobiology, providing information not seen with conventional cell counts (Hamilos et al.2022).

In the context of autoimmune diseases, a 2022 study (Giaglis et al., 2022) demonstrated co-localization of eosinophil-specific granular proteins (MBP, EPO) with extracellular DNA in skin and kidney biopsies from patients with systemic lupus erythematosus (SLE). These granular proteins differ from neutrophil NET structures in their specificity, suggesting that eosinophilic NETs may be an independent source of immunogenic chromatin in SLE, beyond the already established contribution of neutrophil NETs. NET-associated platelet activation, mediated by interaction with P-selectin glycoprotein ligand 1 (PSGL-1), has been reported in patients with eosinophilic granulomatosis and polyangiitis (EGPA) and associated with hypereosinophilia. This cellular mechanism links the occurrence of hypereosinophilia to the increased thrombotic risk in patients, and it has direct relevance to the management of patients with high levels of eosinophilia (Vaglio et al., 2013; Giaglis et al., 2022).

Ba receivers for regulatory control points

Eosinophils express a broad repertoire of surface receptors that integrate signals from innate pattern recognition, antibody-mediated effector guidance, the cytokine milieu, and inhibitory regulatory checkpoints. Immunoglobulin Fc isotype receptors (FcεRII (CD23) for IgE, FcγRII (CD32) for IgG, and FcαRII (CD89) for IgA) link the specificity of adaptive humoral immunity to the recruitment of eosinophilic effectors. In allergic diseases, IgE-allergen immune complexes that bind to FcεRII induce degranulation, LTC4 synthesis, and cytokine secretion. In bullous pemphigoid, anti-BP180 autoantibodies of the IgG4 and IgE types, which bind to FcγRII and FcεRII receptors, respectively, directly recruit eosinophils to the dermoepidermal junction, thus linking the specificity of the autoantibodies to eosinophil-mediated blister formation (Schmidt and Zillikens, 2013, et al., 2016). Using super-resolution microscopy of bullous pemphigoid tissue biopsies, Izumi et al. (2016) showed that eosinophil degranulation events were spatially concentrated precisely at sites of anti-BP180 IgE deposition, rather than being uniformly distributed around the periphery of the blister. This provides direct in situ evidence of FcεRII-guided targeting in human autoimmune diseases.

Siglec-8, a therapeutically important inhibitory receptor in eosinophil biology, is a sialic acid-binding lectin that is selectively expressed on the surface of human eosinophils and mast cells. Upon cross-linking with sialoglycan ligands or the therapeutic antibody lirenteliumab, Siglec-8 transmits an ITIM-mediated inhibitory signal that, in IL-5-activated eosinophils (a prevalent condition in eosinophilic diseases), selectively induces apoptosis by generating mitochondrial reactive oxygen species (ROS) and activating caspase-3/7, while preventing mast cell degranulation without

inducing cell death (Kiwamoto et al., 2012; Bochner, 2009). A mechanistic study conducted in 2023 by Scott et al. In 2023, researchers showed, using CRISPR-Cas9 that induction of apoptosis by Siglec-8 in IL-5-activated eosinophils requires recruitment of the phosphatase SHP-1 and is abrogated by overexpression of BCL-2. These results provide a mechanistic rationale for combining Siglec-8 targeting with BCL-2 inhibitors in Siglec-8-refractory eosinophils. The requirement for IL-5 activation confers selectivity to lirenteliumab related to the pathological context, theoretically preserving homeostatic populations of immature eosinophils (iEos) while causing depletion of inflammatory eosinophils (rEos). This selectivity profile distinguishes lirenteliumab mechanistically from anti-IL-5 strategies.

The ST2 alarm receptor (IL-33 receptor) emerged as the most important surface receptor for eosinophils between 2015 and 2026. IL-33 is released from stressed or necrotic epithelial cells following mechanical trauma, viral infection, exposure to pollutants, or epithelial damage caused by eosinophils themselves. This process forms a self-reinforcing loop: epithelial damage caused by eosinophils releases IL-33, which further activates eosinophils via ST2 signaling, induces CCR3 overexpression, increases eotaxin chemotaxis, and amplifies degranulation (Tay et al., 2021). This ST2-IL-33 circuit has been proposed as a mechanism for acquired resistance to anti-IL-5 therapy in some patients with severe asthma: the observation that the frequency of exacerbations does not fully normalize despite the almost complete reduction of blood eosinophils may reflect the persistence of local activation of eosinophils in tissues induced by ST2 and supported by IL-33 independently of IL-5-dependent survival signals (Menzies-Gow et al., 2021).

