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Synergy of Interleukin (IL)-5 and IL-18 in eosinophil mediated pathogenesis of allergic diseases

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ABSTRACT

Eosinophils are circulating granulocytes that have pleiotropic effects in response to inflammatory signals in the body. In response to allergens or pathogens, exposure eosinophils are recruited in various organs that execute pathological immune responses. IL-5 plays a key role in the differentiation, development, and survival of eosinophils. Eosinophils are involved in a variety of allergic diseases including asthma, dermatitis and various gastrointestinal disorders (EGID). IL-5 signal transduction involves JAK-STAT-p38MAPK-NFκB activation and executes extracellular matrix remodeling, EMT transition and immune responses in allergic diseases. IL-18 is a classical cytokine also involved in immune responses and has a critical role in inflammasome pathway. We recently identified the IL-18 role in the generation, transformation, and maturation of ($CD101^+CD274^+$) pathogenic eosinophils. In, addition, several other cytokines like IL-2, IL-4, IL-13, IL-21, and IL-33 also contribute in advancing eosinophils associated immune responses in innate and adaptive immunity. This review discusses with a major focus (1) Eosinophils and its constituents, (2) Role of IL-5 and IL-18 in eosinophils development, transformation, maturation, signal transduction of IL-5 and IL-18, (3) The role of eosinophils in allergic disorders and (4) The role of several other associated cytokines in promoting eosinophils mediated allergic diseases.

Abbreviations: 2-CDA, 2-Chlorodeoxyadenosine; AD, atopic dermatitis; AP-1, activator protein 1; AR, allergic rhinitis; APRIL, A proliferation-inducing ligand; ASC, adaptor protein; BCL-X_L, B-cell lymphoma-extra large; Btk, Bruton's tyrosine kinase; C/EBP, CCAAT/enhancer binding protein; CARD, C-terminal caspase-recruitment domain; CCL, chemokine (C-C motif) ligand; CCR3, CC-chemokine receptor 3; CD, cluster of differentiation; c-fos, FBJ murine osteosarcoma viral oncogene homolog; c-jun, proto-oncogene; CLC, Charcot-Leyden crystal protein; COPD, chronic obstructive pulmonary disease; CRTH2, Chemoattractant receptor homologous molecule expressed on T helper type 2 cells; CXCL, chemokine (C-X-C motif) ligand; CXCR, CXC chemokine receptor; DAMPs, damage-associated molecular patterns; DC, dendritic cell; EC, Eosinophilic cystitis; ECE, eosinophilic cellulitis; ECO, eosinophilic colitis; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EF, eosinophilic fasciitis; EG, eosinophilic gastritis; EGE, eosinophilic gastroenteritis; EGF, epidermal growth factor; EGID, eosinophilic gastrointestinal disorders; EGPA, eosinophilic granulomatosis with polyangiitis; EM, eosinophilic myocarditis; EMT, epithelial-mesenchymal transition; EOE, eosinophilic esophagitis; EP, eosinophilic pneumonia; EPX, eosinophil peroxidase; ERK, extracellular signal-regulated kinase; FcεRI, Fc fragment of IgE receptor I; FGF, fibroblast growth factor; FIP1L1-PDGFRA, factor interacting with PAPOLA and CPSF1-like-1–platelet-derived growth factor receptor; FOXP3, forkhead box P3; Gal-10, galectin-10; GATA, globin transcription factor; GI, gastrointestinal; GM-CSF, granulocyte macrophage-colony stimulating factor; GTPase, guanine binding protein Rac1; HES, hypereosinophilic syndrome; hIL-5Rα, human interleukin-5 receptor alpha; HLA-DRB4, HLA Class II histocompatibility antigen-DR Beta 4 Chain; HS1, hematopoietic lineage cell-specific protein1; ICAM-1, Intercellular adhesion molecule 1; IFN-γ, interferon gamma; IgE, immunoglobulin E; IkB kinase, inhibitor of nuclear factor kappa-B kinase; IL, interleukin; ILC2s, type 2 innate lymphoid cells; iNKT, invariant natural killer T cells; IRAK, interleukin-1 receptor-associated kinase 1; JAK, Janus kinase; JNK, c-Jun N-terminal protein kinase; LFA-1, lymphocyte function-associated antigen 1; MAPK, mitogen-activated protein kinases; MBP, major basic protein; MPO, myeloperoxidase; MyD88, myeloid differentiation primary response 88; NADPH, nicotinamide adenine dinucleotide phosphate; NFκb, nuclear factor kappa B subunit; NK, natural killer; NLRP3, NLR family pyrin domain containing 3; OVA, ovalbumin; p50, nuclear factor kappa-B P50 Subunit; p65, transcription factor p65; PAMPs, pathogen-associated molecular patterns; PDGFRα, platelet-derived growth factor receptor alpha; PE, pulmonary eosinophilia; PI3K, phosphoinositide-3-Kinase; Pim-1, proto-oncogene serine/threonine-protein kinase-1 Pim-1; PKCζ, Protein kinase C zeta; PMN, polymorphonuclear neutrophils; PU.1, transcription factor PU.1; PYD, pyrin domain; Raf-1, Raf-1 proto-oncogene serine/threonine kinase; Ras, retrovirus-associated DNA sequences; rIL-15, recombinant interleukin-15; rMIL-21, recombinant mouse interleukin-15; Shc, Src homology 2 domain containing transforming protein 1; SHP2, protein-tyrosine phosphatase 2C (PTP-2C); SIGLEC, sialic acid binding immunoglobulin-like lectin; SIGLECF, sialic acid binding Ig-like lectin; STAT, signal transducer and activator of transcription; TARC, thymus and activation-regulated chemokine; TFH cell, follicular helper T cells; TGF-β1, transforming growth factor beta 1; Th2, T helper cell type 2; TLR, toll-like receptor; TNF-α, tumor necrosis factor alpha; TRAF6, TNF receptor associated factor 6; TREG cells, regulatory T cells; VEGF, vascular endothelial growth factor

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1. Introduction

Eosinophils are likely first observed in 1846 by Wharton Jones and named by Paul Ehrlich in 1879, with time they have traditionally considered effector cells in the innate immune system. Eosinophils are granulocytic leukocytes that develop in the bone marrow from pluripotent progenitors and share many features with neutrophils, including growth and development in the bone marrow. In contrast with neutrophils, eosinophils exit the bone marrow and reside in the bloodstream with a half-life of ~18 h and migrate to the thymus, gastrointestinal tract under homeostatic conditions. Eosinophils arise from hematopoietic $CD34^+$ progenitor cells in the bone marrow and are of 5% of total white blood cells in healthy subjects. Eosinophils are distinguished phenotypically by their bilobed nuclei and cytoplasmic granules filled with cytotoxic and immunoregulatory proteins [1]. Mature eosinophils in the blood are less than 400 per mm^3. Eosinophils respond to signals from cytokines, chemokines, and other proinflammatory mediators via cell-specific receptors most notably by cytokine interleukin-5 (IL-5) and the eotaxin chemokines. During eosinophilopoiesis, eosinophils acquire IL-5Rα and IL-18Rα on the cell surface and differentiate under the influence of both IL-5 and IL-18 [2]. Transcription factors play a crucial role in eosinophilic lineage commitment in the bone marrow to maturation and development of eosinophils. Eosinophilic progenitors express C/EBPα, C/EBPε, PU.1, and GATA-1 and GATA-2 [3]. The increased production of eosinophils is observed in various allergic conditions, skin diseases, parasitic infections, and reactions to drugs. Peripheral blood and tissue eosinophilia are hallmarks of parasitic helminth infection chronic asthma and allergic diseases and play a role in host defense [4]. Eosinophils migrate from bone marrow to the specific tissues on exposure with allergens and execute immune responses [5]. Eosinophils display pleiotropic effects such as lymphocyte homeostasis, PMN activation, basophil degranulation, mastocytosis, macrophage phagocytosis, Th2/DC's stabilization, epithelial cell differentiation, neurite outgrowth, fat tissue homeostasis, glucose metabolism, tissue repair and fibrosis, cardiovascular morbidity, bronchospasm, pathogen defense, antigen presentation, extracellular pathogen trap, parasite antibody-dependent cell mediated cytotoxicity [6].

Eosinophils are key innate regulator cells. Under homeostasis, eosinophils are distributed in the blood, lung, thymus, uterus, adipose tissues, mammary gland, spleen and the lamina propria of the gastrointestinal (GI) tract [7]. However, under the allergic condition, the mature eosinophils under the influence of IL-5 and eotaxin are released from bone marrow to bloodstream and recruit target tissue and modulate immune reactions. Eosinophils also regulate adaptive immune reactions and modulate lymphocyte recruitment and homeostasis. Th2 cells produce the cytokine IL-5, which promotes eosinophil production, priming, and survival, and IL-13, which induces local cells to produce eotaxins, which attract circulating eosinophils into their niche eosinophils and are critical for T-cell homing in the lung. Eosinophil-deficient ΔdblGATA-1 mice reduced Peyer's patch development, and T helper cell cytokine production was observed, highlighting the promoting role of eosinophils on lymphocyte homeostasis [8–10]. Bone marrow eosinophils co-localize with plasma cells during their maturation, secrete the cytokines APRIL and IL-6 and contribute to the survival of bone marrow plasma cells. B cell process of IgA class switching was recently found to be positively regulated by GI eosinophils in the intestinal tissue [8,10]. Eosinophils promote B cell proliferation upon eosinophil activation in mice [11].

