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REVIEW



Commonality of the IL-4/IL-13 pathway in atopic diseases

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ABSTRACT

Introduction: Allergy results from an aberrant Type 2 inflammatory response, triggered by a wide range of environmental antigens (allergens) that lead to various immune responses, culminating in the production of immunoglobulin E (IgE). Two key cytokines, interleukin (IL)-4 and IL-13, are critical to the induction and perpetuation of the Type 2 response, and have been implicated in multiple atopic diseases.

Area covered: This review summarizes recent milestone developments that have elucidated components of the pathogenesis of atopic diseases such as atopic dermatitis (AD), asthma, and chronic sinusitis with nasal polyposis (CSwNP).

Expert commentary: Several therapeutic agents that selectively target potentiators of the Type 2 pathway have shown efficacy in one or more of these atopic diseases, but few agents have proven to be broadly applicable across all three atopic diseases. Dupilumab, a human monoclonal antibody that simultaneously inhibits signaling of IL-4 and IL-13, has demonstrated significant clinical efficacy in AD, asthma, and CSwNP. The fact that these diseases often occur as comorbidities and respond to the same therapy suggests that there is a common underlying pathogenic pathway, and that IL-4 and IL-13 cytokines are central to regulating the pathogenesis of these atopic diseases.

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1. Introduction

Atopy is the genetic predisposition to develop allergic symptoms triggered by environmental antigens (allergens), potentiated by an underlying aberrant Type 2 inflammatory process. Type 2 immunity encompasses the activity of the T helper type 2 (TH2) phenotype of CD4⁺ T cells, their innate counterpart, the group 2 innate lymphoid cells (ILC2), granulocytes (including eosinophils, mast cells and basophils), the associated Type 2 cytokines (interleukin [IL]-4, IL-5, IL-9, and IL-13) and immunoglobulin-E (IgE). In contrast, Type 1 immunity refers to responses mediated by TH1 and TH17 cells, cytotoxic T cells, group 1 and group 3 ILCs, and production of the canonical pro-inflammatory cytokine, interferon- γ . Type 1 immunity provides protection from pathogens such as bacteria, viruses, and fungi, while the evolutionary function of Type 2 inflammation is to eliminate environmental toxins and macroparasites [1]. Each physiological response induced by Type 2 inflammation (e.g. mucus production, keratinocyte hyperplasia, itch, bronchoconstriction, sneezing, coughing, tearing, vomiting, and diarrhea) [2,3] is aimed at effectively purging these pathogens from the body. When these responses are exaggerated or misdirected at allergens, allergy symptoms develop. The signs and symptoms of atopy can involve multiple organ systems, including the skin, airways, sinuses, and even gut, with a spectrum of severities ranging from mild local irritation to life-threatening systemic reactions. In addition, there is a tendency for symptoms of atopic diseases to present as comorbidities or extend to other tissues

with age; for example, the ‘atopic march’ is the progression of childhood atopic diseases, starting with AD and advancing to food allergy, then allergic rhinitis, and finally asthma [4–6]. The diversity of allergic symptoms and their severity is a consequence of the broad scope of the Type 2 inflammatory process.

Targeting downstream components of Type 2 pathway has led to treatments for allergic rhinitis, atopic dermatitis, and allergic asthma; treatments such as antihistamines, topical corticosteroids, phosphodiesterase 4 (PDE4) inhibitors, leukotriene receptor antagonists, and anti-IgE and anti-IL-5 therapies are effective for some respective indications. However, they are insufficient for treating patients with all forms of severe disease or atopic comorbidities [7–14]. Identifying and targeting common pinch-points in the allergic pathway has the potential to provide more broadly applicable treatment strategies.

An emerging body of evidence suggests that two sister cytokines, IL-4 and IL-13, are key drivers of multiple atopic diseases [15]. IL-4 and IL-13 are potent mediators of the induction and effector phases of Type 2 inflammation. IL-4 is the differentiation factor polarizing naive CD4⁺ T cells to TH2 phenotype [16], a growth factor for B cells, an initiator of isotype class switching to IgE [17,18], and an activator and driver of chemotaxis of eosinophils [17,19–21]. IL-13 also influences isotype class switching to IgE [22] and eosinophil chemotaxis [19,20], but has distinct roles from IL-4 in mediating goblet cell hyperplasia and smooth muscle contractility