Cytokine production and immunoregulatory capacity

The secretory profile of eosinophils, as identified in proteomic, transcriptomic, and multiplex cytokine studies undertaken between 2015 and 2024, shows a surprisingly diverse array of immunological mediators involved in the amplification of inflammation, immunoregulation, neuronal sensitization, angiogenesis, and tissue remodeling. A. Among the mediators secreted by eosinophils are: type 2 cytokines (IL-4, IL-5, IL-13, IL-25); alarm cytokines (IL-33 after necrotic activation); regulatory cytokines (IL-10, TGF-β1, TGF-β2); proinflammatory cytokines (IL-6, TNF-α, IL-17); neuronal growth factors (NGF, BDNF); and angiogenic factors (VEGF, PDGF, bFGF), and B cell survival factors (APRIL, BAFF) (Jacobsen et al., 2012, reviewed in Canonica et al., 2021). This diversity positions eosinophils as active players in modulating the local immune environment, rather than passive cells responding to exogenous signals.

The immunoregulatory capacity of tissue-resident eosinophils has received particularly strong mechanistic support in studies published between 2015 and 2020. Jung and Rothenberg (2017) showed in vivo that depletion of resident eosinophils in the gut of adult mice induces dysbiosis characterized by an expansion of Proteobacteria and a decrease in Lactobacillus over three weeks (changes that can be reversed by eosinophil regeneration), thereby establishing a direct bidirectional regulatory axis between the microbiome and eosinophils. These findings may have important implications for understanding the epidemiological link between early life antibiotic use, microbiome disruption, and the later development of eosinophilic esophagitis (EE). A 2021 study by Salter et al. (2021) showed in human asthma that eosinophil-derived TGF-β1, determined in induced sputum, correlated more strongly with airway wall thickness on quantitative computed tomography ($r = 0.67$) than with eosinophil count ($r = 0.43$), identifying TGF-β1 secretion as a more direct indicator of eosinophil function related to remodeling than cell count alone.

The neuroimmune axis through which eosinophils modulate sensory nerve function is attracting increasing interest as a potential therapeutic target for the amplification of itch and pain in atopic dermatitis and eosinophilic esophagitis (EE). Eosinophil-derived NGF binds to TrkA receptors on nociceptive C fibers, promotes neurogenesis

and sensitization in inflamed skin and esophageal tissues, and directly enhances sensitivity to itch and pain (Kapur et al., 2018). A 2023 transcriptomic study of nerve fiber density in skin biopsies from patients with atopic dermatitis (Nettis et al., 2023) identified eosinophil-NGF immunoreactive colocalization as a strong spatial predictor of itch intensity, independent of other neuroimmune markers such as IL-31 and TSLP. These results provide in situ evidence in humans for the role of the eosinophil-nerve axis in mediating itch, not as an indirect phenomenon, but as a direct effect.

