



REVIEW

Current and Emerging Strategies to Inhibit Type 2 Inflammation in Atopic Dermatitis

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ABSTRACT

Type 2 immunity evolved to combat helminth infections by orchestrating a combined protective response of innate and adaptive immune cells and promotion of parasitic worm destruction or expulsion, wound repair, and barrier function. Aberrant type 2 immune responses are associated with allergic conditions characterized by chronic tissue inflammation, including atopic dermatitis (AD) and asthma. Signature cytokines of type 2 immunity include interleukin (IL)-4, IL-5, IL-9, IL-13, and IL-31, mainly secreted from immune cells, as well as IL-25,

IL-33, and thymic stromal lymphopoietin, mainly secreted from tissue cells, particularly epithelial cells. IL-4 and IL-13 are key players mediating the prototypical type 2 response; IL-4 initiates and promotes differentiation and proliferation of naïve T-helper (Th) cells toward a Th2 cell phenotype, whereas IL-13 has a pleiotropic effect on type 2 inflammation, including, together with IL-4, decreased barrier function. Both cytokines are implicated in B-cell isotype class switching to generate immunoglobulin E, tissue fibrosis, and pruritus. IL-5, a key regulator of eosinophils, is responsible for eosinophil growth, differentiation, survival, and mobilization. In AD, IL-4, IL-13, and IL-31 are associated with sensory nerve sensitization and itch, leading to scratching that further exacerbates inflammation and barrier dysfunction. Various strategies have emerged to suppress type 2 inflammation, including biologics targeting cytokines or their receptors, and Janus kinase inhibitors that block intracellular cytokine signaling pathways. Here we review type 2 inflammation, its role in inflammatory diseases, and current and future therapies targeting type 2 pathways, with a focus on AD.

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Key Summary Points

Aberrant type 2 immune responses are associated with allergic conditions characterized by chronic tissue inflammation, including atopic dermatitis.

Immune dysregulation in such diseases is often highly complex and involves many different cell types and inflammatory mediators.

Studies of drugs targeting type 2 immune mediators have helped clarify the biologic mechanisms underlying type 2 immunity while also providing tremendous therapeutic advances for diseases involving type 2 inflammation.

DIGITAL FEATURES

This article is published with digital features, including an infographic, to facilitate understanding of the article. To view digital features for this article, go to <https://doi.org/10.6084/m9.figshare.19609980>.

INTRODUCTION

Immune-mediated diseases involve aberrant responses to self-antigens and/or inappropriate activation of cellular and cytokine responses leading to chronic inflammation and tissue damage [1]. Type 2 immunity originally evolved to protect hosts from parasitic helminths or toxins [2–5], but aberrant type 2 inflammation underlies numerous chronic inflammatory pathologies, including atopic dermatitis (AD) and asthma. The pathways underlying type 2 inflammatory diseases are diverse and may vary by age and ethnicity but often share common mediators that can be therapeutically targeted.

Mechanistic characterization of these drug targets will improve our understanding of the efficacy and safety of therapeutic immunomodulation. Here, we provide an overview of type 2 inflammation, its role in inflammatory diseases, and therapeutic approaches to disease control. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

IMMUNE RESPONSE AND ASSOCIATED INFLAMMATION

Immune Pathways and Their Role in Homeostasis

The immune system consists of the innate system, which recognizes conserved pathogenic features and provides initial defense mechanisms, and the adaptive system, which acts with specificity and provides long-term immune memory through effector T cells and antibody production by B cells [1, 6]. These two branches are intrinsically coordinated. Antigen-presenting cells (APCs), part of the innate immune system, process and present antigen on major histocompatibility complex (MHC) molecules to activated lymphocytes, members of the adaptive immune system [7]. APCs also produce cytokines and display costimulatory signals facilitating lymphocyte activation and differentiation, usually along one of three main differentiation pathways: types 1, 2, and 3 (Fig. 1) [8–11].

Type 1 immunity evolved to protect against intracellular pathogens such as bacteria, protozoa, and viruses and is characterized by group 1 innate lymphoid cells (ILC1s), T-helper (Th) 1 cells, and T-cytotoxic (Tc) 1 cells. Intercellular communication facilitates the elimination of infected cells through the release of proinflammatory cytokines including interferon (IFN)- γ , interleukin (IL)-1 β , IL-12, and tumor necrosis factor (TNF), promoting phagocytic activation and cytolytic activity. ILC1s also induce B cells to produce immunoglobulin (Ig) G, IgM, and IgA (but not IgE) [7, 12].

Type 2 immunity evolved to ensure epithelial barrier integrity and protection against

helminth parasites and noxious environmental substances [2–5]. Its main cellular components are group 2 ILCs (ILC2s), Th2 cells, and Tc2 cells that release signature cytokines, including IL-4, IL-5, IL-9, and IL-13 [5]. These type 2 mediators contribute to the recruitment of innate effector cells such as eosinophils and mast cells and promote B-cell isotype class switching to IgE production [2, 7, 10, 12, 13]. Type 2 immune mechanisms, together with mediators such as histamine and prostaglandins, induce a coordinated response of epithelia, sensory neurons, and smooth muscle cells to expel parasites by triggering an itch/scratch reflex followed by wound repair [4, 5, 14]. Unlike most microorganisms, helminths do not “outrun” the immune system through rapid replication but instead rely on downregulating host immunity, leading to chronic infection [3]. Moreover, helminths tend to be endemic, and repeat exposure is common, increasing the need for a robust memory response.

Type 3 immunity is driven by the group 3 ILCs (ILC3s), Th17, and Tc17 cells. These cells are characterized by production of the IL-17 and IL-22 families of cytokines and coordinated neutrophilic activation that protects against extracellular bacteria and fungi through tissue inflammation, phagocytosis, and pathogen lysis [7, 15, 16].

ROLE OF TYPE 2 INFLAMMATION IN DISEASE

Immune dysregulation can lead to inappropriate activation of inflammatory pathways upon microbial and nonmicrobial stimuli. Aberrant type 2 responses have been associated with allergic conditions, including AD, asthma, allergic rhinitis, and food allergy. Type 2 inflammatory pathways have also been implicated in other disorders characterized by elevated levels of eosinophils, mast cells, and/or IgE, such as chronic rhinosinusitis with nasal polyposis (CRSwNP), eosinophilic esophagitis, chronic urticaria, bullous pemphigoid, and prurigo nodularis [17–19].

Key Players in Type 2 Inflammation

In the absence of helminth infection, inappropriate stimulation of type 2 immunity is triggered by allergens, irritants, noxious microenvironmental cues (i.e., temperature, pH), bacteria, viruses, and endogenous host molecules and lacks a downmodulating effect mediated by helminths [3, 20]. Allergens presented by APCs induce naïve Th0 cell polarization to the Th2 phenotype, a process orchestrated by IL-4 and leading to the production of type 2 inflammatory cytokines [10, 20, 21]. Because the type 2 immune response evolved to combat helminths transmitted through the skin and mucosal surfaces, aberrant reactions to antigens are typically found at the epidermal and epithelial barriers. Epidermal or epithelial barrier dysfunction often occurs in inflammatory diseases, including AD, asthma, and chronic rhinitis. Compromised barrier integrity facilitates entry of allergens, irritants, and infectious agents, and damaged or stressed epidermal and epithelial cells release thymic stromal lymphopoietin (TSLP), IL-25 (also known as IL-17E), and IL-33 (alarmins), triggering type 2 inflammatory cytokine production by ILC2s and Th2 cells [13, 22, 23].

Type 2 cytokines: Signature cytokines of type 2 immunity include IL-4, IL-5, IL-9, IL-13, and IL-31, mainly secreted from immune cells, and IL-25, IL-33, and TSLP, mainly secreted from nonimmune cells (Table 1) [13, 24–27].