[23–25]. The overlap in the functions of IL-4 and IL-13 may be due to receptor and cytokine expression patterns. IL-4 and IL-13 signal through two potential heterodimeric receptors with a shared receptor moiety, IL-4 receptor alpha chain (IL-4R α). IL-4R α pairs with the γ chain to form a Type I heterodimer for IL-4 signaling [26], expressed primarily on hematopoietic cells (e.g. lymphocytes, monocytes, and macrophages) [27]. The Type II receptor complex comprises IL-4R α partnering with IL-13R α 1, which can be activated by either IL-4 or IL-13 [28,29] (Figure 1). The Type II heterodimer is more widely expressed in nonhematopoietic cells such as keratinocytes, hair follicles, epidermal sebaceous, sweat glands, epithelial and smooth muscle cells, and fibroblasts [30]. In addition, certain neurons express IL-4R α and IL-13R α 1, suggesting a neuro-immune connection [31]. A second IL-13 receptor, IL-13R α 2, binds to IL-13 with approximately 50 times greater affinity than IL-13R α 1 [32], however IL-13R α 2 lacks a signaling motif and has a truncated cytoplasmic domain suggesting that it functions as a decoy receptor for IL-13. IL-13R α 2 is expressed in nonhematopoietic cells and overexpressed on some cancer cells [33]; its role in atopic disease has not been fully explored. Innate cells, such as ILC2, natural killer T (NKT) cells and basophils, are abundant producers of IL-4 and IL-13 [34] and TH2 cells secrete IL-4, and to a lesser extent IL-13. These cytokines produced from T helper cells are secreted locally and concentrated at the interface where cells couple, the immune synapse, allowing the responder cell efficient and directional access to these cytokines [35–37].

Given the pleiotropic effects of IL-4 and IL-13, preclinical and clinical evidence of their activity in atopic disease has been widely reported [15,38,39]. In turn, several biologics targeting these cytokines have advanced to late-stage clinical development for asthma and AD and have provided insights into the molecular mechanisms of these atopic diseases (Table 1). This review focuses on the clinical advancements using therapies that target IL-4 and IL-13 in

atopic diseases, including atopic dermatitis (AD), asthma, and chronic sinusitis with nasal polyposis (CSwNP).

2. Atopic dermatitis

AD is a highly prevalent, chronic inflammatory skin disorder which manifests as inflamed, itchy, and lichenified skin widely distributed over the body. In moderate-to-severe disease, the skin can be dry, rough, flaky, cracked, and sting, bleed or ooze for several days of the week [59]. While usually thought of as a pediatric condition due to 20% prevalence in children [60], AD is common in adults, occurring as a life-long disease or with onset in adulthood, afflicting almost 7% of the US adult population [61].

The burden of adult AD was recently characterized in a study of patients with moderate-to-severe disease, highlighting its multidimensional impact on patient sleep, psychological health, and quality of life. Itch, the hallmark of the disease, is intractable and severe-to-unbearable in 60% of these patients, the majority of whom experience itching every day, several hours a day [59]. As a consequence, sleep is significantly affected; 68% of patients have trouble falling asleep or wake up often during the night [59]. In addition, AD is associated with neuropsychiatric issues and impairment of normal day activities. A significant proportion of patients can be classified as experiencing anxiety or depression based on Hospital Anxiety and Depression Scale [52,59]. The itchy, sore, painful skin exhibited by a majority of patients leads to embarrassment and interference in usual activities, from what-to-wear to impacting work/study and leisure [59].

A complex interplay between genetic, environmental factors and inflammation leads to alternations in the skin of atopic dermatitis patients. Genetic mutations, most notable is loss-of-function *FLG*, can cause abnormalities to skin barrier defense allowing the surface to be more penetrable to allergen or other environmental toxins [62]. In addition, most