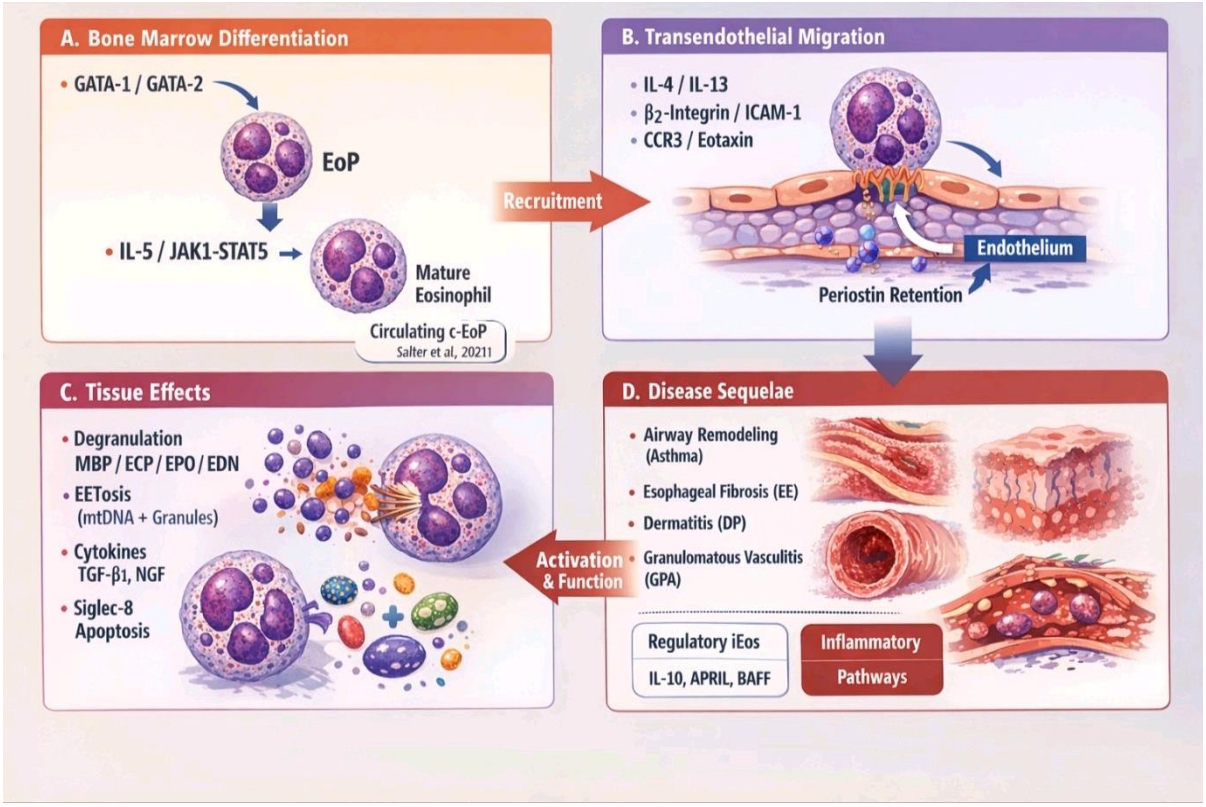

Figure 2. Eosinophil activation cascade: IL-5-induced bone marrow differentiation and tissue effector effects

Role of Eosinophil in Allergic Disorders

Numerous illnesses are linked to eosinophilic inflammatory reactions. The bone marrow, spleen, lymph nodes, thymus, and other hematopoietic and lymphatic organs are home to eosinophils. Furthermore, eosinophils physically migrate in the female reproductive tract, the mammary gland, and digestive tract organs (excluding the esophagus). It is uncertain what their physiological purpose is. Because of their great affinity for the acidic dye eosin, eosinophils are easily recognized in blood and tissues ((Simon & Simon, 2007). Eosinophils play a crucial role in the immune mechanisms that drive hypersensitivity. They are typically drawn to affected tissues, where they release granule-derived cationic proteins along with various lipid mediators. Research examining these cationic proteins has produced substantial evidence indicating that they can injure surrounding cells and disrupt normal tissue function within inflamed allergic sites (MD, 1997). An aberrant infiltration of eosinophils in the digestive tract is the hallmark of eosinophil-associated gastrointestinal diseases (EGID). The gastrointestinal (GI) system may be affected by a rise in eosinophils in one area or multiple areas. Eosinophilic esophagitis (EE), which involves eosinophil infiltration of the esophagus, is the

most commonly diagnosed form. Eosinophilic gastritis, enteritis, colitis, and gastroenteritis are further recognized types. Despite being less common than EE, these disorders are thought to have comparable underlying causes and therapeutic approaches.Symptoms like trouble swallowing, vomiting, and discomfort in the abdomen are frequent in patients with EGID. Children with EE may exhibit stunted growth or failure to thrive, while adults with the condition may exhibit symptoms similar to gastric reflux disease (GERD) or episodes of food impaction (DeBrosse & Rothenberg, 2008).