IL-4 is produced by many cell types, including activated Th2 cells, ILC2s, basophils, eosinophils, mast cells, natural killer T cells, and macrophages [40–46]. It plays a central role in Th2 differentiation and drives isotype class switching of B cells, mainly to IgE and IgG4 (human) or IgG1 (mouse) [47–50]. IL-4 also promotes alternative activation of macrophages, eosinophil migration, and production of other type 2 cytokines, indicating that it is a key upstream immunomodulator and driver of type 2 inflammation [51–53]. IL-4 facilitates two major axes for type 2 inflammatory cell recruitment to the skin. First, vasopressin-activated calcium-mobilizing receptor (VCAM) 1 upregulation of endothelial cells leads to













INFLAMMATORY PATHWAY	TYPE 1	TYPE 2	TYPE 3
Primary immune cells	 Macrophage  Th1  ILC1  NK	 Th2  ILC2  Mast cell  Basophil  Eosinophil	 Neutrophil  Th17  ILC3
Key cytokines	<div style="display: flex; flex-wrap: wrap;"> <div style="border: 1px solid gray; padding: 2px; margin: 2px;">IFNγ</div> <div style="border: 1px solid gray; padding: 2px; margin: 2px;">TNF</div> <div style="border: 1px solid gray; padding: 2px; margin: 2px;">IL-6</div> <div style="border: 1px solid gray; padding: 2px; margin: 2px;">IL-12</div> <div style="border: 1px solid gray; padding: 2px; margin: 2px;">IL-18</div> <div style="border: 1px solid gray; padding: 2px; margin: 2px;">IL-2</div> </div>	<div style="display: flex; flex-wrap: wrap;"> <div style="border: 1px solid gray; padding: 2px; margin: 2px;">IL-4</div> <div style="border: 1px solid gray; padding: 2px; margin: 2px;">IL-5</div> <div style="border: 1px solid gray; padding: 2px; margin: 2px;">IL-13</div> <div style="border: 1px solid gray; padding: 2px; margin: 2px;">IL-31</div> </div>	<div style="display: flex; flex-wrap: wrap;"> <div style="border: 1px solid gray; padding: 2px; margin: 2px;">IL-17</div> <div style="border: 1px solid gray; padding: 2px; margin: 2px;">IL-6</div> <div style="border: 1px solid gray; padding: 2px; margin: 2px;">IL-22</div> <div style="border: 1px solid gray; padding: 2px; margin: 2px;">IL-23</div> </div>
Function	<ul style="list-style-type: none"> • Antitumor activity • Cellular immunity: antiviral/antibacterial • Suppression of type 2 	<ul style="list-style-type: none"> • Humoral immunity: antiparasitic helminths • Neutralizes toxins • Regulates wound repair and regeneration • Suppression of type 1 	<ul style="list-style-type: none"> • Regulation of intestinal epithelial barrier • Responses to extracellular bacteria and fungi
Examples of consequence of dysregulation and associated disease	<ul style="list-style-type: none"> • Ankylosing spondylitis • Atherosclerosis • Autoimmune gastritis • Diabetes mellitus • Hashimoto thyroiditis • Inflammatory bowel disease • Multiple sclerosis • Rheumatoid arthritis • Sarcoidosis 	<ul style="list-style-type: none"> • Allergy • Anaphylaxis • Type 2 asthma • Atopic dermatitis • Chronic obstructive pulmonary disease with type 2 inflammation • Chronic rhinosinusitis with nasal polyps 	<ul style="list-style-type: none"> • Ankylosing spondylitis • Multiple sclerosis • Psoriasis • Rheumatoid arthritis • Uveitis

Fig. 1 Overview of types 1, 2, and 3 inflammation. This diagram represents immune concepts that do not occur in complete isolation. *IFN γ* interferon- γ , *IL* interleukin, *ILC*

innate lymphoid cell, *NK* natural killer, *Th1/2* T helper type 1/2 cell, *TNF* tumor necrosis factor

perivascular infiltration of very late antigen-4-expressing granulocytes (eosinophils, basophils, and mast cells, but not neutrophils). Th2 cell CCR4 expression, binding to C–C motif chemokine ligand 17 (CCL17, also known as thymus and activation-regulated chemokine [TARC]) and CCL22 (also known as macrophage-derived chemokine [MDC]) on endothelial cells, skin-resident dendritic cells (DCs), and Langerhans cells facilitates inflammatory cell skin-homing [54, 55]. IL-4 drives these processes at low picomolar concentrations given its high affinity for its receptor [28, 56].

IL-13, which shares a receptor subunit with IL-4, is also implicated in type 2 inflammation. Some overlap in the inflammatory effects of IL-13 and IL-4 occurs, and both have been implicated in fibrosis and wound healing [57–61]. In aberrant inflammatory states, both cytokines contribute to barrier disruption by inhibiting

keratinocyte differentiation, promoting epidermal hyperplasia [62], and reducing expression of epidermal structural proteins and antimicrobial peptides [62–68]. IL-13 also directly stimulates tissue remodeling and production of mucus in the respiratory epithelial barrier [39]. In vivo differences between IL-13 and IL-4 derive from their relative productions and receptor expression in different cell types. Notably, because they lack IL-13R α 1 expression, naïve T cells respond to IL-4 but not IL-13, highlighting the unique role of IL-4 in Th2 cell development [69].

IL-5 is the most potent mediator of eosinophil function. Produced by Th2 cells, ILC2s, and mast cells, its receptor, IL-5R α , is selectively expressed on eosinophils, basophils, and some mast cells [31, 45, 46, 70]. IL-5 controls eosinophil growth, differentiation, migration, and survival. IL-4 and IL-13 promote eosinophil

trafficking to the site of inflammation, in part by mediating production of IL-5 and chemokines, such as CCL26 (also known as eotaxin-3) and CCL17, and induction of adhesion molecules such as VCAM-1 in endothelial cells [56, 71–73].

IL-9 is produced primarily by T cells but also by mast cells, eosinophils, and ILC2s. It promotes T-cell growth, proliferation, and survival, B-cell IgE production, and mast cell proliferation and differentiation; it also stimulates secretion of mucus by mucosal epithelial cells [74]. IL-9 plays a critical role in type 2 immunity against parasitic worm infection and has been implicated in allergic inflammation [32, 74].

IL-31 is primarily produced by Th2 cells, implying the requirement for the upstream presence of IL-4. Some IL-31 production has been observed by CD8⁺ T cells, monocytes/macrophages, DCs, keratinocytes, eosinophils, basophils, mast cells, and fibroblasts [25]. This cytokine plays a critical role in histamine-independent pruritus [37] and can alter epidermal barrier function in vitro [75].

Type 2 alarmins: Type 2 alarmins IL-25, IL-33, and TSLP are released by epidermal and epithelial cells in response to external insults and enhance innate and adaptive immune responses by triggering downstream signaling pathways.

IL-25 plays a prominent role in enhancing production of type 2 cytokines (IL-4, IL-5, IL-13, IL-33, and TSLP) from Th2 cells and ILC2s [76]. It may play an important role in AD and asthma as levels of IL-25 are elevated in tissues biopsied from these patients [77].

IL-33 plays a role in the development of allergic diseases by acting on innate cell types such as ILC2s, basophils, and mast cells, and is elevated in patients with allergic airway diseases [78]. Its receptor is found on memory Th2 cells, suggesting a contribution of IL-33 to activation of Th2 cells [79].

TSLP promotes cytokine production from Th2 cells and ILC2s and plays a role in polarizing DCs to induce a Th2 response [80–82]. TSLP-activated DCs induce an inflammatory Th2 response through expression of the OX40 ligand (also known as CD252 or tumor necrosis factor receptor superfamily member 4 [TNFSF4])

[83]. TSLP expression is high in acute and chronic AD lesions, and expression of TSLP in skin is correlated with AD severity [81, 84]. TSLP release in keratinocytes can also trigger itch by acting on TRPA1-positive sensory neurons [85].

Signaling Mechanisms Driving Type 2 Inflammation

The polarization of naïve Th0 cells toward a Th2 phenotype is predominantly regulated by the cytokine milieu. IL-4 causes Th0 cells in the lymph nodes to bind (via T-cell receptors) to antigens presented by MHC class II molecules on APCs. The polarized and activated Th2 cells release IL-4, IL-5, IL-9, IL-13, and IL-31 and migrate to germinal centers. In the germinal centers, in the presence of IL-4 and IL-13, follicular helper T cells situate in near B cells to induce isotype class switching and differentiation to antigen-specific, IgE-producing plasma cells. IgE travels via circulation and binds to its antigen and FcεRI receptors on basophils and mast cells [86]. IL-4 and IL-13 can directly upregulate FcεRI expression at the cell surface, which may prime FcεRI-expressing innate cells for activation [56]. Bound IgE on basophils and mast cells confers a selective response to the target antigen [86]. When activated, basophils and mast cells degranulate and release histamine, proteoglycans (e.g., heparin), proteolytic enzymes, leukotrienes, and cytokines to further drive vasodilation and inflammation [87].