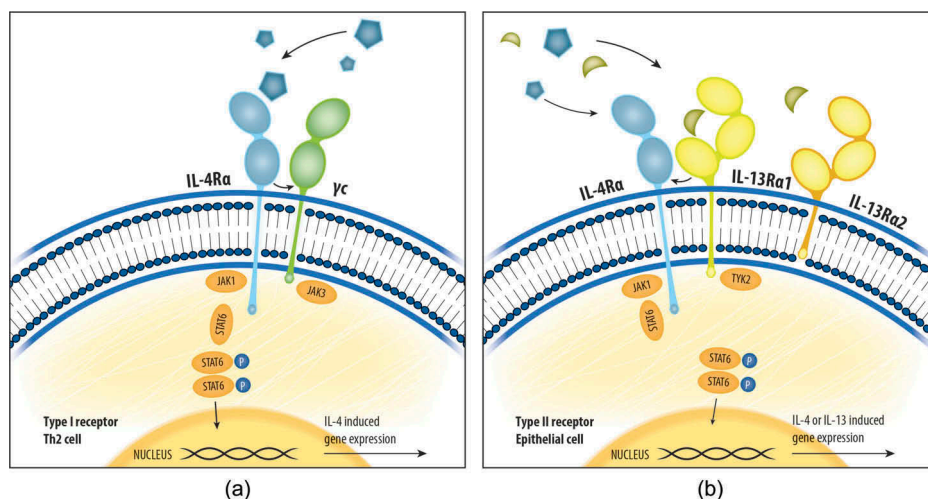


Figure 1. Receptor system for IL-4 and IL-13.

a) IL-4 binds to the Type I receptor which comprises of IL-4R α and common cytokine receptor γ -chain (γ c). b) Both, IL-4 and IL-13 bind to the Type II receptor complex which comprises of IL-4R α and IL-13R α 1. IL-13 also binds to IL-13R α 2 with higher affinity than IL-13R α 1. The accessory receptor chains (e.g. γ c, IL-13R α 1) are expressed on different specific cell types. Binding of these cytokines, IL-4 and IL-13, to their respective receptor complexes leads to activation of protein kinases, JAK1 or JAK3, or Tyk2 and subsequently phosphorylation of the transcription factor, STAT6. Phosphorylated STAT6 dimerizes and translocates to the nucleus to activate IL-4- and IL-13-induced genes transcription (e.g. periostin) [26–29]. Hexagon depicts IL-4, half-circle depicts IL-13.

Table 1. Therapies targeting IL-4 and/or IL-13.

Target	Drug (sponsor)	Molecule properties	Indications (phase of development)	Development status	Reference
IL-4	Altrakinccept (ImmuneX/Amgen)	Recombinant human soluble IL-4 receptor	Asthma (Phase 2)	Discontinued	[40]
	Pascolizumab (GlaxoSmithKline)	Humanized monoclonal antibody to IL-4 (IgG1) $K_D = 45$ pM	Asthma (Phase 2)	Discontinued	[41]
IL-13	Anrukizumab (Wyeth)	Humanized monoclonal antibody to IL-13 (IgG1) $K_D = 14$ pM	Asthma (Phase 2)	Discontinued	[42]
	Lebrikizumab (Genentech/Roche)	Humanized monoclonal antibody to IL-13 (IgG4) $K_D > 10$ pM	Asthma (Phase 3)	Discontinued in asthma	[43,44]
IL-4 and IL-13	Talokinumab (MedImmune/AZ)	Human monoclonal antibody to IL-13 (IgG4) $K_D = 165$ pM	Asthma (Phase 3)	Active in AD	[45,46]
	IL-4/IL-13 Cytokine Trap (Regeneron)	Engineered receptor fusion protein of IL-4R α and IL-13R1	AD (Phase 2)	Active	[47]
	Pitrakinra (Aerovance)	Recombinant human IL-4 variant (PEGylated form in AD)	Asthma (Phase 2)	Discontinued	[48,49]
	AMG317 (Amgen)	Human monoclonal antibody to IL-4R α (IgG2) $K_D = 180$ pM	Asthma (Phase 2)	Discontinued	[50,51]
	Dupilumab (Regeneron/Sanofi)	Human monoclonal antibody to IL-4R α (IgG4)	Asthma (Phase 3)	Active	[52–57]
	MEDI9314	Human monoclonal antibody to IL-4R α	AD (Phase 3)	BLA-filed in AD	
	SAR-156597 (Sanofi)	Bi-specific antibody for IL-4 and IL-13	CSwNP (Phase 3)	Active	Sponsor website, NCT02669667
	QBX258 (Novartis)	Combination of two human antibodies, VAK-694 (anti-IL-4) and QAX-576 (anti-IL-13, IgG1)	AD (Phase 1) Idiopathic pulmonary fibrosis (Phase 2)	Active	Sponsor website, NCT02345070
			Asthma (Phase 2)	Not reported	[58], NCT01479595