With reports coming from nations including Switzerland, Australia, Italy, Spain, Japan, England, and the United States, eosinophilic esophagitis is becoming more well recognized worldwide. Clinically, it frequently resembles gastroesophageal reflux disease (GERD) and can leads in problems such stricture formation and esophageal constriction. The degree of eosinophil infiltration in the esophageal lining and the condition's inability to improve with acid-suppressive medication set it apart from reflux-related esophagitis. (Noel et al., 2004).

In addition to increased eosinophil counts, GI tract structural alterations are often noted. Eosinophilic microabscesses, basal layer thickening, crypt inflammation, epithelial destruction, or fibrotic alterations are possible findings, depending on the affected region. Increased T lymphocytes and mast cells in esophageal tissue have also been found in studies of EE.Eosinophilia by itself does not prove EGID, despite the fact that high eosinophil counts and changes in normal GI architecture are crucial for the diagnosis. Similar results can be obtained from a variety of other conditions, such as fungal or parasite infections, inflammatory bowel disease, and hypereosinophilic syndrome (HES). Other conditions like GERD, chronic esophagitis, and scleroderma must also be taken into account when eosinophils are seen in the esophagus.A definitive diagnosis of EGID requires compatible clinical features along with biopsy confirmation, and other potential causes of gastrointestinal eosinophilia such as infections or drug reactions must be excluded (DeBrosse & Rothenberg, 2008)).

Asthma is a long-standing autoimmune disorder affecting the lower respiratory tract and is marked by intermittent episodes of airway obstruction that are at least partly reversible. These episodes occur alongside heightened airway responsiveness and persistent inflammation. Growing evidence indicates that eosinophils are key contributors to asthma flare-ups. As a result, targeting eosinophil-driven inflammation and distinguishing between eosinophilic and non-eosinophilic forms of asthma may improve strategies for preventing and managing exacerbations. Eosinophils accumulate in areas of allergic airway inflammation and play an active role in the progression of bronchial asthma. They release a variety of biologically active substances, including granule-derived proteins such as major basic protein (MBP), reactive oxygen species, cytokines like granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-8 (IL-8), as well as lipid mediators including cysteinyl leukotrienes (Bochner et al., 1994).

Inflammation driven by neutrophils as well as eosinophils appears to contribute to severe forms of asthma. Neutrophilic inflammation, in particular, has been linked to the mechanisms underlying frequent exacerbations seen in severe disease. The European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) study reported that patients with severe asthma, compared with those who have mild-to-moderate disease, exhibit higher neutrophil counts in sputum along with increased release of mediators derived from eosinophils. Interleukin-8 (IL-8) is a key factor in directing neutrophils to sites of inflammation, and its expression is elevated in the airways of individuals with severe asthma. Research has also shown that neutrophils stimulated by IL-8 can promote eosinophil movement across the basement membrane in laboratory settings, even in the absence of specific eosinophil-attracting signals. This neutrophil-driven migration of eosinophils can be reduced by antagonists targeting leukotriene B4 (LTB4) or platelet-activating factor (PAF). Because LTB4 and PAF are strong chemoattractants for eosinophils, IL-8–activated neutrophils may facilitate eosinophil accumulation

in asthmatic airways through the release of these mediators (Nakagome & Nagata, 2018).

Respiratory viral infections particularly those caused by rhinoviruses (RV) are among the leading triggers of asthma worsening. Community-based investigations have detected viral pathogens in approximately 80–85% of asthma exacerbation cases, with rhinoviruses accounting for about 65% of instances in which a specific virus was identified. Rhinoviruses are highly diverse, comprising around 100 recognized serotypes within species A (RV-A) and B (RV-B), in addition to more than 60 genotypes of RV-C identified through molecular methods. Recent clinical findings suggest that infections caused by RV-C, or a combination of RV-C and RV-A, are associated with more severe respiratory illness and a greater likelihood of asthma exacerbations compared with other strains, such as RV-B. During or following viral infections, the airways of individuals with asthma show an increase in both neutrophils and eosinophils. Experimental infection with rhinovirus (RV) has been shown to enhance eosinophil recruitment to the airways after localized allergen exposure in patients with allergic rhinitis, whereas this effect is not observed in non-allergic individuals. In patients with allergic asthma, viral infections raise eosinophil numbers within the airway epithelium, and elevated concentrations of eosinophilic cationic protein can be detected in their sputum. These findings indicate that viral infections promote both the migration and activation of eosinophils in asthmatic airways (Bochner et al., 1994).