The IL-4Rα receptor chain is involved in both IL-4 and IL-13 signaling and is critical to the type 2 response. It can form two types of IL-4R complexes. When IL-4 binds to IL-4Rα, it recruits either the common gamma chain (γc) to form the type I receptor or IL-13Rα1 to form the type II receptor. IL-13 binds to IL-13Rα1 and recruits IL-4Rα, forming the type II receptor [39, 88]. Myeloid cells express both types of receptors; nonhematopoietic cells predominantly express type II receptors, and lymphocytes mainly express type I receptors [39]. IL-4Rα is also expressed on sensory neurons, and activation of neuronal IL-4Rα plays a critical role in chronic itch [89]. IL-4 can activate

Table 1 Type 2 inflammatory cytokines

Cytokine	Source cell	Receptor	Major signaling pathway	Target cell	Downstream effect, including pathologic effect occurring under dysregulated conditions	
IL-4 [13, 28–30]	Th2 cells	IL-4R α and γ c	STAT6	Hematopoietic cells	T-cell differentiation to Th2 and survival	
	Basophils			Th cells	Class switching to IgE	
	Eosinophils	IL-4R α and IL-13R α 1		B cells	B-cell proliferation	
	Mast cells			Eosinophils	Effector cytokine of type 2 inflammation	
	NK cells	IL-13R α 1		Epithelial cells (including keratinocytes)	Eosinophilia	
	ILC2s				Smooth muscle cells	IgE production
	B cells	IL-13R α 1		Fibroblasts (lymphocytes, myeloid cells, non-hematopoietic cells)	Fibroblasts	Production of type 2 cytokines/chemokines (IL-5, IL-9, IL-13, CCL17, CCL11/24/26)
	Fibroblasts				Upregulation of MHC class II production	
	Monocytes	IL-13R α 1		Fibroblasts (lymphocytes, myeloid cells, non-hematopoietic cells)	Mast cells	Mast cell proliferation, activation, recruitment, and survival
	Epithelial cells				Basophils	Basophil activation and recruitment
	Smooth muscle cells	IL-13R α 1		Fibroblasts (lymphocytes, myeloid cells, non-hematopoietic cells)	Mast cells	Polarization of macrophages to an M2 phenotype for wound repair
						Downregulation of filaggrin expression
		IL-13R α 1		Fibroblasts (lymphocytes, myeloid cells, non-hematopoietic cells)	Mast cells	Barrier dysfunction
	Inflammation					
	IL-13R α 1	Fibroblasts (lymphocytes, myeloid cells, non-hematopoietic cells)	Mast cells	Inhibition of epidermal differentiation		
				Reduction of lipid production		
	IL-13R α 1	Fibroblasts (lymphocytes, myeloid cells, non-hematopoietic cells)	Mast cells	Inhibition of AMP		
				Itch		
IL-5 [13, 31]	Th2 cells	IL-5R α and β c	STAT1/3/5	Basophils	Eosinophil proliferation, maturation, migration, recruitment, and survival	
	ILC2s			Eosinophils		
	Mast cells			Mast cells	Basophil proliferation, maturation, activation, migration, and survival	

Table 1 continued

Cytokine	Source cell	Receptor	Major signaling pathway	Target cell	Downstream effect, including pathologic effect occurring under dysregulated conditions
IL-9 [24, 32]	T cells	IL-9R α and γ c	STAT1/3/5 MAPK	Lymphocytes	Mast cell production
	ILC2s			Mast cells	Degranulation
	Mast cells			Eosinophils	T-cell proliferation and Th2 cytokine production
	Eosinophils			Macrophages	Ig production and class switch (IgE)
	Neutrophils			Neutrophils	Mast cell proliferation
	Osteoblasts			Epithelial cells	Production of mucus (and potentially hypersecretion of mucus)
	NK cells				Eosinophilia
IL-13 [13, 28, 30]	Th2 cells	IL-4R α and	STAT6	Hematopoietic cells	Effector cytokine of type 2 inflammation
	Basophils	IL-13R α 1		B cells	Eosinophilia
	Eosinophils	IL-13R α 2		Eosinophils	IgE production
	Mast cells			Monocytes	Class switching to IgE
	NK cells			Epithelial cells (including keratinocytes)	Production of mucus (and potentially hypersecretion of mucus)
	ILC2s			Smooth muscle cells	Smooth muscle contractility
	Epithelial cells			Fibroblasts	Epithelial hyperresponsiveness
	Smooth muscle cells				Polarization of macrophages to an M2 phenotype for wound repair
	Fibroblasts				Downregulation of filaggrin expression
	Monocytes				Barrier dysfunction
	B cells				Inflammation
			Goblet cell hyperplasia		
		Itch			

Table 1 continued

Cytokine	Source cell	Receptor	Major signaling pathway	Target cell	Downstream effect, including pathologic effect occurring under dysregulated conditions
IL-25 [27, 33–35]	Epithelial cells	IL-17RA and IL-17RB	STAT5 Act1	Th2 cells ILC2s Mast cells Eosinophils Basophils DCs	Production of type 2 cytokines (IL-4, IL-5, IL-13, IL-33, TSLP) from Th2 and ILC2s Promotes Th2 polarization and inflammation Macrophage differentiation IgE production Decreases filaggrin Hypersecretion of mucus Eosinophilia Airway inflammation/hyperresponsiveness
IL-31 [25, 36, 37]	Th2 cells (primary source) CD8 ⁺ T cells Mast cells Mature dendritic cells Basophils Keratinocytes Macrophages Eosinophils Fibroblasts	IL31RA and OSMR β	STAT1/3/5 PI3K/AKT MAPK	Epidermal keratinocytes Dorsal root ganglia Basophils Eosinophils Mast cells Macrophages	Proinflammatory cascade/inflammation Chemotaxis/cell migration Regulates cell proliferation Tissue remodeling Epidermal barrier function Decreasing filaggrin expression Itch Hyperkeratosis Inhibition of terminal differentiation Alters barrier protein expression

Table 1 continued

Cytokine	Source cell	Receptor	Major signaling pathway	Target cell	Downstream effect, including pathologic effect occurring under dysregulated conditions
IL-33 [33, 36, 38]	Epithelial cells Endothelial cells Fibroblast-like cells Myofibroblasts	ST2 (member of Toll-like/IL-1RSF) and IL-1RAcP	TRAF6 IRAK4 AP-1	Mast cells ILC2s Eosinophils Tregs Basophils DCs	Proinflammatory cascade/inflammation Enhances IFN γ , IL-5, and IL-13 production Inhibition of AMP Stimulates Th2 cytokines from ILC2s Downregulation of filaggrin Airway hyperresponsiveness Airway remodeling Eosinophilia
TSLP [29, 30, 39]	Keratinocytes/skin epithelium	IL-7R α and TSLPR	STAT5	DCs (LCs) T cells ICL2 cells B cells Mast cells Basophils Eosinophils	Promotes type 2 responses Promotes Th2 cytokine production from Th2 and ICL2 cells and Th2 polarization Inhibits Treg function

AKT, protein kinase B, AMP, adenosine monophosphate, AP-1 activator protein 1, βc common beta chain, γc common gamma chain, *CCL* C–C motif chemokine ligand, *COPD* chronic obstructive pulmonary disease, *DC* dendritic cell, *IBD* inflammatory bowel disease, *IFN γ* interferon-gamma, *Ig* immunoglobulin, *IL* interleukin, *IL-1RAcP* IL-1 receptor accessory protein, *ILC* innate lymphoid cell, *IRAK* interleukin-1 receptor associated kinase, *LC* Langerhans cell, *MAPK* mitogen-activated protein kinase, *MHC* major histocompatibility complex, *NK* natural killer, *OSMR β* oncostatin M receptor β , *PI3K* phosphatidylinositol 3-kinase, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *STAT* signal transducer and activator of transcription, *Th cell* T helper cell, *TRAF* TNF receptor associated factors, *Treg* T regulatory cell, *TSLP* thymic stromal lymphopoietin

human sensory neurons, and sensory neuron-specific genetic deletion of IL-4R α in mice attenuates both itch and skin inflammation, further suggesting that IL-4R α critically mediates chronic itch. Moreover, activation of neuronal IL-4R α sensitizes sensory neurons to multiple other pruritogens. IL-4 was shown to significantly amplify scratching behavior to low doses of pruritogens such as histamine [90].

These data suggest that type 2 cytokines may act as master regulators of chronic itch by intensifying itch responses to multiple pruritogens present in inflamed skin [89]. Once IL-4 and IL-13 bind to the receptor, they initiate an intracellular signaling cascade involving mainly signal transducer and activator of transcription (STAT) 6, which translocates to the nucleus and

induces transcription of type 2 response genes [39].

A key type 2 cytokine signaling pathway is the Janus kinase (JAK)-STAT pathway. Dimerization of cytokine receptors upon binding with cytokines induces auto- and trans-phosphorylation of the noncovalently associated intracellular JAKs. There are four JAK molecules (JAK1, JAK2, JAK3, and tyrosine kinase-2 [TYK2]), and the type of JAK involved depends on the components of the receptor complex (in the case of IL-4 and IL-13 signaling: JAK1 for IL-4R α , JAK3 for γ c, and JAK2 or TYK2 for IL-13R α 1). Their redundant nature accounts for the role of JAKs in a wide variety of biologic processes, including immunity, inflammation, cell division, development, tumor formation, and cell death [91].