Eosinophils act as antigen-presenting cells. Eosinophils can present antigen to T cells. GM-CSF–treated eosinophils induce antigen-specific T-cell clone proliferation [12]. Upon allergen exposure, eosinophils present antigens by costimulation of MHC class II [13,14]. Eosinophils in the airway lumen migrate to the draining lymph node and promote antigen-specific T-cell proliferation *ex vivo*. Eosinophils, alone or via dendritic cells, drive Th2 polarization. Upon allergen stimulation, eosinophils produce Th2 cytokines (IL-4, IL-5, and IL-13). Eosinophils regulate dendritic cells and Th2 pulmonary immune responses [15]. Eosinophils suppress Th17 and Th1 responses via DC regulation. Eosinophil products can serve as Th2 adjuvants via DC regulation.

Eosinophils also regulate T-cell development in the thymus. Eosinophils recognize PAMPs and defense against viral, parasitic and bacterial infection. Eosinophils and mast cells mutually potentiate in asthma and eosinophilic esophagitis. Mast cells support the survival and activation of eosinophils by secreting IL-5. Eosinophil MBP activates mast cells and basophils, and release cytokines, histamine, and TNF-α [6]. Eosinophils play a key role in tissue destruction and repair. Epithelial cells of various tissues stimulate eosinophil secretion of TGF-β and fibroblast growth factors and play a role in tissue repair and also promote wound healing [16–19].

Adipose tissue residential eosinophils regulate local cytokine milieu and glucose homeostasis. Eosinophils play a role in adipose tissue macrophage polarization and glucose metabolism critical for maintaining adipose tissue M2 macrophages [20]. Human eosinophils promoted dorsal root ganglia neuron branching. Peripheral dorsal root ganglia and airway neurons produce eotaxins to chemoattract eosinophils [21,22]. Eosinophils producing nerve growth factor and neurotrophins regulate neuronal activity [23]. Eosinophils in the GI tract play a role in homeostasis and disease contexts, such as in EGID promoting IgA class-switching, enhancing intestinal mucus secretions, determining intestinal microbiota and inducing the development of Peyer's patches [8,10].

The current review summarizes the most recent advances in our understanding on the contributions of IL-5 and IL-18 to the growth, transformation, and maturation of eosinophils to the maintenance of innate and adaptive immune responses in various allergic diseases. The review also briefs the current pharmacotherapy available to treat various eosinophil-mediated allergic diseases.

2. Eosinophilic constituents

Eosinophil constitutes a wide variety of molecules such as adhesion molecules, adhesion receptors, apoptosis and signaling factors, chemoattractant receptors, chemokines, cytokine and receptors, Fc receptors, growth factors and its receptors, lipid body contents, lipid mediators and its receptors, pattern recognition receptors, granule-derived receptors, eosinophil-derived granule proteins, enzymes and reactive oxygen intermediates. Eosinophils morphology, cell-surface receptors, and intracellular contents differ between species. Particularly interleukin-5 receptor subunit-α (IL-5Rα) and CC-chemokine receptor 3 (CCR3), as well as sialic acid binding immunoglobulin-like lectin 8 (SIGLEC-8) in humans, and SIGLEC-F (also known as SIGLEC-5) in mice. In addition, eosinophil also has CRTH2 receptor that helps in the recruitment of eosinophils in allergic condition via binding its ligands [24]. Eosinophilic granular proteins comprises, major basic protein-1 and -2 (MBP-1, MBP-2), eosinophil peroxidase (EPX), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), Charcot-Leyden crystal protein/Galectin-10 (CLC/Gal-10). These are routinely studied as markers of eosinophil activation, and we recently reported that IL-18 influence in the increase production of these toxic proteins during allergic condition [2].

2.1. Major basic protein

MBP comprised more than 50% of the granule protein and localized in the core of the eosinophil secondary granules. MBP-1 damages cells by disrupting the lipid bilayer membrane or altering the activity of enzymes within tissues [25]. MBP-1 stimulates mediator (histamine) release from basophils and mast cells, activates neutrophils and platelets, and augments superoxide generation by alveolar macrophages. MBP-2 is expressed only in eosinophils and exhibits similar functions *in vitro* like MBP-1 [26–28].

2.2. Eosinophil peroxidase (EPX/EPO)

EPO is a heme peroxidase found in eosinophils, and its gene located on chromosome 17. Its activities include the oxidation of halide ions to bactericidal ROS, the cationic disruption of bacterial cell walls, and the post-translational modification of protein amino acid residues [29–31]. EPO also mediates protein nitration in allergic airway inflammation in mice. 3-nitrotyrosine (3NT) formation after allergen challenge is dependent on EPO activity, particularly in eosinophils [32].

2.3. Eosinophil cationic protein (ECP)

ECP is a basic cationic protein located in the eosinophil primary matrix and is released during degranulation of eosinophils. ECP possess helminth-toxic and ribonucleolytic activities. ECP is assayed as one of the predictive markers of eosinophil activation in biological fluids in diseases like asthma, bullous pemphigoid severity and outcome [32,33]. ECP exerts cytotoxicity to parasites, bacteria, and virus and make pores on the cell membrane and kill the cell by osmotic lysis by the passage of water and other small molecules [34].

2.4. Eosinophil-derived neurotoxin (EDN)

EDN is released from eosinophil granules by cytokines and other proinflammatory mediators [35]. EDN is an active ribonuclease and capable of generating soluble ribonucleotides from insoluble tRNA [36]. Eosinophils upon activation with bacteria release EDN. Eosinophils in response to *Staphylococcus aureus*, release EDN [37]. EDN induces production of MMP-9 from the nasal epithelium and involves in the pathogenesis of chronic eosinophilic rhinosinusitis [38]. Eosinophil-derived neurotoxin correlated with the disease severity of AD and considered as a serum biomarker for disease severity in atopic dermatitis [39].

2.5. The Charcot-Leyden crystal protein/Galectin-10 (CLC/Gal-10)

CLC expression was increased in asthma, allergic reactions, and fungal and helminthic infections and related to the histological grade and with the number of eosinophils in the lesion of celiac disease patients and also higher in eosinophilic cystitis [40,41]. CLCs upon their phagocytosis by primary human macrophages induce the release of the IL-1β and activate the NLRP3 Inflammasome. CLC functions as a T cell-suppressive molecule in eosinophils [42]. Neutralization of galectin-10 partially abrogated the suppressive function of the eosinophils, and recombinant galectin-10 was able to suppress T cell proliferation [43]. The components of eosinophils and their functions are described in Fig. 1 and Table 1.

3. IL-5 mediated signal transduction and eosinophils development and survival

Interleukin 5 (IL-5) plays a vital role in the activation, terminal differentiation, growth and survival of eosinophils at the early stage and the sites of inflammation. Eosinophils highly express the interleukin-5Rα on their surface and also release significant amounts of IL-5 [67]. IL-5 signals via the IL-5 receptor (R) α chain and β chain (βc) complex [68]. Upon activation, IL-5 signaling is initiated by the α-chain that binds IL-5 with low affinity, and dimerization with the βc-subunit forms high-affinity receptor [69]. IL-5 activation induces phosphorylation of a series of cellular proteins such as βc, HS1, Shc, Btk, JAK1, JAK2, STAT1, STAT3, STAT5, PI3K, MAPKs. Phosphorylation of these proteins activates down-stream molecules such as Pim-1, c-fos, c-jun, NFκb, and thus induce cell survival and proliferation, immune responses and eosinophil number [70–76]. JAK2 is associated with hIL-5Rα, whereas JAK1 is associated with hIL-5Rα. JAK1 and JAK2 are activated upon IL-5 stimulation. JAK2 and STAT5 activation are essential for IL-5-dependent signal transduction in eosinophils and B cells [77,78]. IL-5 also activates, SHP2 and Raf-1 and Raf-1 regulate degranulation. Ras GTPase-ERK activation is vital for IL-5 mediated cell survival, and proliferation [79]. The inhibitors for kinases demonstrated the role of kinases in eosinophils activation [80]. In eosinophils p38 MAP kinases are activated, whereas its activation is inhibited in dying eosinophils [81]. The inhibitor for p38 MAP kinase SB239063 abolish lung eosinophilia in mice, another inhibitor SB203580 enhances apoptosis of eosinophils [82,83]. However, there is a concern that these inhibitors might have side effects as they target signaling mechanisms in various cell types. In addition to eosinophil survival, IL-5 also inhibits eosinophil apoptosis, via NF-κB mediated induction of BCL-X_L and play a role in the survival of eosinophils [84,85] (Fig. 2).