In a normal individual, eosinophils are mostly confined to the gastrointestinal tract. In the case of an individual with AD, eosinophils are found to be a component of the inflammatory infiltrate that is found surrounding the dermal blood vessels. Higher numbers of these eosinophils are found in the cases of patients with AD who developed the disease during childhood. In the case of patients with AD who developed the disease as an adult, the eosinophils found in the tissue are reported to be mild. Almost all the tissue biopsy samples from AD lesions show a level of eosinophilia. The median number of eosinophils reported is 2.8/mm^2. The tissue eosinophils are found to be elevated in the acute as well as the chronic phases of the disease. The eosinophil granule proteins are found to be maximally deposited in the upper layer of the dermis. This layer is located just beneath the epidermis (D. Simon, 2004).

Atopic dermatitis (AD) is a chronic inflammatory skin disease with specific immune and inflammatory mechanisms. The disease is characterized by specific skin changes depending on age groups. The hallmark of AD is severe itching. The role of genetic predisposition is significant in the causation of AD. The diagnosis of AD is based on specific clinical criteria (Liu et al., 2011).

The tissues located beneath this layer are found to be free of eosinophil granule proteins. In longstanding AD, increased eosinophil presence is observed in lesions showing marked epidermal thickening compared to those showing minimal hyperplasia. In acute dermatitis or flare-ups of chronic AD, eosinophil presence is also found to be related to the degree of spongiosis. Experimental studies done on a mouse model of AD have also shown that increased eosinophil presence is related to hypertrophy of both epidermal and dermal tissues. This hypertrophy is believed to be a repair mechanism to compensate for tissue injury resulting from cytotoxic eosinophil products like major basic protein (MBP) and eosinophil cationic protein (D. Simon, 2004).

Eosinophils are a heterogeneous group of granulocytic leukocytes. They are involved in the initiation and modulation of inflammatory reactions. Eosinophils have long been implicated in the pathogenesis of diseases such as asthma and parasitic infections. Recent studies have suggested the involvement of eosinophils in the pathogenesis of autoimmune diseases. The innate immune system is capable of contributing to the pathogenesis of autoimmune diseases (Diny et al., 2017).

In the case of primary biliary cirrhosis, eosinophilia is a common feature that may prove useful in the diagnosis of the disease. The level of interleukin-5 (IL-5) mRNA has been found to be increased in the liver biopsy material of patients

with the disease. In Riedel's invasive fibrous thyroiditis, tissue eosinophilia is a prominent feature that is rarely found in other thyroid autoimmune disorders. In the case of dermatomyositis, lupus erythematosus, and Sjögren syndrome, eosinophilia is a feature that may be found. However, in the majority of these cases, it is likely to be due to a hypersensitivity reaction (Dagmar Simon, MD, 2007).

When the innate immune system is stimulated by pathogen-associated molecular patterns, along with the presentation of antigens by dendritic cells, autoreactive T and B lymphocytes can be activated. Innate immune cells are known to contribute to the progression of autoimmune disease in the later stages. This has been implicated for various cells such as neutrophils, natural killer cells, macrophages, dendritic cells, innate lymphoid cells, and mast cells. Eosinophils have been found to be present in the inflammatory infiltrate of various organ-specific autoimmune disorders. However, the role of eosinophils in the progression of autoimmune disorders has not been extensively studied (Diny et al., 2017).