Atopic Dermatitis

AD is a chronic, relapsing, pruritic, systemic inflammatory disease affecting up to 20% of children and 2–8% of adults worldwide [92, 93]. It often begins in early childhood [93, 94]. Recent research has expanded our understanding of the pathogenesis of AD, which is thought to involve genetic and environmental factors that predispose an individual to epidermal barrier dysfunction and type 2 inflammation [95, 96]. There is considerable heterogeneity within AD [29, 97]; however, type 2 inflammation is the principal driving mechanism (Fig. 2) [98–100]. Type 2 inflammation leads to defects in the epithelial barrier, allowing entry of allergens/pathogens, where they are taken up by Langerhans cells and other APCs [101]. Disruption to the epithelial barrier also stimulates the release of alarmins (e.g., IL-25, IL-33, TSLP) from keratinocytes. Alarmins induce production of type 2 mediators such as IL-4 and IL-13 by innate immune cells, thereby shaping the immune response toward the type 2 pathway, and the subsequent recruitment of mast cells, basophils, eosinophils, alternatively activated macrophages, and allergen-specific IgE into the dermal layers [100, 102, 103]. Continued activation of type 2 immunity leads to chronic inflammation with emergence of memory Th2 cells, sensitization of sensory neurons to a range

of pruritogens, an amplified itch–scratch cycle, and skin barrier disruption resulting in a clinical picture characterized by erythema, induration, papulation, excoriation, and in more chronic stages, lichenification [19]. The T-cell receptor OX40 (also known as CD134 or tumor necrosis factor receptor superfamily member 4 [TNFRSF4]) and the OX40 ligand contribute to Th2 memory cell formation and are thought to play a role in AD pathogenesis [104, 105]. Th2 cells are increased in young children with AD, suggesting that systemic components of inflammation may predispose nonlesional skin to a pathologic response upon allergen exposure [106]. Genetic risk factors may predispose patients to AD; many patients have a loss-of-function mutation in *FLG*, but this alone is insufficient to develop disease [93, 107].

Barrier protein expression is regulated by both external and internal stimuli, including IL-4, IL-13, and IL-31. In AD, excessive IL-4, IL-13, and IL-31 levels downregulate the expression of several skin barrier proteins, including filaggrin (FLG) [64, 108], loricrin [66, 109], and involucrin [65, 67, 68]. Dysfunction of the epidermal barrier can itself further promote type 2 inflammation through the production of alarmins. Alarmins IL-33 and IL-25 are believed to trigger ILC2 activation and overexpression of IL-13 in the skin; this leads to the recruitment of activated Th2 cells via induction of Th2 cell-recruiting chemokines such as CCL17 and further increases IL-4/IL-13 expression within the skin. This pathway is believed to play a critical role in chronic inflammation in AD [110]. IL-4 and IL-13 also induce the production of periostin, a matricellular protein that plays a role in chronic inflammation, skin fibrosis, and pruritus [111]. Periostin promotes the production of inflammatory cytokines by keratinocytes, amplifying chronic inflammation [112].

Lesional skin in AD exhibits significantly more Th2 cells, ILC2s, and basophils than healthy skin [113, 114], and serum IgE levels are often increased in patients with AD. Basophils in AD skin are a key producer of peripheral IL-4 [115–117]. The basophil response has been shown to precede the ILC2 response, and the IL-4 produced by basophils induces the proliferation and activation of cutaneous ILC2s in a

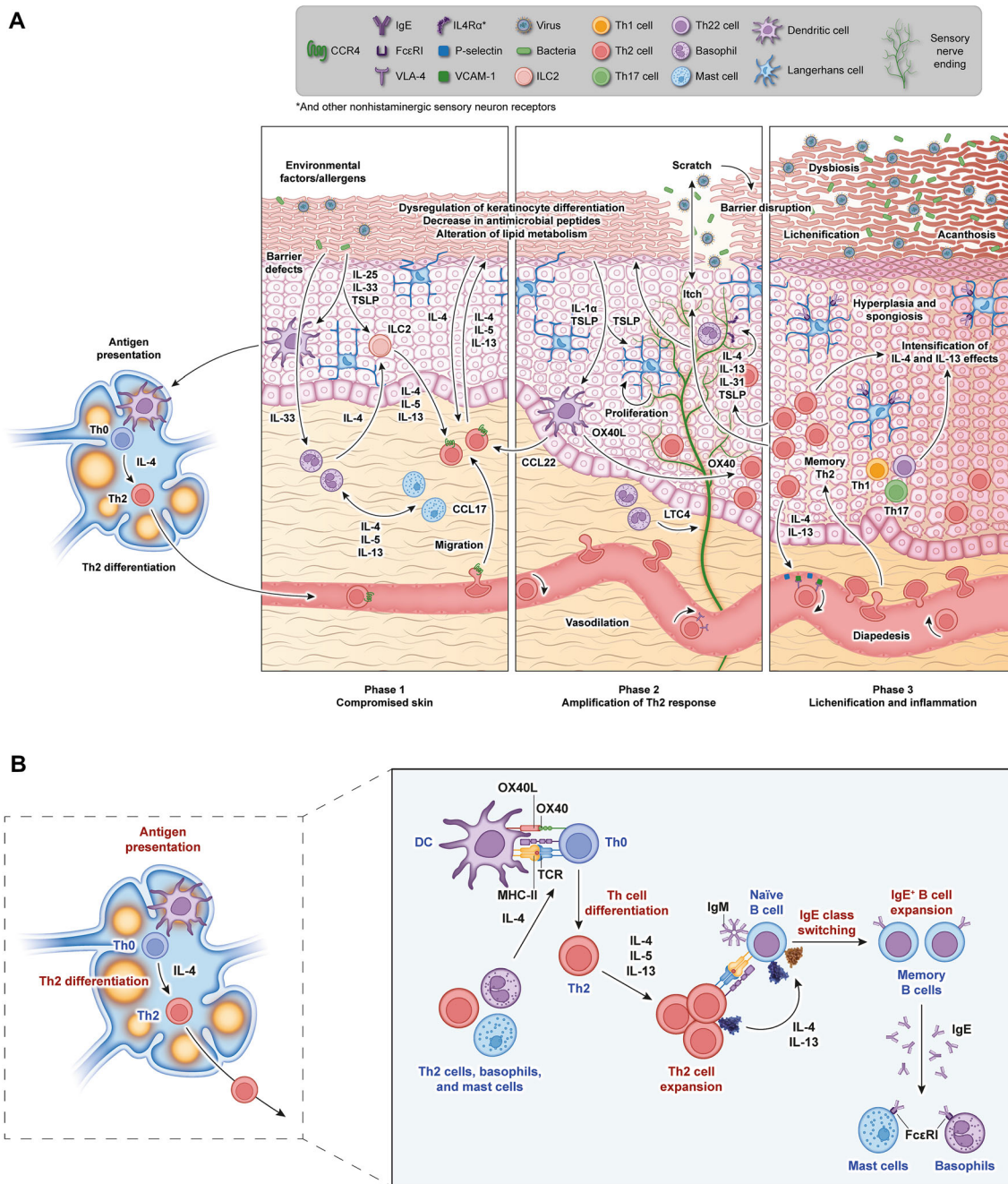


Fig. 2 Pathologic inflammation in AD (**A**), and IL-4 as a key driver of Th2 differentiation and activation (**B**). *CCL17* C–C motif chemokine ligand 17, *DC* dendritic cell, *Ig* immunoglobulin, *IL* interleukin, *ILC* innate

lymphoid cell, *LTC4* leukotriene C4, *MHC-II* major histocompatibility complex II, *TCR* T-cell receptor, *TSLP* thymic stromal lymphopoietin, *VCAM-1* vasopressin-activated calcium-mobilizing receptor 1

manner independent of IgE or the Th2 induction that occurs in the lymph nodes, underscoring the role of peripheral IL-4 in AD pathogenesis [115].

Recent genomic studies support widespread dysregulation of immune and barrier function genes in AD [118–121]. Transcriptome profiling from tape-stripped skin samples indicate upregulation of genes associated with the Th2 response, including IL-4 and IL-13, and downregulation of genes associated with barrier function in lesional versus nonlesional skin [119–121]. In children with early-onset AD, the genes encoding the IL-4 receptor and the chemokine CCL17 were upregulated compared with healthy skin [121].