4. IL-18 mediated signal transduction in inflammation

Interleukin-18 (IL-18) is an 18 kDa pro-inflammatory cytokine has been identified as an IFN-γ-inducing factor, and is a member of the IL-1 family of cytokines and display pleiotropic effects in inflammation and allergic diseases [86]. The pro-IL-18 expression observed in immune cells like monocytes, macrophages, dendritic cells, Kupffer cells and also in other cell types like keratinocytes, articular chondrocytes, synovial fibroblasts and osteoblasts [87]. Human eosinophils isolated from BALF and blood express IL-18 mRNA and protein [88]. Pro-IL-18 is cleaved by caspase1 and form IL-18. IL-18 recognizes heterodimeric IL-18 receptors IL-18Rα and IL-18 Rβ, and signals via MyD88, IRAK,

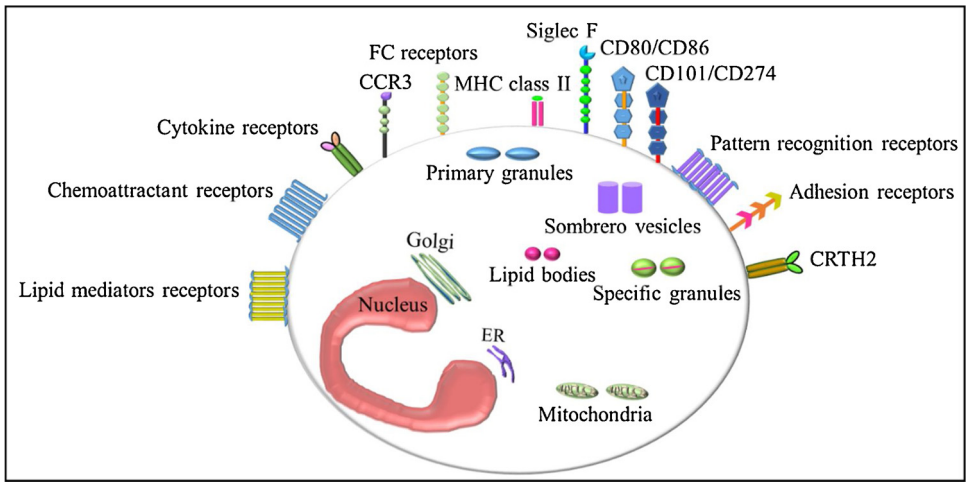

Fig. 1. Eosinophil constituents.

Table 1
Eosinophil constituents and function.

Eosinophil constituents	Molecules	Function	Reference
Adhesion molecules	Integrins, β1, β2, β7, selectins	eosinophil recruitment, T cell proliferation	[4,44,45,46]
Adhesion receptors	LFA1, CR3, CR4, VLA4, CD44, CD62L, PSGL1, CD34		
Apoptosis and signaling factors	CD30, CD45, CD52, CD69, CD95	Eosinophil survival and apoptotic cell death	[47,48]
Chemoattractant receptors	CCR1, CCR3, CCR4, CCR5, CCR6, CCR8, CCR9, CXCR2, CXCR3, CXCR4, C5aR, C3aR, FPR1	Adhesion of eosinophils to the endothelial cells, Chemoattractant to immune cells and the site of allergic inflammation.	[49,50]
Chemokines	CCL3, CCL5, CCL7, CCL8, CCL11, CCL13, CXCL1, CXCL10, CXCL11, CXCL12		
Cytokines and receptors	IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, IL-11, IL-12, IL-13, IL-16, IL-17, IL-18, IL-25, IFN-γ, GM-CSF, TNF, IL-2R, IL-3R, IL-4R, IL-5R, IL-9R, IL-10R, IL-13R, IL-17R, IL-23R, IL-27R, IL-31R, IL-33R, IFNγR, GM-CSFR,	Activation, proliferation, and maturation of eosinophils. Induction of inflammatory response, induce overexpression of adhesion molecules and promote airway remodeling.	[51]
Fc receptors	FcαR, FcγRII, FcεRI, FcεRII,	eosinophil survival, degranulation, and generation of leukotrienes	[46,52]
Growth factors and receptors	NGF, PDGF, SCF, VEGF, EGF, TGFα, TGFβ, APRIL, TSLPR, KIT, TGFβR	Play role in pulmonary hypertension, allergic asthma, allergic rhinitis, and allergic urticarial–angioedema, allergic inflammation Stimulates T cells, B cell proliferation and differentiation, and eosinophil differentiation from peripheral progenitors, growth and differentiation of mast cell progenitors residing in tissues, wound-healing and tissue remodeling, fibrosis, and tissue repair, extracellular matrix protein deposition, stromal fibrosis and basement membrane thickening.	[53,54,55,56,57,58,59,60,61,62]
Lipid body contents	Leukotriene C4, leukotriene D4, leukotriene E4, Thromboxane B2, Prostaglandin E1, Prostaglandin E2, 15-hydroxyeicosatetraenoic acid, Platelet-activating factor	Activation of platelets, neutrophils and leukocyte recruitment and, increase airway reactivity, vascular permeability and induction of bronchoconstriction and mediates asthma and allergic rhinitis.	[49,63]
Lipid mediators	Leukotriene $C_4/D_4/E_4$, Eotoxin $C_4/D_4/E_4$, Prostaglandin E_1, E_2, $F_{1\alpha}$, 5-HETE, 5,15-and 8,15-diHETE, platelet activating factor, Thromboxane B2		
Lipid mediators receptors	DP2 prostaglandin receptor (CRTH2), DP1 prostaglandin receptor, EP2 prostaglandin receptor, Leukotriene B4 receptor, Platelet-activating factor receptor		
Pattern recognition receptors	Dectin-1, TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR9, TLR 10, NOD1, NOD2, RIG-1, RAGE	Recognition of self, bacterial, viral and fungal signals. Activation of immune responses and release of pro-inflammatory chemokines, cytokines, granule proteins, leukotrienes, and reactive oxygen species. Activation of the adhesion system and cellular trafficking. Play a role in airway inflammation and hyper-reactivity.	[64]
Granule-derived proteins	Major basic protein (MBP)-1, MBP-2, Eosinophil peroxidase (EPO), Eosinophil-derived neurotoxin (EDN or RNase2), Eosinophil cationic protein (ECP or RNase3)	Local tissue damage, mast cell and basophil degranulation, airway mucus production and elevation of reactive oxygen species	[26,51]
Enzymes	β-glucuronidase, matrix metalloproteinase 9, α-mannosidase, Phospholipase A2, 5-lipoxygenase, 15-lipoxygenase, leukotriene C4 synthase, lysozyme, NADPH oxidase, Acid phosphatase, collagenase, arylsulphatase B, histaminase, phospholipase D, catalase, nonspecific esterase,	Aid in the migration of eosinophils through basement membranes, tissue remodeling, degrade phospholipids of Gram-negative bacteria and to cause airway inflammation and smooth muscle contraction, defense of microorganisms	[48,65]
Reactive oxygen intermediates	O_2, H_2O_2, hydroxyl radicles, singlet oxygen	Induce inflammatory response and T cell proliferation	[66]

TRAF6 and degradation of IκB kinase and phosphorylates p50 and p65 complexes and induces NFκB signal transduction. On the other hand, IL-18 mediated TRAF6 also phosphorylates MAPK, ERK, and JNK and induce AP-1 activation. These responses play a role in IL-18 mediated immune activation of T cells, B cells, NK cells, macrophages, mast cells and dendritic cells (Fig. 4). IL-18 mediated Th1/Th2 response leads to B-cell activation via the release of cytokines IFNγ and IL-4 [89,90]. Infection with pathogens like bacteria, virus, and fungi, and irritants exposure like silica, asbestos, and bleomycin, challenge activates NLRP3 inflammasome via PAMPS and DAMPs in immune cells and increase IL-1β secretion [91–94]. NLRP3 activation involves activation of adaptor protein ASC, and its sequestration in the nucleus to cytosol that interact with NLRP3 through its PYD and with caspase-1 through its CARD domains (9, 57). Activated caspase-1 cleaves IL-1β and IL-18, in the cytoplasm and these cytokines are released to the extracellular milieu and activate NLRP3-TLR-MYD88-NFκB signal transduction [95] (Fig. 5). NLRP3 inflammasome responses drive steroid-resistant asthma [39]. NLRP3 inflammasome formation is observed in the development of COPD and many other inflammatory diseases [96].

5. Role of IL-18 in eosinophils development and maturity

Previously, Ougura et al. [97] described that IL-18 induces neutrophils, eosinophils, and lymphocytes with an elevation in IL-5 and GM-CSF levels. Most recently, we first time implicated the role of IL-18 in eosinophils differentiation and transformation of IL-5 differentiated naïve eosinophils into the $CD101^+CD274^+$ pathogenic eosinophils [98]. We showed that eosinophil subsets are not present in naïve IL-18 gene-deficient mice and an increase in the human blood and tissues in diseases state. Importantly, IL-18 is induced in most allergic disease and all eosinophils accumulated in the tissues of allergic patients are expressing $CD101^+CD274$ [98].