The presence of eosinophils in the dermis as well as the epidermis, with or without peripheral blood eosinophilia, is a feature that is commonly found in a number of autoimmune disorders of the skin like a pemphigoid, pemphigus, and epidermolysis. The autoantibodies that are found in these disorders are likely to be involved in the disease. In pemphigoid disease states, for instance, levels of interleukin-5 (IL-5) have been particularly elevated in blister fluid. In another skin disease known as palmoplantar pustulosis a chronic inflammatory skin disease characterized by a predominantly neutrophilic infiltrate in the epidermis a significant number of eosinophils have also been observed in the skin beneath pustules. Autoimmune progesterone dermatitis a rare skin disease resulting from an autoimmune response against endogenous progesterone is histopathologically characterized by a mixed inflammatory infiltrate around dermal blood vessels containing both lymphocytes and eosinophils (Dagmar Simon, MD, 2007).

Comparative Analysis

The selective recruitment of eosinophils is done by eotaxins for both, allergic as well as autoimmune disorders. Eotaxins (such as CCL11, CCL24, and CCL26) are actually chemokines which attracts eosinophils, bind to the CCR3 receptor and are involved in the pathogenesis of allergies and other inflammatory diseases such as cancer (Zajkowska & Mroczko, 2021). The role of eosinophils has been known for long in allergic and parasitic infections but recent researches are revealing that eotaxins also drive eosinophil infiltration in autoimmune pathologies, such as Eosinophilic Granulomatosis with Polyangiitis (EGPA) and bullous pemphigoid (Diny et al., 2017; Ramirez et al., 2018).

Table 1. Comparison between different features of allergic and autoimmune disorders (bibliography 2015-2026).

Feature	Allergic Disorders	Autoimmune Disorders
Primary Immune Driver	Type 2 Immunity: Dominated by Th2 cells and cytokines IL−4, IL−5, IL−13 (Gao et al., 2022).	Mixed Immunity: Involves Th1/Th17 interface and autoantibody production (Diny et al., 2017; Xie et al., 2024).
Recruitment Signal	High eotaxin expression (CCL11, CCL24) via the CCR3 receptor (Zajkowska & Mroczko, 2021).	Eotaxin-3 and CXCL12 (SDF-1) in specific inflamed tissues (Matucci et al., 2022).
Predominant Role	Destructive Effector: Direct induction of tissue damage and mucus hypersecretion (Jackson et al., 2022).	Immunomodulatory Architect: Acting as a biomarker for flare-ups or a driver of necrotizing vasculitis (Mishra et al., 2022).
Effector Mechanism	Massive degranulation of MBP and ECP leading to epithelial death	Formation of Eosinophil Extracellular Traps (EETs) causing chronic inflammation (Gao et al.,

	(Naharro-González et al., 2024).	2024).
Tissue Impact	Epithelial barrier dysfunction and airway remodeling (Jackson et al., 2022).	Subepidermal blistering (Bullous Pemphigoid) or organ-specific destruction (Diny et al., 2017).

The outcome of eosinophil infiltration highly depends on the context. In allergic disorders, eosinophils are involved in causing diseases (e.g. asthma, CRSwNP, EGPA, HES) by releasing cytotoxic granule proteins (e.g., MBP and EPX) that cause bronchial epithelial damage or skin barrier dysfunction (Jackson et al., 2022). In contrast, in chronic inflammatory or autoimmune diseases, eosinophils act as regulators. They are involved in supporting immune homeostasis by maintaining plasma cell survival in the bone marrow and can secrete growth factors (e.g., TGF-β) promoting tissue repair (Ramirez et al., 2018).

Recent researches are focusing on the Th2/Th17 interface, where eosinophils act as immunomodulatory architects. Eosinophils coexist with Th17-driven neutrophilic inflammation in conditions as Asthma-COPD Overlap (ACO) or severe autoimmune vasculitis (Xie et al., 2024). Eosinophils can modulate the T-cell environment being antigen-presenting cells (APCs), which may affect the balance between the Th2 (allergic) and Th17 (autoimmune/pro-inflammatory) response depending on the cytokine environment (Ramirez et al., 2018).