One of the cardinal symptoms of AD is debilitating itch, which can lead to scratching and excoriation that disrupt the epithelial barrier, perpetuate the inflammatory response, and can lead to epidermal thickening and lichenification [19, 122]. Pruritus is regulated by a range of immune mediators and leads to neurocutaneous anatomical alterations. In patients with AD, lesions have increased sensory nerve density in the epidermis and dermis [123], and altered expression of neuropeptides, neurotrophins, and neurotransmitters is seen in the skin and nerves of the dermis. Increased expression of PGP9.5, amphiregulin, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and substance P have been observed, with a contrasting decrease in semaphorin 3A expression [124]; these mediators are associated with nerve fiber penetration of the epidermis in patients with AD.

Basophils and mast cells release inflammatory mediators, including histamine and tryptase, that contribute to itch [102, 123]. Histamine elicits a range of proinflammatory and pruritic effects, primarily via histamine 1 and histamine 4 receptors. Histamine regulates production of NGF and semaphorin 3A in keratinocytes, promotes IL-31 release from Th2 cells, and directly activates sensory neurons [125]. Recent studies also reveal a critical role for basophils in acute itch flares in AD. Following activation by allergen-specific IgE, basophils produce IL-4 and promote itch through mast cell-independent leukotriene C4-CysLTR2

signaling [126, 127]. Chronic itch in AD appears to be a distinct entity from acute itch, with signaling via a variety of nonhistaminergic nerve fiber pathways, including IL-4Ra and IL-31R [89, 128].

IL-31 is a key mediator of pruritus and is increased in lesional skin in patients with AD. IL-31 not only stimulates sensory nerves but also promotes sensory nerve fiber elongation and branching [129]. It regulates brain-derived natriuretic peptide, upregulating its release in the skin and acting as a neuroimmune link to drive the sensory pathways that result in itch. IL-31 receptor signaling involves JAK1 and JAK2 [25, 130, 131]. The primary source of IL-31 is Th2 cells. IL-4, but not IL-13, upregulates the histaminic H4 receptor (H4R) on CD4⁺ Th2 cells, and, in turn, H4R activation on T cells upregulates IL-31 production [132]. More recently, IL-4 and IL-13 were shown to directly stimulate sensory neurons and promote itch [89, 133]. The gene for IL-4R α is widely expressed across neuronal subsets, and IL-4 enhances responsiveness to pruritogens, including IL-31, histamine, and chloroquine [89]. By promoting neural hypersensitivity, IL-4R α may therefore play a role in the prolonged or outsized reactions to pruritogens seen in patients with AD.

Although the pathogenesis of AD is predominantly a type 2 immune response, types 1 and 3 immune responses also contribute to disease, especially in chronic stages. The type 3 cytokines IL-17 and IL-22 are upregulated in the skin of patients with AD, mainly in patients with relatively low IgE levels [97]. IL-17 reduces expression of FLG and involucrin [134]. Th1 cell activation appears to occur more in the chronic phase of AD after prolonged inflammation at the epithelial barrier. Early-onset AD in children is characterized by relatively strong activation of the Th2 axis and increased Th17 cytokine levels compared with adult-onset AD [106, 135]. Asian patients typically have a higher expression of Th17 and Th22 cytokines and lower activation of Th1 cytokines in AD skin lesions than European–American patients; however, Th2 cytokines are upregulated consistently regardless of ethnicity or disease stage [136, 137].

INHIBITION OF TYPE 2 INFLAMMATION

Overview

Targeted immune-modulating therapies provide a specific, effective treatment approach that is less prone to adverse events (AEs) than broad-spectrum immunosuppressant therapy. Biologic therapies have been developed for conditions mediated by type 1 and/or type 3 immunity, such as rheumatoid arthritis (RA), psoriasis, Crohn disease, hidradenitis suppurativa, and ankylosing spondylitis. Therapies for conditions mediated by type 2 inflammation have been similarly developed, with therapies for asthma and AD leading the way. Licensed biologics or biologics in advanced clinical stages targeting type 2 cytokines in AD include lebrikizumab (IL-13), tralokinumab (IL-13), mepolizumab (IL-5), and reslizumab (IL-5); those targeting type 2 cytokine receptors include dupilumab (IL-4R α), benralizumab (IL-5R α), and nemolizumab (IL-31RA α); and IgE-targeting therapies include omalizumab and ligelizumab (Fig. 3). The clinical efficacy of these biologics has significantly advanced our understanding of the pathogenic role of type 2 cytokines in diseases such as AD, asthma, and CRSwNP, and has spurred the development of biologics targeting other mediators associated with type 2 inflammation, such as alarmins; for example, IL-33 (astegolimab, etokimab, itepekimab, MEDI-3506), IL-33R (melrilimab), and TSLP (tezepelumab), which are at various stages of development.

Some biologics, including those that target TNF, IL-17, and IL-12/-23, have been associated with an increased risk of opportunistic and/or serious bacterial, fungal, or viral infections [138]. This finding may be attributed to the role of type 1 or type 3 immunity and IFN γ (which has antimicrobial properties and signals via JAK1 and JAK2) in preventing bacterial, fungal, and viral infections [139]. In theory, targeting type 2 inflammation could increase the risk of helminth infections, although no evidence currently exists.

Biologics demonstrating lack of efficacy may also be useful for understanding the precise mechanisms underlying type 2 inflammatory diseases and their treatment. For example, although peripheral blood eosinophil numbers are typically elevated in patients with AD, and eosinophil numbers appear to correlate with disease activity [140], reducing peripheral blood eosinophil numbers through IL-5 inhibition (mepolizumab) failed to yield clinically significant improvements in AD [141, 142]. These findings suggest that IL-5-mediated elevations in eosinophil levels are not likely a primary source of the inflammatory cascade in AD. Similarly, although biologics targeting IgE (omalizumab and ligelizumab) have shown some clinical efficacy in AD, treatment efficacy has been inconsistent, suggesting that elevated IgE is not a predominant clinical factor in AD [143].

Biologic Therapy

Dupilumab: The central and pleiotropic role of IL-4 and IL-13 in type 2 inflammatory conditions make these cytokines attractive therapeutic targets, with beneficial downstream effects for patients [30, 144]. Dupilumab is a fully human monoclonal antibody against IL-4R α , which inhibits both IL-4 and IL-13 signaling and is approved for patients with type 2 inflammatory diseases, including AD, asthma, and CRSwNP [145, 146]. In multiple, randomized, placebo-controlled phase 3 clinical trials, dupilumab improved signs, symptoms, and quality of life (QoL) in adults and adolescents with moderate-to-severe AD and in children (aged ≥ 6 years) with severe disease [147–152]. Dupilumab also demonstrated acceptable safety and long-term efficacy, with continued improvements in AD signs and symptoms for up to 4 years in adults with AD [153, 154]. The most common AEs associated with dupilumab are listed in Table 2, including conjunctivitis and injection-site reactions.

Previous analyses have shown that treatment with dupilumab normalizes the AD transcriptome by downregulating markers of type 2 inflammation (IL-13, IL-31, CCL13, CCL17,

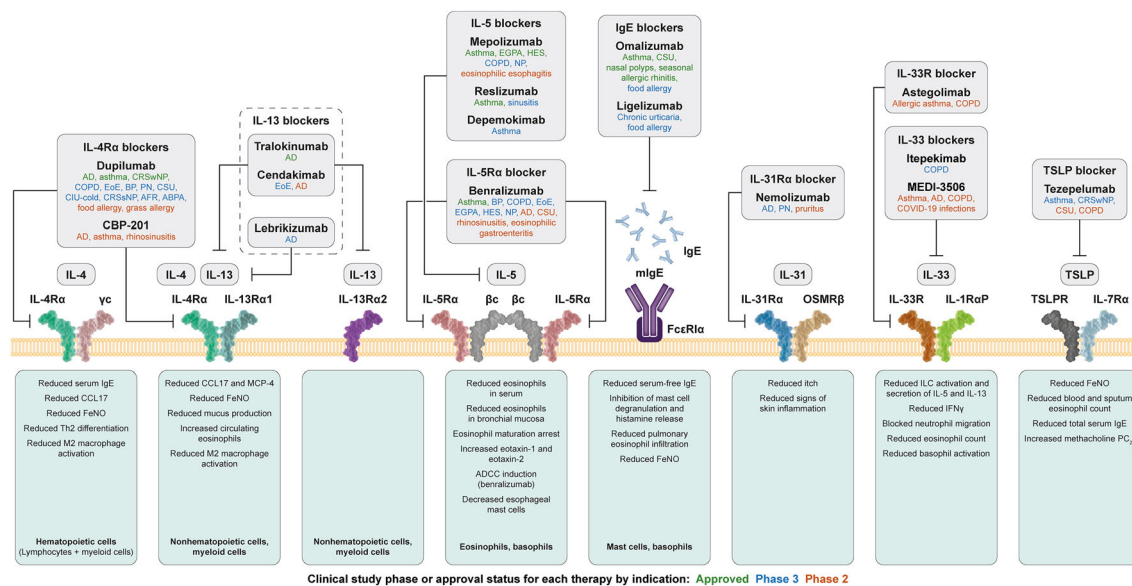


Fig. 3 Biologics that inhibit type 2 molecules. *AD* atopic dermatitis, *ADCC* antibody-dependent cellular cytotoxicity, *ABPA* allergic bronchopulmonary aspergillosis, *AFR* allergic fungal rhinosinusitis, *BP* bullous pemphigoid, *CCL17* C–C motif chemokine ligand 17, *COPD* chronic obstructive pulmonary disorder, *CRS_sNP* chronic rhinosinusitis without nasal polyposis, *CRS_wNP* chronic rhinosinusitis with nasal polyposis, *CIU* chronic idiopathic urticaria, *CSU* chronic spontaneous urticaria, *EGPA* eosinophilic granulomatosis with polyangiitis, *EoE*