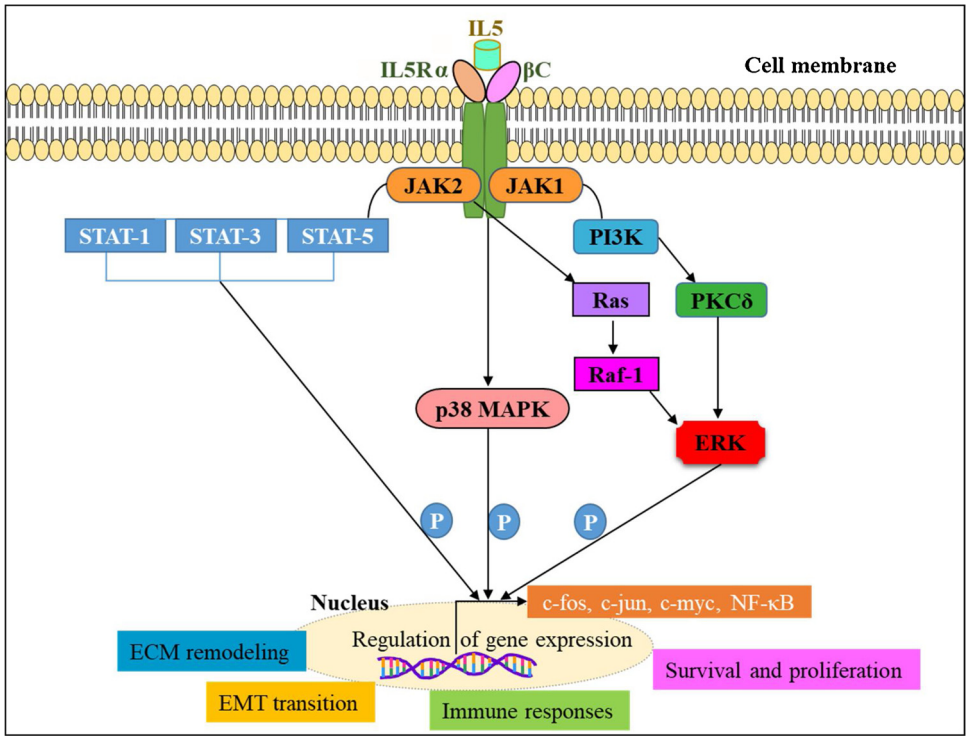

Fig. 2. IL-5 mediated cell signaling in eosinophils.

In addition, Kumano et al. [99] earlier showed that Interleukin-18 enhances eosinophil deposition in the airways of mice immunized and sensitized with oval albumin. Further reports showed the role of IL-18 in eosinophil-mediated tumoricidal activity against a Colo-205 carcinoma cell line by upregulating LFA-1 and ICAM-1, however neutralization of IL-18 reduced eosinophil-mediated Colo-205 apoptosis and inhibited cell-cell adhesion [100]. IL-18 is critical cytokine involved in activation of iNKT cells and ICAM in promoting human EoE, additionally IL-18 *in vitro* also stimulates human iNKT cells and endothelial cells and induce eosinophil-active cytokines IL-5 and IL-13 [101]. We previously reported that IL-18 induce iNKT cell activation to release the eosinophil activating cytokine IL-5, as IL-5-deficient mice and iNKT cell-deficient (CD1d null) mice do not induce EoE in response to intranasal IL-18 challenge. Thus allergen-induced IL-18 has a significant role in promoting IL-5 and iNKT dependent EoE pathogenesis in mice [102]. IL-18 overexpression induces Th1, Th2 cytokine-mediated airway inflammation in mice with an increase in IFN-γ, IL-13, eotaxin levels and $CD4^+$ T cells in ova sensitized mice [103].

6. Importance of IL-5 and IL-18 in eosinophils biology

IL-5 is a well established eosinophils differentiation, growth, and survival factor for eosinophils. Previous studies demonstrated that IL-5 levels were increased in asthma, allergy, and inflammation [104–106]. Thus IL-5 selectively affects eosinophil biology and is involved in a wide variety of allergic/inflammatory diseases mediated by eosinophils and is a therapeutic target for eosinophil-associated diseases.

Role of IL-18 in asthma development was studied in a model of airway hyperresponsiveness, and peribronchial eosinophilic inflammation of mice. Administration of mice with anti-human IL-18 antibodies protected against eosinophil-mediated airway inflammation and demonstrated the role of IL-18 in the development of asthmatic inflammation [107]. The current review signifies the critical synergetic role of IL-5 and IL-18 in eosinophils transformation from naïve eosinophils to pathogenic eosinophils. These understandings will provide an important input in eosinphils biology and future therapeutic interventions for eosinophils associated allergic diseases.

7. Eosinophils mediate immune responses

In general eosinophils defense helminth parasites by the release of cytotoxic granular proteins via degranulation mechanism [108]. Neutrophils infiltrate to the site of allergen exposure or inflammation. Eosinophil major basic protein stimulates PI3K and PKCζ and releases superoxide via activation of NADPH oxidase [109]. MBP also enhance neutrophil adherence receptor CR3, thus enhance the inflammatory role of neutrophils in allergic diseases [110]. The transmembrane migration of eosinophils was observed upon coincubation of eosinophils with neutrophils and stimulation with IL-8, and this provides evidence that neutrophils migrate in response to IL-8 and leads to eosinophils accumulation in the airways in asthma [111]. Classical M1 type macrophages are proinflammatory and are activated by IFN-γ and LPS and release IL-12, IL-6, TNF-α, and CXCL10, CCL3. Alternatively, M2 macrophages exhibit anti-inflammatory activity and are activated by Th2 cytokines IL-4 and IL-13 via induction of STAT6 activation and release cytokines in asthma and allergic diseases [112,113]. Depletion of alveolar macrophages increased eosinophils in bronchoalveolar lavage fluid of ovalbumin (OVA)-sensitized mice model of asthma, and transfer of unsensitized alveolar macrophages abrogated these changes [114]. IL-33 differentiates eosinophils from $CD117^+$ progenitors in IL-5 dependent manner and enhances airway inflammation with an increase in eosinophils and macrophages [115].

Mast cells interact with eosinophils on IgE activation or dexamethasone challenge, and this interaction helps in eosinophils survival and communication and mediated by CD48, and 2B4 mediate mast cell–eosinophil interactions and increase eosinophil survival [116]. In another study of allergen-induced EOE model, Niranjan et al. [117], identified an increase in esophageal mast cell numbers in parallel with eosinophils and promoted muscle cell hyperplasia and hypertrophy. Mastocytosis and mast cell degranulation observed in the esophagi of patients with esophageal esophagitis [118]. Mast cell-mediated chemokine release leads to the recruitment of eosinophils and natural killer

(NK) cells, through CCL11 and CXCL8 [119]. Mast cells alone are also able to mediate Th17 mediated allergic reactions independent of eosinophils via IL-33 response in eosinophil-deficient ΔdblGATA mice model following OVA inhalation [120].

Basophils also play a key role in acute and chronic allergic reactions. Basophils secrete IL-4, and IL-13 and promote Th2 dependent immunity [121,122]. Nakashima et al. [123] reported that basophils induce eosinophils upon interaction with mesenchymal fibroblasts in murine irritant contact dermatitis model via reactive oxygen species production. Upon allergen exposure, dendritic cells acquire the allergen and present to the draining lymph node, and the cells mature and induce T cell and B cell responses. Dendritic cell number increase with allergen exposure. Activation of TLR4 leads to DC migration and recruitment and induce Th2 responses [124]. On the other hand, eosinophil recruitment regulated by classical dendritic cells subsets. During memory stage of chronic asthma with allergen exposure in mouse cDC1s secrete CCL17 and CCL22 and recruit eosinophils and promote early eosinophil infiltration, as a part of type 2 immune response by lung CD24 − CD11b + DC2s by producing NO on day 1.5, and further this process is inhibited by releasing TGF-β1 on day 2.5 by CD24 + cDC2s [125].

Eosinophils also induce diverse immune responses upon allergen exposure and mediate cellular, humoral immune response and help defense the host immune system. Eosinophils induce Th2 immune response that involves the presentation of antigen to CD4 + T cells and Th2 differentiation, IL-4, IL-13 cytokine release within lymph nodes and tissues and secretion of EDN and recruitment of Th2 to cells under inflammation. Previous studies also demonstrated the central role of Th2 cells and eosinophils in allergic responses, and mice lacking IL-13, a Th2 cytokine and pre eosinophilic cytokine IL-5 neutralization displayed *Aspergillus fumigatus* clearance [126]. Eosinophils induce B cell proliferation, survival, antibody secretion and plasma cell maintenance, proliferation, and survival (Fig. 3). IL-5 Tg hypereosinophilic mice with profound B cell expansion showed a decrease in B cell lymphocytosis upon genetic deletion of eosinophils. Also, patients with idiopathic hypereosinophilic syndrome (HES) revealed a correlation between eosinophils levels and circulating B cell numbers [11,127–129]

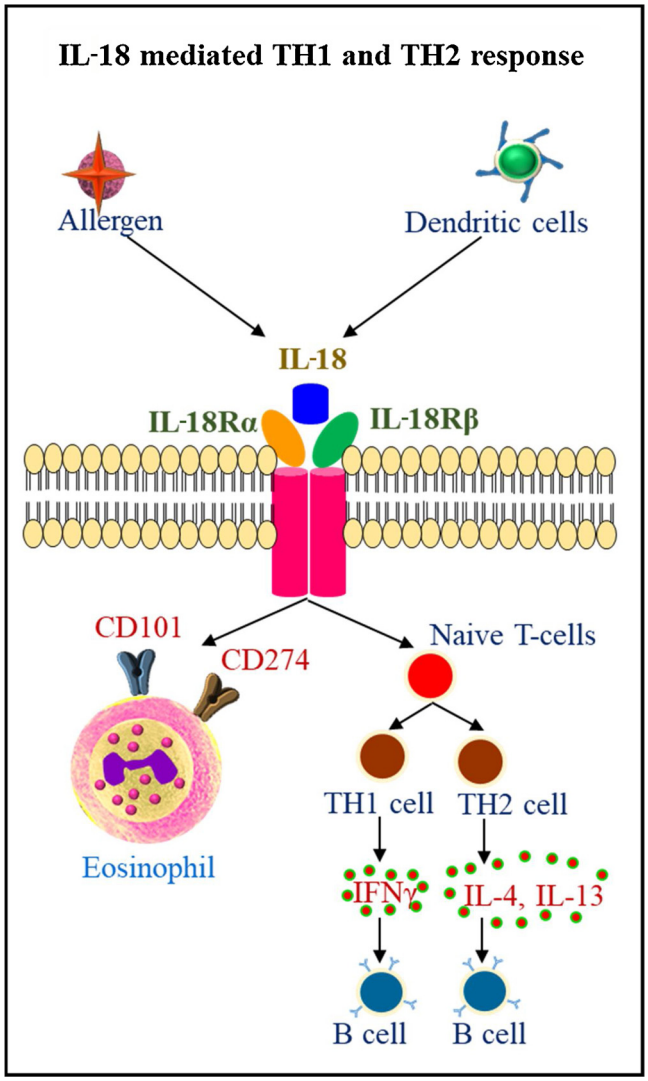

Fig. 4. Role of IL-18 in inflammation and eosinophil mediated allergic diseases.