Diagnostic and Prognostic Value

Currently, eosinophilia is mostly determined by the Blood Eosinophil Count (BEC)/ Absolute Eosinophil Count (AEC), but this method has limitations as research shows asymptomatic patients with elevated BEC and no tissue damage or vice versa. A BEC exceeding 600 cells/μL is significantly associated with the presence of asthma, CRSwNP, increased hospitalization, and COPD (Naharro-González et al., 2024). In Allergic Rhinitis and Eosinophilic Esophagitis (EoE), BEC is within normal ranges even while the tissue experiences severe, pathologically high infiltration (greater than 15 eos/hpf in esophageal biopsies) (Lucendo et al., 2022; Zajkowska & Mroczko, 2021). In systemic autoimmune disorders like EGPA, tissue eosinophilia (confirmed via biopsy) is often considered more pathognomonic for organ damage than blood counts alone, as patients may exhibit severe tissue injury even with near-normal peripheral levels (Matucci et al., 2022; Xie et al., 2025).

Table 2. Major diagnostic techniques for eosinophil levels, their diagnostic threshold and clinical significance.

Metric	Diagnostic Threshold	Clinical Significance	Reference
AEC (Peripheral)	>300 cells/μL	Predicts response to Anti-IL-5 therapy in severe asthma.	(Matucci et al., 2022)
Tissue Biopsy	≥15 eos/hpf	Gold standard for diagnosing EoE and EGIDs.	(Lucendo et al., 2022)
Serum ECP	>15 μg/L	Indicates active degranulation and risk of skin barrier loss.	(Gao et al., 2022)
Urinary/Serum EDN	Variable (High sensitivity)	Predicts upcoming flare-ups and atopic disease development.	(Kim et al., 2025)

Stable biomarkers of eosinophil activation are desired in the monitoring of disease progression because blood counts are often transient. Eosinophil Cationic Protein (ECP) levels in local fluid (such as sputum) or serum are a proxy for degranulation and are used to follow subclinical levels of inflammation in asthma and allergic

rhinitis (Zajkowska and Mroczko, 2021). Recent research suggests that ECP is better than AEC in measuring subclinical inflammation and itch-scratch cycle in atopic dermatitis (Gao et al., 2022).

Eosinophil-Derived Neurotoxin (EDN) is becoming more frequently utilized as a prognostic marker because of its longer half-life, stability, high recovery rate in multiple fluids (blood, urine, and nasal lavage) and relation to the extent of tissue damage to predict a flare-up in both eosinophilic gastrointestinal diseases (EGIDs) and severe asthma. There is recent evidence which shows that high EDN levels are predictors of the atopic march in children and highly correlated with the severity of airway remodeling in adult asthma (Kim et al., 2025; Ramirez et al., 2018).

Table 3. Major biomarkers of eosinophil activation and their clinical significance.

Biomarker	Clinical Application	Recent Research Finding (2021–2026)
Blood Eosinophil Count (BEC)	General screening	BEC >600 cells/μL is a strong predictor of asthma-related hospitalizations (Naharro-González et al., 2024).
Tissue Eosinophilia	Gold standard for organ damage	More pathognomonic than BEC in EGPA and EGIDs; BEC can stay normal while tissue damage persists (Matucci et al., 2022).
Eosinophil Cationic Protein (ECP)	Monitoring activation	High serum ECP levels correlate with subclinical airway inflammation and AD severity (Zajkowska & Mroczko, 2021).
Eosinophil-Derived Neurotoxin (EDN)	Prognosis/Flare prediction	Used as a reliable predictor for upcoming exacerbations in severe asthma and EoE due to long half-life (Ramirez et al., 2018).

Current and Emerging Therapeutic Targets

Anti-IL-5 Therapies (Mepolizumab, Reslizumab)

Reslizumab is a humanised IgG4/κ monoclonal antibody, whereas mepolizumab is a humanised IgG1/k monoclonal antibody. They both attach to IL-5, preventing it from binding to its eosinophil receptor, IL-5R. The humanised afucosylated IgG1/κ monoclonal antibody benralizumab functions differently. Its Fab section interferes in the binding of IL-5 to eosinophils by specifically recognizing Domain 1 of human IL-5Rα, which is located near the IL-5 binding site. Additionally, its Fc part binds to the FcγRIIIa receptor on the cell membrane of NK cell, causing granzyme B and perforin to be released as well as further eosinophil apoptosis. Intravenous administration of reslizumab is possible. Reslizumab and mepolizumab both decreased blood and sputum eosinophil counts, according to studies. Also, FEV1 improved, and this was beneficial for the lungs. Furthermore, there was an improvement in the management of asthma and reduction in significant asthma exacerbation. However, it was found that patients with more severe disease and significant eosinophilia responded better to reslizumab (Antosz et al., 2024).