eosinophilic esophagitis, *FeNO* fractional exhaled nitric oxide, *HES* hypereosinophilic syndrome, *IFN γ* interferon-gamma, *IgE* immunoglobulin E, *IL* interleukin, *MCP-4* monocyte chemoattractant protein-4, *NP* nasal polyps, *OSMR β* oncostatin-M specific receptor subunit β , *PC20* provocative concentration causing a 20% drop in FEV1 from baseline, *PN* prurigo nodularis, *TSLP* thymic stromal lymphopoietin, *TSLPR* thymic stromal lymphopoietin receptor

CCL18 [also known as pulmonary and activation-regulated chemokine, PARC], CCL22, CCL26, periostin) and Th17/Th22 activity (IL-17A, IL-22) while normalizing gene products associated with barrier function, such as FLG [183–185]. Another study suggests that dupilumab might suppress ILC2 and Th2 cell populations [186].

In phase 3 trials in asthma, dupilumab reduced the rate of severe exacerbations and improved lung function as evidenced by increased forced expiratory volume in the first second compared with control in patients with uncontrolled, moderate-to-severe asthma and glucocorticoid-dependent severe asthma [187, 188]. In two phase 3 trials in adults with CRSwNP that was uncontrolled despite prior treatment with systemic corticosteroids, surgery, or both, dupilumab treatment significantly reduced polyp size, roentgenographic

sinus opacification, and severity of symptoms compared with controls [189]. These findings suggest the potential for dupilumab to curtail AD progression in children and adolescents, although further evaluation is required [190, 191].

Two different analyses of multiple, randomized, placebo-controlled trials of dupilumab in adults with moderate-to-severe AD demonstrated that dupilumab reduced the risk of serious and severe infections as well as nonherpetic skin infections, and did not increase the overall infection rates, compared with controls. Clinically important herpes viral infections (eczema herpeticum, herpes zoster) were less common with dupilumab than placebo [192–194]. Dupilumab also reduced overall infections and skin infections in children and adolescents with moderate-to-severe AD [195], and it reduced upper and lower respiratory infections and anti-

Table 2 Common adverse events

Therapy	Adverse events reported in prescribing information ($\geq 5\%$ incidence)	Adverse events reported in patients with AD in phase 3 primary manuscripts ($\geq 5\%$ incidence)
Abrocitinib	<i>AD</i> : nasopharyngitis, nausea, headache [155, 156]	Acne, AD, headache, nasopharyngitis, nausea, URTI, vomiting [95, 157]
Baricitinib	<i>AD</i> : herpes simplex, increased LDL cholesterol <i>RA</i> : increased LDL cholesterol, URTI [158, 159]	Diarrhea, elevated blood CPK, headache, herpes simplex, nasopharyngitis [160]
Benralizumab	<i>Asthma</i> : headache, pharyngitis [161]	N/A
Delgocitinib	Not approved	Contact dermatitis, nasopharyngitis [162, 163]
Dupilumab	<i>AD</i> : blepharitis, conjunctivitis, ISRs <i>Asthma</i> : ISRs <i>CRSwNP</i> : ISRs [145, 146]	AD exacerbation, asthma, bronchitis, headache, influenza, nasopharyngitis, oral herpes, sinusitis, skin infections, URTI, vomiting [147, 148, 150, 152, 164]
Fezakinumab	Not approved	URTI [165]
Lebrikizumab	Not approved	Conjunctivitis, fatigue, headache, herpes viral infections, infections, ISRs, nasopharyngitis, skin infections, URTI [166, 167]
Mepolizumab	<i>Asthma</i> : back pain, fatigue, headache, ISRs [168]	N/A
Nemolizumab	Not approved	Abnormal cytokines, ISRs, musculoskeletal and connective-tissue symptoms, nasopharyngitis, skin infections, worsening of AD [169]
Omalizumab	<i>Asthma</i> : pain, arthralgia <i>Nasal polyps</i> : headache, ISRs <i>CSU</i> : headache, nasopharyngitis [170]	AD aggravation, AD exacerbation, asthma exacerbation, headache, infected AD, iron deficiency, rash, runny nose, skin infection, URTI, urticaria, viral infection, wheezing [171]
Reslizumab	No adverse events reported at $\geq 5\%$ incidence [172]	N/A
Ruxolitinib	<i>Myelofibrosis</i> : bruising, dizziness, flatulence, headache, UTI, weight gain [173]	Nasopharyngitis [174]
Tofacitinib	<i>UC</i> : nasopharyngitis, elevated cholesterol levels, headache, URTI, increased blood CPK, rash, diarrhea, herpes zoster [175]	N/A
Tralokinumab	<i>AD</i> : conjunctivitis, URTI, ISRs [176, 177]	Conjunctivitis, headache, pruritus, URTI, viral URTI [178, 179]

Table 2 continued

Therapy	Adverse events reported in prescribing information ($\geq 5\%$ incidence)	Adverse events reported in patients with AD in phase 3 primary manuscripts ($\geq 5\%$ incidence)
Upadacitinib	<i>AD</i> : acne, headache, herpes simplex, increased blood CPK, URTI <i>RA</i> : increased blood CPK, URTI [180, 181]	Acne, elevated blood CPK, headache, nasopharyngitis, URTI [182]

N/A indicates an absence of published phase 3 clinical trial data in AD

AD atopic dermatitis, *CPK* creatine phosphokinase, *CRSwNP* chronic rhinosinusitis with nasal polyposis, *CSU* chronic spontaneous urticaria, *ISR* injection-site reaction, *LDL* low-density lipoprotein, *N/A* not applicable, *RA* rheumatoid arthritis, *UC* ulcerative colitis, *URTI* upper respiratory tract infection, *UTI* urinary tract infection

infective medication use in adults and adolescents with moderate-to-severe asthma and adults with severe CRSwNP [196]. Dupilumab laboratory safety data also support the long-term use of dupilumab in children, adolescents, and adults without the need for routine laboratory monitoring [164, 197, 198].

The efficacy of dupilumab in AD, asthma, and CRSwNP supports the central roles of IL-4 and IL-13 in inflammatory disease pathology [30, 199]. Trials are ongoing in other conditions sharing elements of type 2 immune dysregulation (Fig. 3).

Tralokinumab and lebrikizumab: Tralokinumab is an anti-IL-13 recombinant humanized IgG4 λ monoclonal antibody that binds to IL-13, thereby inhibiting signaling via the IL-13R α 1 and IL-13R α 2 receptors. Tralokinumab is approved in the USA and European Union for the treatment of moderate-to-severe AD in adults [176, 177]. In three phase 3 trials (ECZTRA 1, ECZTRA 2, and ECZTRA 3) in adults with moderate-to-severe AD, tralokinumab improved AD signs and symptoms and QoL and was well tolerated up to 52 weeks [178, 179]. In two phase 3 trials evaluating tralokinumab in patients with severe, uncontrolled asthma (STRATOS 1 and 2), the primary endpoints were not met [200], suggesting that inhibition of IL-13 signaling alone is insufficient to treat patients with severe asthma. Table 2 lists the

most common AEs associated with tralokinumab.

Lebrikizumab, a humanized IgG4 κ monoclonal antibody, binds to IL-13 at an epitope distinct from that of tralokinumab, preventing heterodimerization of the IL-4R α and IL-13-IL-13R α 1 complex [30, 166]. Lebrikizumab is currently in phase 3 trials in patients with AD after demonstrating efficacy and an acceptable safety profile in phase 2 trials [166, 167]. In two phase 3 trials (LAVOLTA I and II), lebrikizumab failed to show a consistent reduction in asthma exacerbations in patients with uncontrolled asthma [201]. The most common AEs associated with lebrikizumab are listed in Table 2.