8. Other cytokines involved in IL-5 and IL-18 mediated eosinophilic allergic diseases

Several cytokines play a critical role in allergic reactions, and contribute to disease pathology through the recruitment and activation of

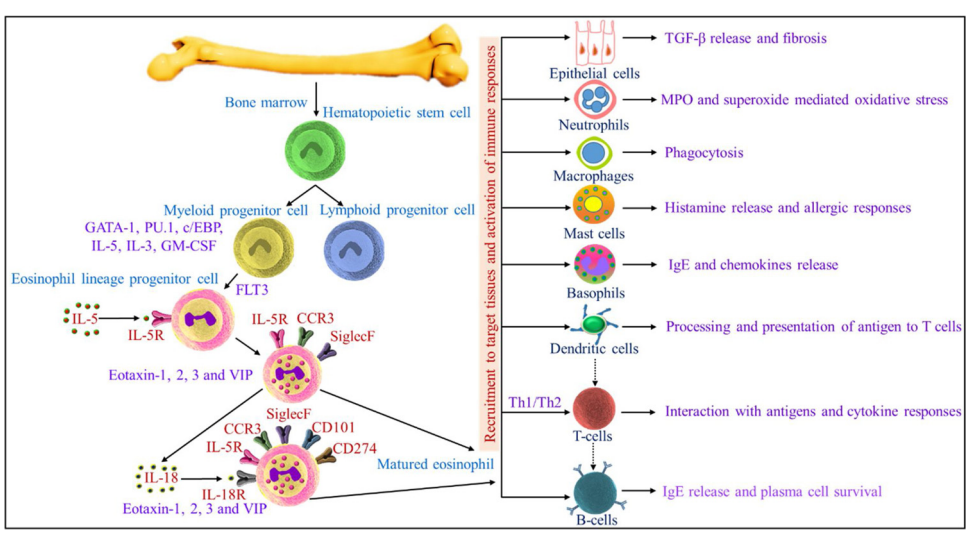

Fig. 3. Production, migration, and recruitment of eosinophils from bone marrow to targeted tissues in eosinophil mediated allergic diseases and activation of innate and adaptive immune responses.

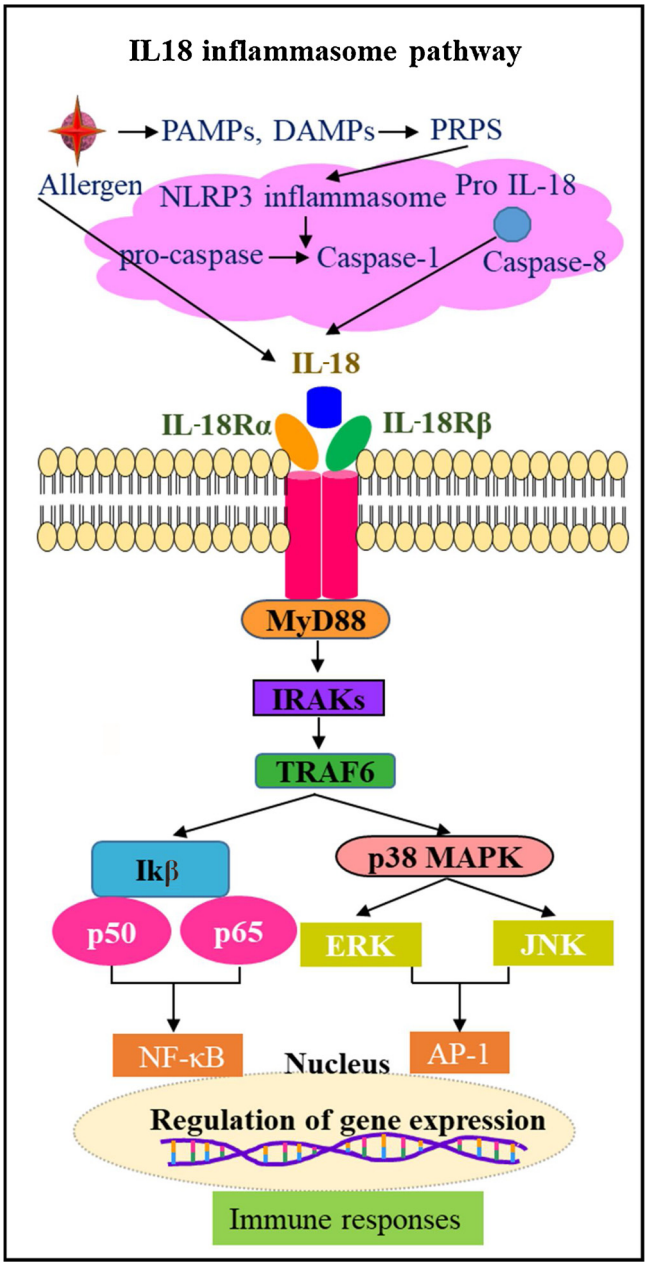

Fig. 5. Role of IL-18 and inflammasome mediated NFκB activation and immune responses in inflammation.

pro-inflammatory molecules and also mediated pro-fibrotic/remodeling events. T helper (Th) cells develop from naïve $CD4^+$-T cells under lineage-specific culture conditions and release cytokines that play pleiotropic effects in allergic diseases. Th2 cells produce IL-4, IL-5, IL-9, and IL-13 and play a role in the protection against helminths. Th17 cells produce IL-17A, IL-17 F, IL-22 and show activity on neutrophils, macrophages, B-cells and protect from bacteria, fungi and play a role in chronic inflammatory and autoimmune disorders [130,131]. Th22 cells production of IL-22 plays a role in adaptive immune response [132]. IL-18 and IL-33 are involved in the activation of both Th1 and Th2 responses and have an important role in promoting adaptive immunity [133].

8.1. IL-4

IL-4 is produced by Th2 cells, basophils, mast cells, and eosinophils and regulates allergic conditions and the protective immune response against helminths and other extracellular parasites. IL-4^+ TFH cell counts were increased in eosinophilic polyp tissues. IL-4 and IL-21 were involved in polyp TFH cell–induced IgE production from naive B cells, and nasal IL-4^+ TFH cell counts correlated highly with local IgE levels *in vivo*, nasal IL-4 + CXCR5 + CD4 + T follicular helper cell counts correlate with local IgE production in eosinophilic nasal polyps [134]. ILC2s promote allergic inflammation, IL-4 production by IL-33-stimulated ILC2s blocks the generation of allergen-specific Treg cells and favors food allergy [135]. Thymic stromal lymphopoietin-elicited basophils promote epicutaneous sensitization to food antigens and subsequent IgE-mediated food allergy through Th2 polarization and IL-4 production [136]. Eosinophils were the major IL-4 expressing cell type in the heart during experimental autoimmune myocarditis. Eosinophils drive the progression of myocarditis to inflammatory dilated cardiomyopathy through IL-4 [137].

8.2. IL-9

IL-9 is a Th2-derived cytokine and an important mediator of allergic inflammation. IL-9 overexpressing mice show increased mast cell numbers in the intestine with inflammation, paneth cell hyperplasia and up-regulation of IL-13-dependent innate immunity mediators in the intestinal mucosa [138]. IL-9 governs allergen-induced mast cell activation, and anti-IL-9 treatment protects from airway remodeling in asthma in mice [139]. Intestinal expression of IL-9 and mast cells are higher in patients with food allergy. In response to IL-33; IL-9-producing mucosal mast cells secrete increased amounts of IL-9 and IL-13 and play a key role in susceptibility to IgE-mediated food allergy [140].

8.3. IL-13

Overexpression of IL-13 in mice promotes asthma and EoE by an IL-5, eotaxin-1, and STAT6-dependent mechanism and increase eosinophils and epithelial cells hyperplasia [141]. However, it is also reorted that IL-5 has a critical role in promoting IL-13 induced disease pathogenesis [117], because IL-13 gene-deficient mice demonstrated development of allergen-induced EoE. Similarly, a report also indicates that esophageal eosinophilia is observedeven in IL-4/IL-13 double gene-deficient and STAT6 gene-deficient mice. Indicating, that anti-IL-4Rα therapy may not protect allergen or cytokine induced gastrointestinal disorders.

8.4. IL-17

IL-17A and IL-17 F are Th17 cytokines produced by $CD4^+$ T cells and implicated in the pathogenesis of various allergic and chronic inflammatory diseases. IL-17^+ cell population was found exclusively in $CD3^+CD4^+$ T cells, and the percentage of Th17 cells increased in peripheral blood of AD patients [142]. IL-17 levels elevated in mouse upon allergen exposure, and IL-17 knockout mice attenuated inflammation with a significant decrease in eosinophils [143]. IL-17 levels elevated in mice infected with the respiratory syncytial virus during OVA-induced allergic airway inflammation [144].