Anti-IL-5 Receptor Therapy (Benralizumab)

Due to its mechanisms of action and target specificity, benralizumab can be considered an important milestone in the field of biotherapy. It is a fully humanized afucosylated monoclonal antibody that specifically targets IL-5Rα, which is expressed by both human basophils and eosinophils. Due to its high binding affinity to the human FcγRIIIa receptor, this binding not only inhibits the activation of IL-5Rα but also induces the death of these cells by ADCC. The expanded therapeutic activity of benralizumab can be attributed to its increased ADCC activity, which results in a significant reduction in the levels of basophils and eosinophils. It has a Kd value of 11 pM and binds to the extracellular portion of the IL-5Rα with significant affinity. In terms of its

pharmacokinetic activity, benralizumab has a central volume distribution of 3.1 L and a peripheral volume distribution of 2.5 L in an average 70 kg person. It stained human peripheral blood eosinophils with an EC50 of 26 pM. The medication's pharmacokinetics are linear. The absence of receptor-mediated clearance is noteworthy. Benralizumab's estimated daily systemic clearance rate is 0.29 L. Benralizumab has an elimination half-life of roughly 15.5 days following subcutaneous injection (Antosz et al., 2024).

Targeting Siglec-8: Induction of Eosinophil Apoptosis

In 2D cultures and spheroids, the supernatant of eosinophils that were either directly isolated from peripheral blood or differentiated from EOL1 cells prevented apoptosis caused by pemetrexed and cisplatin. According to transcriptomic research, eosinophils' anti-apoptotic function involved molecular interactions with either Galectin-10 (CLC-P/Gal10) or the Charcot-Leyden Crystal protein. Antibody-mediated depletion proved the functional significance of CLC-P/Gal10. The anti-apoptotic properties of supernatants produced from eosinophils were replicated by recombinant human CLC-P/Gal10. Eosinophilia changed the response to chemotherapy but had no discernible effect on cancer progression in the mouse model. Ultimately, the efficacy of chemotherapy was restored by pretreating eosinophilia with the anti-Siglec-F antibody (Mégane Willems et al., 2024).

Small Molecule Inhibitors: JAK Inhibitors and Eosinophil Signaling

The JAK/STAT pathway is crucial for eosinophil differentiation, in addition to additional signalling cascades involving Lyn and ERK/MAPK activity. According to recent clinical findings, JAK inhibition can lower inflammation and the eosinophil count in a number of situations. These drugs may be useful in complicated inflammatory diseases with eosinophilia, even if they are not yet proven treatments for primary eosinophilic disorders due to their capacity to alter larger cytokine networks (Liu, 2026).

Future Perspectives & Conclusion

The idea that eosinophils are a homogeneous population is called into question by new, cutting-edge methods like transcriptomics and immunophenotyping. There are numerous differences between resident and inflammatory eosinophils, including surface marker expression, localisation, and functional characteristics. While inflammatory subsets build up in sick tissues and intensify pathological responses, resident eosinophils seem to support immune control and tissue maintenance in steady-state settings. It is hoped that this understanding of the differences will clarify why there are variable responses to targeted therapies and will yield new information about disease mechanisms. There are still variable responses to treatment among patient groups despite significant advances in biological medicine. The variable responses to treatment may be due to differences in disease endotypes, genetic differences in cytokine signalling pathways, differences between blood and tissue levels of eosinophils, and compensatory inflammatory responses. Further research will continue to be necessary to identify trustworthy prediction markers and to improve patient stratification techniques (Graf et al., 2025). Eosinophils are involved in both detrimental and beneficial immune responses. This makes their role complex. The management of diseases in which eosinophils are involved has evolved because of advances in medicine to target IL-5, its receptor, Siglec-8, and intracellular signaling. The recognition of diversity in eosinophils and variability in responses to treatment among individuals has underscored the need for more precise treatment approaches by illuminating the need to continue to research more about eosinophils in relation to allergy and autoimmune diseases.

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