Taken together, the clinical data indicate that inhibiting IL-13 signaling may provide an efficacious treatment option for patients with AD, but treatment failure in asthma underscores the significance of IL-4 in the pathophysiologic nature of type 2 inflammatory diseases.

Nemolizumab: As described above, IL-31 is a key driver of itch in patients with AD. Nemolizumab is a humanized IgG2 κ anti-IL-31 receptor A monoclonal antibody, which prevents IL-31 binding and subsequent downstream signaling. In a small phase 3 trial in Japanese patients with AD, nemolizumab in combination with topical agents resulted in clinically significant improvements in pruritus and some improvements in AD signs, QoL, and sleep compared with controls; AD exacerbations were observed

both in placebo and in nemolizumab groups [169]. Common AEs associated with nemolizumab are listed in Table 2.

Mepolizumab, reslizumab, and benralizumab: A potent mediator of eosinopoiesis, IL-5 is a logical target for type 2 inflammatory conditions [31]. Mepolizumab, reslizumab, and benralizumab are humanized monoclonal antibodies that block IL-5 signaling. Although mepolizumab and reslizumab directly bind to IL-5, benralizumab binds to its receptor (IL-5R α), inducing antibody-dependent cell-mediated cytotoxicity. Based on phase 3 trial data, all three agents are approved for use in patients with severe asthma with an eosinophilic phenotype [202–210]. Clinically meaningful responses were not observed following reslizumab treatment in patients without elevated eosinophil levels [211], suggesting that the efficacy of IL-5 inhibition is primarily a consequence of reducing eosinophil levels. Although none of these agents are approved for use in AD (mepolizumab failed to report meaningful improvements in AD) [141, 142], and mepolizumab has been licensed for eosinophilic granulomatosis with polyangiitis, investigation of their use in other eosinophil-driven conditions is underway. Table 2 lists the most common AEs associated with mepolizumab, reslizumab, and benralizumab.

Omalizumab and ligelizumab: Omalizumab, a humanized anti-IgE antibody, binds to serum IgE, inhibiting its downstream effects. It is approved for use in asthma, chronic spontaneous urticaria, nasal polyps, and seasonal allergic rhinitis [170]. Two phase 3 trials support the use of omalizumab as an adjunctive therapy in patients with severe asthma uncontrolled by conventional therapy [212, 213]. Omalizumab has demonstrated some efficacy in a range of other type 2 inflammatory diseases, including AD [171], CRSwNP [214], and food allergies [215, 216]. Omalizumab has also demonstrated efficacy in the treatment of moderate-to-severe chronic spontaneous urticaria, as did recently ligelizumab (another humanized anti-IgE antibody) in controlling symptoms [217]. For the most common AEs associated with omalizumab, see Table 2.

Fezakinumab: Fezakinumab targets IL-22, a Th22 cytokine that plays a role in skin barrier function [165]. Treatment with fezakinumab was shown to affect multiple pathways related to inflammation and barrier function, although the effects were limited to patients with high IL-22 expression at baseline [218], thereby highlighting the population specificity of some biologics [96]. In a small, randomized phase 2 trial, fezakinumab improved signs and symptoms of moderate-to-severe AD with few common AEs (Table 2).

Astegolimab, etokimab, and itepekimab: Astegolimab is a human IgG2 monoclonal antibody that binds to the IL-33 receptor [219]. Phase 2 trials of astegolimab in patients with AD are underway. Another anti-IL-33 monoclonal antibody, itepekimab, is under investigation for chronic obstructive pulmonary disease [220]. Itepekimab was previously under investigation for the treatment of asthma and AD. However, its efficacy in treating asthma was lower than that of dupilumab, and it is no longer being investigated for the treatment of AD due to lack of efficacy [221, 222]. Etokimab, which binds directly to IL-33, is no longer in clinical development [223, 224].

Tezepelumab: TSLP is released from the epithelium following stress or allergen exposure and is an early promoter of polarization toward Th2 phenotype, the production of type 2 cytokines by ILC2s, mast cells, basophils, and eosinophils [26, 225]. Tezepelumab is a monoclonal antibody that binds directly to TSLP to prevent receptor binding. In a phase 2a trial in patients with AD, the addition of tezepelumab to topical corticosteroids did not significantly improve skin lesions compared with placebo and topical corticosteroids [152]. Tezepelumab also failed to show efficacy in a recent phase 2b study in patients with AD [226] and has been discontinued for further development in AD [227].

In patients with moderate-to-severe asthma, tezepelumab significantly reduced asthma exacerbations compared with placebo, regardless of baseline eosinophil count [228] and improved lung function, asthma control, and health-related QoL [229]. However, in adults with oral corticosteroid (OCS)-dependent

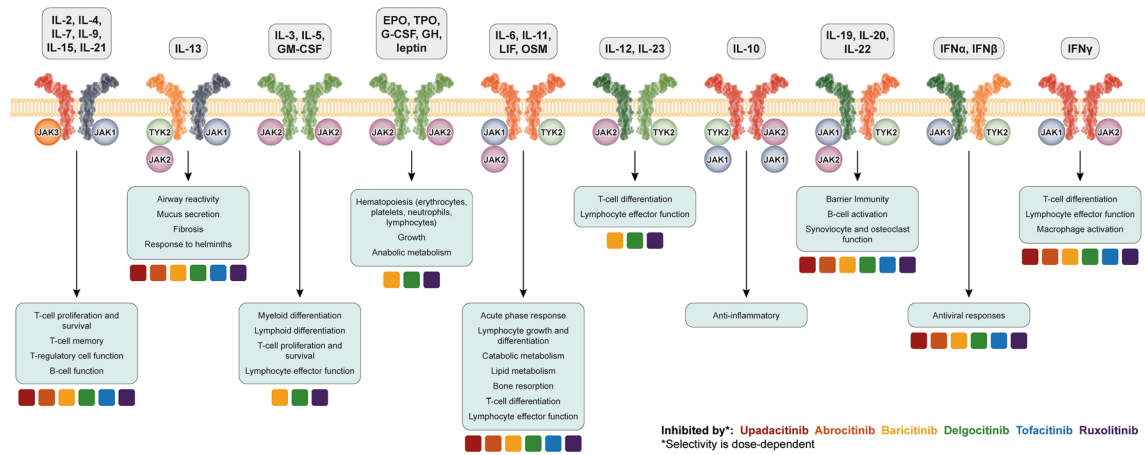


Fig. 4 JAK signaling pathways in type 2 inflammation and JAK inhibitors. Adapted from Schwartz et al. [238]. For simplicity, the depicted receptor subunits do not reflect the extent of differentiation in domain structures of the various JAK cytokine receptors. *EPO* erythropoietin, *G*-

CSF granulocyte colony-stimulating factor, *GH* growth hormone, *GM-CSF* granulocyte macrophage colony-stimulating factor, *IFN* interferon, *IL* interleukin, *JAK* Janus kinase, *LIF* leukemia inhibitory factor, *OSM* oncostatin M, *TPO* thrombopoietin

asthma, tezepelumab did not reduce OCS use without the loss of asthma control [230] but did increase the probability of a reduction in OCS use in patients with high baseline blood eosinophil counts [231].

The inconsistent efficacy of biologics targeting alarmins in treating AD suggests that alarmins may not play a predominant clinical role in eliciting AD pathophysiology but may play a greater role in other type 2 diseases such as asthma.

JAK Inhibitors

More than 50 cytokines signal via intracellular JAK signaling pathways [232] and abnormal JAK–STAT signaling is associated with immune disorders [233], making JAKs a target for treating immune-related diseases. JAK inhibitors have the potential to inhibit signaling from a range of cytokines involved in type 1, type 2, and type 3 pathways (Fig. 4) [234–237].

JAK inhibitors were initially approved for use in RA [159, 180, 239] and have been evaluated for the treatment of type 2 immune diseases such as AD. Tofacitinib is a pan-JAK inhibitor that preferentially inhibits JAK1 and JAK3, and is approved for use in RA, psoriatic arthritis, and

UC [239, 240]. However, safety concerns that have emerged during trials of tofacitinib for other indications may limit the utility of tofacitinib in treating AD. More selective JAK inhibitors in the treatment of AD have revealed a more acceptable safety profile [160].

Delgocitinib has wide-reaching actions against Th1, Th2, and Th17 responses and inhibitory effects against JAK1, JAK2, JAK3, and TYK2; it is approved in Japan as a topical agent to treat AD [241, 242]. In a phase 3 trial of topical delgocitinib in Japanese patients with moderate or severe AD affecting 10–30% of the body surface area, delgocitinib resulted in greater and more rapid improvements in skin signs and pruritus by week 4 compared with the vehicle. Long-term efficacy was demonstrated in two uncontrolled studies of 28 and 52 weeks' duration, respectively [162, 163]. Further study in pediatric patients is ongoing. Common AEs associated with delgocitinib are shown in Table 2.