8.5. IL-21

IL-21 is a member of the type I cytokine family and is produced by $CD4^+$ T cells, natural killer T cells, and Th17 cells and plays a major role in the control of innate and adaptive immune reactions [145]. An increase in serum IL-21 levels in adult atopic dermatitis patients with acute skin lesions was observed in patients [146]. rIL-21 nasal administration ameliorated allergic rhinitis by prevention of IgE production by B cells, eotaxin production by fibroblasts and attenuation of eosinophil infiltration into nasal mucosa [147]. Indicating anti-IL-21 may be effective in eosinophilic allergic patients.

8.6. IL-22

IL-22 play a role in inflammations, allergic diseases, and autoimmunity. IL-22 is mainly produced by innate lymphoid cells, not by Th cells in the inflamed lungs [148]. IL-22 in lesioned skin of chronic AD is higher than in psoriatic lesions [149]. IL-22 elevated in asthma patients and the mouse model of asthma [150,151]. Allergen-sensitized IL-22-deficient mice suffer from significantly higher airway hyperreactivity upon airway challenge with an increase in eosinophil infiltration, lymphocyte invasion and production of CCL17 (TARC), IL-5 and IL-13 in the lung. IL-22 play a role in pathogen elimination and innate lung defense against *Aspergillus fumigatus* mediated by Dectin-1-dependent IL-22 production [152].

8.7. IL-25

IL-25-high subset people had high Th2 cytokine levels serum IgE, with airway and blood eosinophils, airway hyperresponsiveness, and subepithelial thickening [153]. IL-25 neutralization in allergen-exposed mice exhibited a reduction in pulmonary eosinophilia and levels of Th2 associated cytokines, IL-5 and IL-13 and decreased fibrosis, airway smooth muscle hyperplasia and airway hyperreactivity [154].

8.8. IL-33

IL-33 is a nuclear cytokine that belongs to the IL-1 family and plays a crucial role in innate immunity. IL-33 expressed in epithelial cells, lymphoid organs and its levels increased in allergic inflammation and bronchial asthma [155]. Upon allergen challenge IL-33, levels were increased with IL-5 and IL-13 production and airway eosinophilia without T or B cells via $CD25^{+}CD44^{hi}$ lymphoid cells, and this innate type-2 response abolished in IL-33 gene-deficient mice [156].

9. IL-5 generated and IL-18 transformed pathogenic eosinophil mediated allergic diseases

Allergy is a condition that the body responds abnormally to foreign substances. This is due to the hypersensitivity of a person's immune system to a particular or a variety of allergens in the environment. The common allergens include pollen, bee stings, certain foods, dust, mites, molds, drugs, latex, dander, exposure to animals, and seasonal climate change. The common symptoms associated with exposure to allergens include rashes on skins, eczema, hives, edema, inflammation, rhinitis, sneezing, itching, runny/stuffy nose, cough, chest tightness, wheezing or shortness of breath, watery, red or swollen eyes (conjunctivitis) and mucus formation.

Allergic diseases affect approximately 50 million Americans and several people worldwide. The common allergic diseases include asthma, atopic dermatitis or eczema, anaphylaxis, hay fever, sinusitis, urticaria or hives, and eosinophilic esophagitis. Eosinophil mediated allergic diseases listed in Fig. 6.

9.1. Asthma

Asthma is narrowing of airways due to inflammation and an excessive mucous generation that results in coughing, wheezing, chest tightness and shortness of breath. Eosinophilic function in asthma is not clear, and all the asthmatic patients are not eosinophilic. Preclinical models of lung allergy delineated that mice lacking eosinophils still develop airway hyperreactivity [157–159]. Several animal and human studies are correlated with eosinophils mediated asthma development with an increase in IL-5 and IL-18 levels. Eosinophil mediated asthma in humans account 20% with refractory asthma [160]. Increase in IL-5 levels observed in asthma patients with acute respiratory, viral, mixed viral/bacterial, infections, pneumonia, bronchitis [161]. Increased IL-18 levels were observed in asthma patients and correlated with asthma exacerbations [162]. We most recently showed that $CD101^{+}CD274^{+}$ pathogenic eosinophils accumulate in the nasal lavages of asthma and esophageal biopsies of eosinophilic esophagitis patients, respectively. Additionally, these IL-18 responsive eosinophil subsets are also increased in the blood of asthma and eosinophilic esophagitis patients [2]. A similar observations are also reported in the mouse models of asthma and eosinophilic esophagitis.

9.2. Atopic dermatitis (AD) or eczema

Atopic dermatitis or eczema is one of the most prevalent skin disorder and often occurs in children and also may appear in adulthood. AD is genetical or occurs on exposure with allergens and or environmental factors that involve immune dysregulation and impaired skin barrier function and results in red itchy and dryness of the skin [163]. The allergens that enter the skin might be picked via IgE receptor by IgE specific antigen bound to Langerhans cells, and these cells migrate to lymph node and stimulate Th1 cells to differentiate to Th2 cells and promote differentiation of B cells to plasma cells and also induce chemokines, cytokines IL-4, IL-5 and IL-13 and IL-18 release and aid in eosinophil development and release [164]. Pathogenic eosinophilia has been shown to be present in patients with AD [165]. Activated eosinophils in turn also secrete cytokines and chemokines, such as IL-16, IL-12, TGF-β1, and IL-13 and induce immunological reactions. Eosinophil granular proteins deposition and its degranulation observed in AD patients [166]. Topical calcineurin inhibitors like tacrolimus, pimecrolimus, immunomodulatory agents prednisolone, systemic steroid-sparing agents azathioprine, methotrexate, cyclosporine, mycophenolate are available treatments for AD [167,168].

9.3. Anaphylaxis

Anaphylaxis is a life-threatening hypersensitive reaction. The most common allergic reactions of anaphylaxis are exposure to wasp and bee venom, legumes, animal proteins, insect stings, and analgesic medications. The persons that come across anaphylaxis require immediate administration of epinephrine and medical attention. Mast cell signaling via FcεRI and IgE binds to FcεRI, and IgE and antigen-induced signaling events induce immunological reactions and mediate eosinophil-mediated allergic reactions [169]. Glucocorticosteroids, antihistamines, methylxanthines, venom immunotherapy considered for the management of anaphylaxis [170].

9.4. Hay fever or allergic rhinitis

Allergic rhinitis affects 400 million people worldwide [171]. On exposure with allergens such as pollens, grass, and dust mites result in a runny nose, and watery eyes with inflammation of the nose and mucous membranes, fever and the condition referred allergic rhinitis (AR). AR is part of a systemic inflammatory process and is associated with other inflammatory disorders of mucous membranes including asthma, rhinosinusitis, and allergic conjunctivitis. High prevalence of asthma is recorded in people with persistent and severe rhinitis [172]. Upon sensitization, to allergens, dendritic cells present allergens to T lymphocytes and promote Th2 responses and activate $CD4^{+}$ T cells and releases IL-4, IL-5, IL-10, and IL-13 cytokines. IL-4 induces IgE class switch in B lymphocyte and release IgE in the bloodstream that binds with mast cells and basophils. Mast cells release histamine and mediate nasal response. Histamine and TNF-α, leukotriene C4 and prostaglandin D2 contribute to the influx of eosinophils, $CD4^{+}$ T lymphocytes, and basophils by stimulation of expression of adhesion molecules on endothelial cells and cause severe allergic responses and nasal obstruction. $CD4^{+}$ lymphocytes represent IL-5 that also play a role in allergic rhinitis by activation of eosinopoiesis, influx, and survival of eosinophils in nasal tissues [173–176].

Corticosteroids like fluticasone, mometasone, ciclesonide,

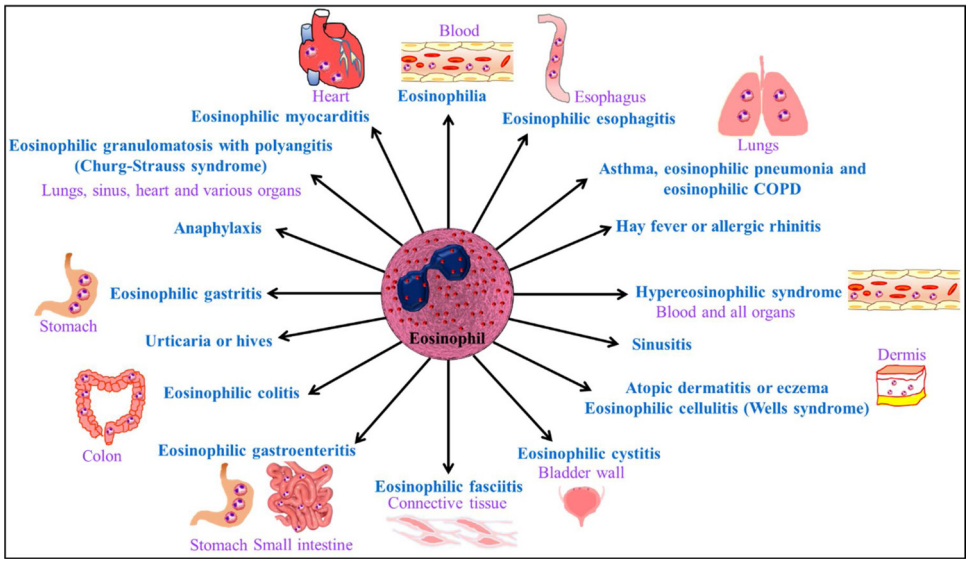

Fig. 6. Eosinophils associated allergic diseases.

triamcinolone, flunisolide, beclomethasone, betamethasone, antihistamines like azelastine, olopatadine, chromones like sodium cromoglicate, nedocromil sodium, anticholinergics like ipratropium bromide, decongestants like ephedrine, pseudoephedrine, xylometazoline; antihistamines like levocetirizine, cetirizine, desloratadine and loratadine, fexofenadine, acrivastine, rupatadine, carebastine and ebastine; corticosteroids like hydrocortisone, prednisolone; antileukotrienes like montelukast and zafirlukast and leukotriene synthesis inhibitors like zileuton; decongestants like pseudoephedrine are advised as a pharmacotherapy for allergic rhinitis. Apart from the medications immunotherapy is also a cure for people with allergic rhinitis [177].