patients with AD have a dysbiosis of the skin microflora with an over-representation of *Staphylococcus aureus* bacteria [63,64]. Mechanical destruction of the skin can be induced by a cycle of itch-scratch [65,66]. All together, these cutaneous manifestations of disease can exacerbate and perpetuate underlying aberrant systemic inflammatory responses. The original model of AD pathogenesis suggested that different phenotypes of T cells contributed to disease in a biphasic pattern, starting with TH2 cells during the acute phase of the lesions, followed by TH1-dominated inflammation in chronic lesions [67]. Recent histological and molecular analysis of AD has clarified the inflammatory patterns of AD lesions and revealed that TH2 and the broader associated Type 2 inflammatory signature were present in both acute and chronic lichenified lesions [68]. These data showed that as the lesions progress, the inflammatory pattern intensifies, with increasing in gene expression of TH2 and also TH1-and TH22-associated cytokines [68]. Cellular analyses of lesional tissue have provided further evidence of cellular diversity in AD lesions. A collection of additional cellular infiltrations (e.g. dendritic cells, mast cells, eosinophils, and ILCs) are detected in the skin of AD patients, which are not present in healthy control tissue [69,70]. The diversity of cell involvement underscores the notion that AD is a T cell-centric disease. ILC2, as a potent source of Type 2 cytokines, are emerging as another potential pathogenic cell type that contributes and propagate AD [70].

In addition to the tissue-specific molecular and histological evidence that highlight Type 2 immune activation exists in AD, elevations in systemic biomarkers of Type 2 activation, IgE and thymus and activation-regulated chemokine (TARC/CCL17), are also highly elevated in patients with AD. The majority of patients with AD have high levels of IgE (from 100 to greater than 10,000 kU/L) [71,72]. These patients were historically classified as having extrinsic form of AD, while patients that lacked elevation in IgE were thought to have another, less-atopic, intrinsic form of the disease [67]. Molecular characterization of AD lesions from patients with extrinsic or intrinsic forms of AD had comparable patterns of Type 2 activation [73,74], narrowing the distinction between these two inflammatory phenotypes defined by IgE. Omalizumab, an anti-IgE therapy that markedly reduced serum IgE (by 97%) [75], was not effective in reducing symptoms of AD after 16 weeks compared to placebo [11]. In addition, reduction in IgE did not correlate with treatment response to effective therapies such as cyclosporine, a calcineurin inhibitor used to treat severe AD [76,77]. While there are limitations to serum IgE as a marker to distinguish different disease pathogenesises or treatment responses, TARC/CCL17 (an IL-4- and IL-13-induced chemokine) levels closely correlate to AD severity and decline rapidly in response to successful cyclosporine treatment [76,78–81].

The current mainstay of treatment of severe AD is systemic immunosuppression such as oral corticosteroids (OCS) or cyclosporine [82]. However, due to the broad mechanisms of action and pleiotropic effects of these agents, prolonged use of either immunosuppressant is associated with significant side effects such as hypertension, headaches, gastrointestinal symptoms, and increased susceptibility to infections. Additionally, fluid retention, glucose intolerance, muscle

weakness, potential bone loss, and suppression of hypothalamic-pituitary-adrenal axis are known effects of OCS [83,84]; elevated creatinine and hypertrichosis have been seen with cyclosporine [85]. While the application of topical corticosteroids or calcineurin inhibitors is usually adequate for treating mild AD, it provides only temporary or modest resolutions of symptoms for more severe forms of AD. These limitations emphasize the need for safer and more effective therapies for AD.

Several biologic therapies selectively targeting immune cytokines have invigorated the pipeline for potential treatment of severe forms of AD. Blocking the activity of IL-31, a known pruritogen, resulted in reduction of itch associated with AD [38,86]; even though targeting the Type 2 mediators, IgE or IL-5 alone was not sufficient to alleviate disease [11,13], IL-4 and IL-13 cytokine inhibitors have demonstrated robust efficacy in reducing itch and other clinical disease end points [52–54] – confirming the role of Type 2 inflammation as a key pathogenic mechanism of this disease.