Ruxolitinib is an inhibitor of JAK1 and JAK2. Oral administration is associated with immunosuppression and increased infection risk [243]. Topical ruxolitinib is approved in the USA for the short-term and noncontinuous treatment of mild-to-moderate AD in non-immunocompromised patients aged at least

12 years whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Approval was based on results from two phase 3 trials (TRuE-AD1 and TRuE-AD2), which investigated topical ruxolitinib cream (0.75% twice daily [BID] and 1.5% BID) in adults and adolescents with mild-to-moderate AD. Both trials met the primary endpoint of Investigator's Global Assessment Treatment Success for both formulations at week 8 [244]. Additional 52-week data demonstrated that topical ruxolitinib is effective at maintaining treatment effect up to 52 weeks with no AEs suggestive of a relationship to systemic exposure observed, and no meaningful changes or trends in hematologic parameters [245]. Common AEs associated with ruxolitinib are listed in Table 2.

Some serious AEs have been reported with pan-JAK inhibitors, including cytopenias (which may arise due to disrupted JAK-mediated signaling of hematopoietic growth factors), gastrointestinal tract perforation (which may arise due to altered JAK signaling for IL-6, IL-22, IL-10, and IL-9, all of which are involved in intestinal barrier function), and malignancy (which may result from T-cell and NK cell dysregulation) [238]. Although these events are uncommon (generally < 5% incidence), they tend to occur at frequencies larger than those observed with biologics [159, 180, 238, 239, 246, 247].

At the appropriate dose, baricitinib selectively inhibits JAK1- and JAK2-mediated signaling. Baricitinib is approved by the European Union and Japan to treat moderate-to-severe AD in adults [158]. In two phase 3 trials in adults with moderate-to-severe AD (BREEZE-AD 1 and 2), baricitinib showed significant improvements in AD skin signs and symptoms at the higher dose (4 mg once daily) for a 16-week period. Improvements in itch began as early as week 1 at 4 mg and week 2 at 2 mg. Both doses reduced nighttime awakenings and skin pain, and improved QoL. Table 2 lists common AEs associated with baricitinib.

Two next-generation JAK inhibitors, which are believed to be more JAK1 selective at certain lower doses, are upadacitinib and abrocitinib [157, 238, 248–250]. JAK1 inhibition blocks

signaling pathways for interferons and a range of cytokines, including IL-4, IL-13, IL-31, TSLP, and IFN- γ .

The central antiviral response is mediated by IFN α and IFN β [251], both of which signal via JAK1 and TYK2. Another central antiviral cytokine, IFN- γ , has antibacterial and antiprotozoan activity and signals via JAK1 and JAK2 [139]. The development and function of natural killer cells capable of killing virus-infected cells depend on IL-15 and IL-7, both of which signal through JAK1- and JAK3-associated receptors [252]. Thus, inhibition of JAK kinases may account for the increased risk of infection, including herpes zoster infection, observed in patients treated with JAK inhibitors [253–260]. Herpes zoster is seen more frequently with JAK inhibitors in patients from Asian regions [257, 259, 260], with crude incidence rates of herpes zoster events (expressed per 100 patient-years) of 9.2 (Japan/Korea), 8.9 (India), 2.7 (Western Europe), and 3.3 (USA/Canada/Australia) in patients treated with tofacitinib [256] and comparable incidence rates in Asian patients treated with baricitinib (Japan: 10.7; Taiwan: 13.0; Korea: 13.1) [258]. This trend has also been noted in patients with plaque psoriasis [261] and in patients with AD treated with upadacitinib [262].

Upadacitinib is approved in the USA, European Union, and Japan for the treatment of AD in adults and adolescents [180, 181]. Table 2 shows the most common AEs associated with upadacitinib. A recent phase 3 trial comparing upadacitinib (30 mg) and dupilumab (300 mg) found that upadacitinib efficacy in reducing AD signs was demonstrated earlier than dupilumab (by week 16) and with greater efficacy compared with dupilumab at week 16, but with no statistical difference at week 24 [263]. Recent data from open-label studies of patients switching from dupilumab to upadacitinib have demonstrated improved efficacy without complete washout of dupilumab, which may suggest enhanced efficacy when these agents are combined [263].

Abrocitinib is approved in the USA for treatment of adults with moderate-to-severe AD [155] and in the UK and Japan for the treatment of moderate-to-severe AD in adults and

adolescents [156]. In a phase 3 trial comparing abrocitinib with dupilumab and placebo in adults with moderate-to-severe AD, abrocitinib demonstrated a greater reduction in signs and symptoms of AD compared with placebo at week 12. The 200 mg (but not 100 mg) dose significantly reduced itch by week 2 compared with dupilumab [95]. Moreover, although significantly more patients achieved a 90% improvement in Eczema Area and Severity Index at week 4 and week 16 with abrocitinib compared with dupilumab, no differences were observed at week 26 [264]. In patients with AD aged 12 years and older (JADE MONO 1 and 2), abrocitinib showed rapid and significant improvements by week 12 compared with placebo. The most common AEs associated with abrocitinib are listed in Table 2.

Overall, by broadly impacting cytokine signaling, JAK inhibitors act rapidly to dampen itch and effectively reduce AD lesions, but longer-term head-to-head comparative studies show that a more targeted approach with a biologic such as dupilumab reaches the same goal [95]. Drawing a direct correlation between JAK selectivity and safety profile has proved challenging, which may be because JAK selectivity is tissue selective and dose dependent; at higher doses, selective JAK inhibitors begin to affect other JAKs [265]. The safety profile of semiselective JAK1 inhibitors in patients with RA suggests that they may also inhibit JAK2 to some extent, particularly at higher doses. For example, dose-dependent thrombocytopenia was observed in clinical trials of abrocitinib for AD and psoriasis [249, 266], suggesting that abrocitinib may inhibit JAK2, which is involved in hematopoiesis, at higher doses. Indeed, abrocitinib is expected to inhibit JAK1, JAK2, and TYK2 *in vivo* [267, 268]. Tofacitinib, which preferentially inhibits JAK1 and JAK3, increased hemoglobin levels at 5 mg, but the effect was diminished at 10 mg [269]. This suggests that tofacitinib may start to inhibit JAK2 at higher doses [270].

To date, studies of JAK inhibitors in type 2 inflammatory disease are mostly limited to AD. Longer studies are required to better understand the role of JAK inhibitors in these diseases. Although selective inhibition of certain JAKs

may hypothetically maximize efficacy while minimizing AEs compared with pan-JAK inhibitors, the selectivity of targeted JAK inhibitors demonstrated *in vitro* may be challenging to maintain *in vivo* [271].

DISCUSSION AND FUTURE PERSPECTIVES

Dysregulation of type 2 immunity can lead to a number of chronic diseases such as AD and asthma. Immune dysregulation in these diseases is often highly complex and involves many different cell types and inflammatory mediators. Despite the multifaceted nature of type 2 inflammatory disease pathophysiology, clinical studies of targeted therapies, such as biologic therapies, suggest that only a few components play a clinically significant role. For example, the relative success of tralokinumab in patients with AD, but not asthma, suggests that IL-13 plays a clinically significant role in AD but, by itself, a lesser role in asthma pathophysiology. The clinical efficacy of dupilumab with targeting both IL-4 and IL-13 in multiple type 2 inflammatory diseases suggests that IL-4 and IL-13 are critical target molecules. Similarly, targeting IgE or TSLP is effective in asthma, but modulating these targets has not yielded consistent results in AD [152, 212, 213, 220, 222, 228, 229, 272]. Although pan-JAK inhibitors have demonstrated efficacy in treating some inflammatory diseases, the broad cytokine inhibition elicited by JAK inhibitors is associated with a number of serious AEs that may limit their therapeutic potential in other populations. More recently, JAK inhibitors with greater selectivity (and a more acceptable safety profile) have demonstrated rapid efficacy in AD. Evaluations in larger populations over time in a wider range of type 2 inflammatory diseases are necessary to better understand the impact of JAK inhibition on type 2 inflammatory diseases. Studies of drugs targeting type 2 immune mediators have helped clarify the biological mechanisms underlying type 2 immunity while also providing tremendous therapeutic advances for diseases involving type 2 inflammation.

Many additional targets for modulation of type 2 immunity have been identified, and development of novel agents will no doubt continue to advance our understanding of type 2 inflammatory diseases.

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