9.5. Chronic hyperplastic eosinophilic sinusitis

Sinusitis is an inflammation of the sinuses that results in mucous formation. Acute sinusitis may be a result of allergens exposure and also results in fever, sore throat, headache and swelling of the face. Chronic sinuses are severe disease process associated with nasal polyposis and develop upon exposure with antigens, allergens, fungal, bacterial agents. Eosinophilic chronic rhinosinusitis is intractable and persistent disease and characterized by an inflammation of the nose and paranasal sinuses with nasal congestion and excessive mucus production and eosinophilic infiltration of nasal polyp tissue. IL-4, IL-5, or IL-1β may be critical for PDGFRα and play a pivotal role in the pathophysiology of eosinophilic and non-eosinophilic chronic rhinosinusitis with nasal polyps [178]. IL-16 may stimulate the migration and persistence of activated eosinophilic granulocytes in eosinophilic chronic rhinosinusitis [179]. Th2 mediated IL-25, IL-33, and IL-31, TGFα is up-regulated in eosinophilic chronic rhinosinusitis [180]. Higher leukotriene C4 levels can be an indicator of the risk of recurrence of nasal polyps in patients with recurrent sinonasal polyps after surgery. Leukotriene receptor antagonists like montelukast and zafirlukast and the leukotriene synthesis inhibitor zileuton are recommended therapeutic measures [180,181]. Intranasal corticosteroids are also therapeutic strategies to modulate nasal mucosa, epithelial repair and regulating tissue remodeling markers, and to reduce tissue eosinophil infiltration [182].

9.6. Urticaria or hives

Body's reactions to allergens cause rashes on the skin that turn to swollen pale red bumps that are itchy and sometimes causes burning, and the condition also referred to as hives. Food allergens, medications, exposure to cold or hot environmental conditions and insect stings are triggers for hives. Eosinophils are recruited upon allergen exposure in urticaria and contribute to the pathogenesis by the release of proinflammatory cytokines, tissue-damaging protein, and immunoregulatory molecules. Eosinophilic granular proteins MBP and ECP observed in urticaria with IL-3, IL-4, IL-5, IL-2, IL-10, IL-12, and GM-CSF, IFN-γ, eosinophilic infiltration with deposits of cationic proteins MBP and EDN and high levels of leukotrienes C4 are observed in the lesioned skin [183]. Medications for urticaria include epinephrine auto-injector, antihistamines, ultraviolet therapy, application of hydrophobic barrier creams, anti-IgE antibody Omalizumab administration [184–188].

9.7. Eosinophilia

The condition where eosinophils count increases < 450 cells per μl of blood is eosinophilia [189]. Eosinophilia observed in a variety of allergic diseases that encountered as a result of increased eosinophil levels or cytokines such as IL-4, IL-5, and IL-13 that may also induce eosinophilia. Transgenic mice expressing IL-5 show eosinophilia [190]. The diagnosis of eosinophilia in patients characterized by an allergic condition like wheezing, rhinitis, or eczema [191]. The common factors that contribute to eosinophilia include exposure to helminth like schistosomiasis; the presence of a pet dog infected with *Toxocara canis*, and hypersensitivity to drugs. Eosinophilia observed in a variety of cancers [192,193]. Parasitic eradication is the main cure for eosinophilia and albendazole is popularly used [194]. Therapeutics for eosinophilia with organ involvement include corticosteroids and IFN-α for the steroid-resistant disease. Other agents for the steroid-resistant disease, which are usually given as long-term maintenance regimens to control organ involvement, include the hydroxyurea, Chlorambucil, Vincristine, Cytarabine, 2-Chlorodeoxyadenosine (2-CdA) Etoposide, Cyclosporine [195].

9.8. Eosinophilic esophagitis (EoE)

EOE is one of the major cause of upper gastrointestinal morbidity with an estimated prevalence of 56.7/100,000 persons. Food sensitization is one of the main reasons for EOE and characterized by esophageal dysfunction with the formation of eosinophilic infiltrate in the esophageal mucosa [196]. Several eosinophils active Th2 cytokines, IL-4, IL-5, IL-13, and IL-18 shown to increase in EoE patients, and the overexpression of these mice promotes disease pathogenesis similar to the human. Our earlier study showed CD274 expressing and non-expressing eosinophils in pediatric and adult EoE patients. CD274

expression on blood eosinophils and blood mRNA expression levels were higher EoE patients and decreased following treatment [197]. Therapeutic approaches for EoE include chronic dietary elimination of allergic food, topical corticosteroid application, and esophageal dilation [198]. Anti-IL-5, anti-IL-13 and anti-IL-4 Ra clinical trials are in progress in most of the allergic diseases including EoE. Currently, the elimination diet and corticosteroids therapy are the best approaches to improve the EoE patients quality of life [199].

9.9. Eosinophilic cystitis (EC)

Eosinophilic cystitis characterized by infiltration of eosinophils and inflammation across the bladder wall. EC is characterized by injury of eosinophils to the bladder tissues resulting in gross hematuria, marked irritation of the lower urinary tract causing dysuria and frequency and fibrosis of the mucosa and muscularis necrosis of bladder wall [200]. Dysregulation of clonal eosinophilic proliferation, resulting in overproduction eosinophils in bladder mucosa with an elevation of IL-4, IL-5, IL-13, IFNγ, and TNFα observed in EC. Cyclophilin inhibitors and, cyclosporine identified as a promising strategy to treat EC [201].

9.10. Eosinophilic fasciitis (EF)

EF characterized by edema and induration of the arms and legs and infiltration of eosinophils. EF diagnosed as inflammation and thickening of collagen bundles in the superficial muscle fascia with infiltration of immune cells. Laboratory diagnosis EF includes eosinophils accumulation in blood, hypergammaglobulinemia, and an increase in erythrocyte sedimentation rate [202]. An increase in T cell population and IL-5 levels observed in EF patients, and the increase in IL-5 levels correlated with enhanced production of eosinophils, their maturation, and recruitment to the inflamed regions [203–206]. Therapy for EF includes administration of corticosteroids and sulfasalazine, cyclosporine, methotrexate, hydroxychloroquine [207].

9.11. Eosinophilic granulomatosis with polyangiitis (EGPA), aka Churg-Strauss syndrome

EGPA is a systemic small-vessel eosinophilic vasculitis observed in association with asthma and eosinophilia. It is characterized by the presence of anti-myeloperoxidase (MPO), anti-neutrophil antibodies in the cytoplasm of 30–38% of patients and most frequently involves peripheral nerves and skin [208]. Apart from genetic background associated with HLA-DRB4 alleles the disease can be triggered by exposure to allergens, infections, vaccinations or drugs such as macrolide antibiotics, leukotriene receptor antagonists and exposure to particulate silica. EGPA is a Th2 mediated disease and the T cells produced Th2 cytokines such as IL-4, IL-13, IL-5, and $CD294^+$ T cells observed with an increase in CCL17 and IL17A and a decrease in TREG cells. Clinical manifestation and laboratory findings demonstrate asthma and rhino-sinusitis, peripheral eosinophilia lung infiltrates due to bronchial plugging by mucus formation is also observed in patients [209]. Cyclophosphamide, Methotrexate, Rituximab, Mepolizumab suggested treatment strategy for EGPA [2010,211].

9.12. Eosinophilic pneumonia (EP)

Eosinophilic pneumonia is a pulmonary disease characterized by diffuse pulmonary infiltrates and an increase in eosinophils in the lungs and bronchoalveolar lavage fluid. EP's are due to lung infections, or drug-induced and off acute and chronic types. Several studies reported that cigarette smoking linked with the development of acute eosinophilic pneumonia. Chronic eosinophilic pneumonia characterized by radiographic evidence of bilateral peripherally located opacities with shortness of breath for several months. Peripheral blood eosinophilia with blood eosinophil count > 1000/mL and increase in serum IgE level, erythrocyte sedimentation rate, C-reactive protein, and platelet counts [212,213]. Corticosteroid treatment with intravenous methylprednisolone or oral prednisone and omalizumab were considered an effective strategy for EP [214,215].

9.13. Hypereosinophilic syndrome (HES)

HES is characterized by a marked increase in eosinophils (> 1500 eosinophils/mm^3) and its associated pathology with eosinophil-mediated end-organ damage. HES is also associated with cardiovascular complications with endomyocardial fibrosis and thrombosis [216]. HES patients showed clonal T-cell receptor rearrangements and IL-5 producing T cells characterized by $CD3^-CD4^+$ T cells [217]. HES also may be due to interstitial chromosomal deletion on 4q12 leading to the creation of the FIP1L1-PDGFRA fusion gene (F/P^+variant) [218]. Corticosteroids, hydroxyl urea, vincristine, prednisone, hydroxycarbamide, and interferon-α, mepolizumab (anti–IL-5 mAb), imatinib mesylate, cyclophosphamide, 6-thioguanine, methotrexate, cytarabine, 2-CDA, alemtuzumab, cyclosporine, intravenous immunoglobulin are suggested therapy for HES [219,220].

9.14. Eosinophilic COPD

Chronic obstructive pulmonary disease is a lethal disease and is the 4th leading cause of deaths worldwide (WHO 2015). IL-18 overexpression is linked with emphysematous lesions and mediates Th1, Th2, and Th17 cytokine responses [221]. Increased expression of IL-18 was observed in COPD patients and correlated with disease severity [222–224]. Due to the pathogenic role of eosinophils in COPD clinical results demonstrated the benefits of monoclonal antibodies targeting IL-5 in severe eosinophilic COPD. Mepolizumab, a humanized monoclonal antibody, reduces eosinophil counts in blood and tissues by blocking IL-5, through binding to eosinophil surface receptors [67,225]. Mepolizumab at a dose of 100 mg was associated with a lower annual rate of moderate or severe exacerbations than placebo among patients with COPD and an eosinophilic phenotype and suggested that eosinophilic airway inflammation contributes to COPD exacerbations [226].

9.15. Eosinophilic myocarditis (EM)

EM is an acute life-threatening cardiac inflammatory disease that is characterized by eosinophilic infiltration and has a poor prognosis and requires endomyocardial biopsy for definitive diagnosis. EM often accompanied by eosinophilia and is associated with immune dysfunctions. The clinical observation of patients with EM is with abrupt impairment of left ventricular ejection fraction and high risk of malignant arrhythmias. Thus, corticosteroid therapy, some form of inotropes and mechanical circulatory support for recovery in patients with EM was supportive and beneficial. Elevated IL-5 levels were observed in patients with EM and anti-IL-5 therapy by administration of Mepolizumab improved cardiac function [227]. Despite the progress in understanding the EM further clinical trials and awareness of disease progress and treatment are required for treating patients with EM [228,229]. Induction of EM in hypereosinophilic IL-5 Tg mice resulted in eosinophilic myocarditis with ventricular and atrial inflammation and progress to dilated cardiomyopathy [137].

9.16. Eosinophilic cellulitis (ECE)/ Wells syndrome

ECE also was known as Wells syndrome is a hypersensitivity of the dermis against a variety of exogenous and endogenous antigenic stimuli and is usually seen in adults and rarely in children. ECE represents acute pruritic dermatosis, with scarring and flame figures of the skin with an accumulation of inflammatory cells and eosinophilic debris. IL-5 overproduction might contribute to eosinophil accumulation [230]. $CD4^+CD7-T$ cells may be implicated in IL-5 production and

recruitment of dysregulated eosinophils in ECE [231]. IL-4 and IL-13 mediated activation of CD163 + M2 macrophages might also contribute to the recruitment of eosinophils in ECE [232]. IL-2 mediated platelet activation stimulated activation CD25 expressing eosinophils degranulation and release of eosinophilic cationic protein and tissue damage documented in ECE [233]. Treatment measures of ECE include corticosteroids, dapsone, antihistamines, colchicine, interferon-α, antimalarial drugs, and immunosuppressive agents like cyclosporine and azathioprine, and tacrolimus [234–237].

9.17. Pulmonary eosinophilia (PE)

Following allergen exposure in pulmonary eosinophilia characterized by eosinophilia, goblet cell metaplasia, and increased Th1, Th2, Th17 cells mediated cytokine production. Particularly, Th17 cells mediated IL-17 play a key role in immune reactions in pulmonary eosinophilia following *A. fumigatus* exposure in mice. Inflammation attenuated in IL-17 knockout mice challenged with *A. fumigatus* with a significant decrease in eosinophils, conidial clearance, and the early transient peak of $CD4^+$ $CD25^+$ $FoxP3^+$ cells was blunted explaining the role for IL-17 in driving Th2-type inflammation to repeated inhalation of fungal conidia [143]. Therapy for PE includes prednisolone, methylprednisolone, and oral glucocorticoids, inhaled glucocorticoids [238]. The JAK-3 inhibitor CP-690550 acts as an anti-inflammatory agent for pulmonary eosinophilia in a mouse model [239].

9.18. Eosinophilic gastrointestinal disorders (EGID)

EGID's selectively affect the gastrointestinal tract with inflammation and accumulation of eosinophils in the absence of known causes for eosinophilia like drug reactions, parasitic infections, and malignancy. The common factors for EGID's are genetic, food sensitization and persons with EGID often have an atopic disease. EGID symptoms include difficulty in swallowing, vomiting, reflux, abdominal and chest pain. IL-5, IL-13, and IL-18 implicated in the EGID pathogenesis. The diagnosis for EGID is through biopsies from endoscopy and/or colonoscopy [240,241]. The common EGID's described below.

9.18.1. Eosinophilic colitis (ECO)

It's a rare form of the eosinophilic gastrointestinal disease and observed in neonates and also in young adults. The pathophysiology associated with ECO is altered hypersensitivity and associated with food allergy in infants, and in adults, it is T lymphocyte-associated. Common symptoms include abdominal pain, weight loss, and diarrhea, mucosal injury and malabsorption [242]. ECO characterized by eosinophilic infiltration in the colon, which is also associated with high serum IgE, and IL-5 levels. Treatment for ECO includes administration with glucocorticoids, antihistamines, leukotriene receptors antagonists and drugs that target IL-5 and IgE levels [243].

9.18.2. Eosinophilic gastritis (EG)

EG is commonly confined to stomach eosinophilic inflammation; however it also represents coexisting eosinophilic accumulation in the esophagus. Blood eosinophil counts, and accumulation of $MIB\text{-}1^+$, $CD117^+$ mast cells, and $FOXP3^+$ T-reg cells, activated T cells, are increased in patients with EG. Cytokine-like IL-4, IL-5, IL-13, IL-17, IL-18 and CCL26 was also significantly increased in EG patients that may correlate with elevated eosinophil levels or vice versa [244]. Therapies for EG include a dietary restriction in patients allergic to milk, egg, soy, wheat, nuts, seafood, red meats and other foods [245].

9.18.3. Eosinophilic gastroenteritis

EGE is commonly associated with food allergy and characterized by abdominal pain, dysphagia, nausea, vomiting, and diarrhea. EGE characterized by the eosinophilic accumulation in the gastrointestinal tract, serum IgE levels are also observed in EGE patients [246]. IL-3, IL-5 and GM-CSF accumulation observed along with eosinophil levels in EGE. Eotoxin associated eosinophil accumulation seen in lamina propria of stomach and intestine [247]. Treatment for EGE includes administration of corticosteroids like fluticasone, prednisolone and budesonide and mast cell stabilizer cromolyn, leukotriene receptor antagonists like montelukast [248].

10. Conclusion and future perspectives

Eosinophils are normal constituents of the GI tract, mammary glands, and bone marrow, and play roles in development and homeostasis of these organs. In the present review, we discussed the evolution of the eosinophil as a multi-factorial leukocyte with pleiotropic functions, and the significance of IL-5, IL-18 and other cytokines in eosinophil associated allergic diseases. Although historically eosinophils are considered as cells that exhibit defense against parasites, the vast majority of data supports that eosinophils are pleiotropic multifunctional leukocytes that promote allergy and allergic diseases and elicit innate and adaptive immune responses upon hyperactivity to allergens. In Th2 type inflammation/allergy IL-4, IL-5, IL-9, IL-13, IL-18, IL-25, and IL-31 cytokines play a critical role. Several studies carried out in humans, and animal models of eosinophil allergic diseases revealed that among these cytokines IL-5 and IL-18 play a major role in eosinophil differentiation, maturation, development, transformation, migration, accumulation and elicit immune reactions. Small molecule antagonists of CCR3, CRTH2 or eosinophil inhibitory receptors might also be an effective strategy to treat eosinophils in allergic diseases. Therapies with molecules that block IL-5 or and IL-18 signaling might be promising to treat eosinophil-mediated allergic diseases. Although anti-IL-5 antibody therapy for allergic diseases remains elusive, a potential of humanized anti-human-IL-5Rα mAb treatment or anti-hIL-18Rα mAb treatment or in combination for asthmatic and allergic disease patients may be beneficial as a therapeutic strategy in the treatment to eliminate and control eosinophils and subsets of eosinophilic phenotypes that mediate allergic diseases. Blockade of eosinophils production in bone marrow, transformation into pathogenic eosinophils, inhibition of eosinophil activation and factors that contribute to eosinophil apoptosis is also interesting strategies for eosinophil depletion in allergic diseases. In summary, we propose the initiation of the anti-IL-18 clinical trial to block the transformation of naïve eosinophils into the pathogenic eosinophils. Anti-IL-18 therapy may maintain the eosinophils associated innate immunity and restrict disease pathogenesis by restricting the maturation of pathogenic eosinophils. Thus, we need additional studies using genetically engineered IL-5 and IL-18 double gene-deficient mice for *in vivo*, characterization of the immunobiology eosinophils associated disease pathogenesis.

Conflict of interest

No author has any conflict of interest.

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