Dupilumab (Regeneron and Sanofi), a fully human monoclonal antibody specific to IL-4R α that blocks both IL-4 and IL-13 signaling, has demonstrated consistent and unprecedented

efficacy on multiple AD disease end points, across seven clinical studies, as monotherapy and as an add-on to topical corticosteroids (TCS) [52–54]. The largest studies to date, two Phase 3 trials with identical designs (Liberty AD SOLO1 and SOLO2, N = 1,379) [52], replicated the robust disease improvement seen in earlier dupilumab Phase 2b studies [54]. The study population was patients with moderate-to-severe disease covering 50% of the body surface area who were not adequately controlled with topical medications. After 16 weeks, both dupilumab dosing regimens used in the studies (300 mg weekly or every other week) resulted in 36–38% of patients achieving 0 or 1 (clear or almost clear) and a 2-point reduction on the Investigator Global Assessment (IGA) (0–4 scale), the primary end point, compared to 8–10% of patients on placebo. The secondary end points demonstrated the consistency of the therapeutic effect of dupilumab. Approximately 50% of patients had a 75% reduction in the Eczema Area and Severity Index (EASI), a composite measure of the severity and extent of erythema, induration, papulation, edema, excoriations, and lichenification (0–72 scale), compared to 15% on placebo (Figure 2; Table 2); two times as many patients on placebo required rescue medication than

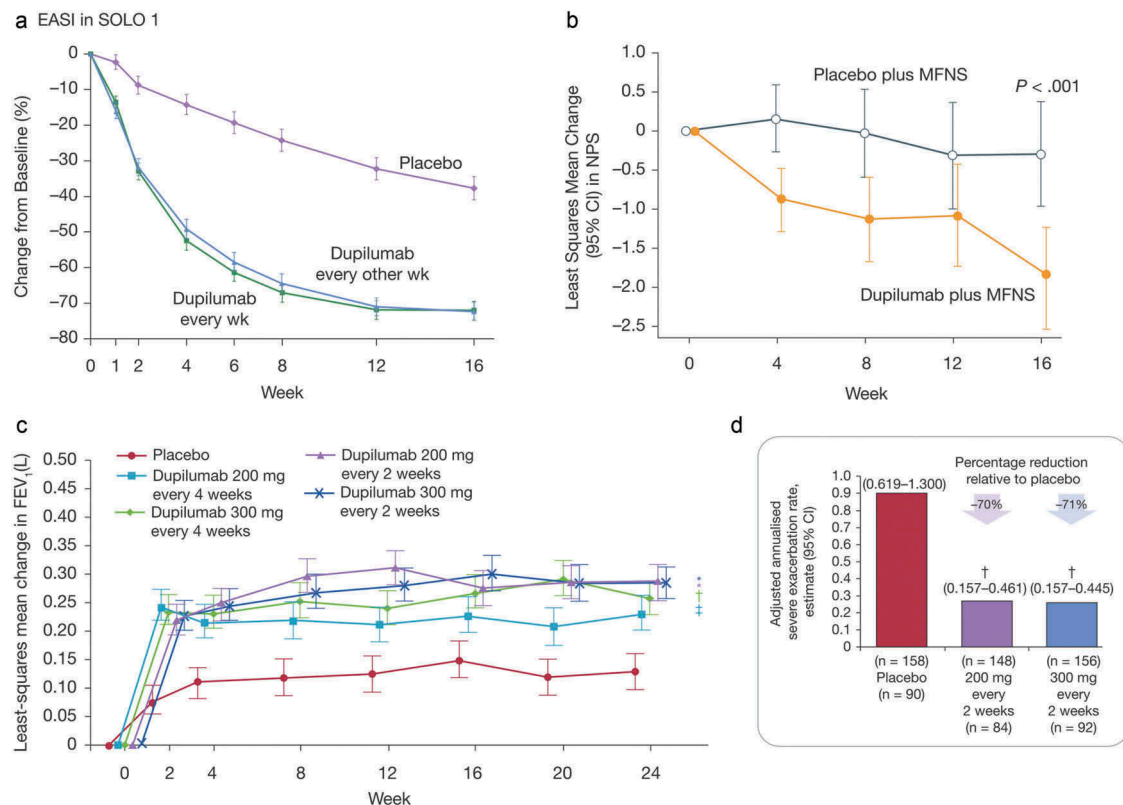


Figure 2. Treatment response of dupilumab across three allergic diseases with distinct affected tissues (skin, sinuses, lung).

a) Least-squares mean percent changes from baseline in the Eczema Area and Severity Index (EASI). $p < 0.001$ vs. placebo. Error bars represent standard errors.¹ b) Endoscopic nasal polyp score (NPS) by treatment group. P value comparisons are for week 16 vs. placebo MFNS. Error bars indicate 95% CIs.² c) Improvement in FEV₁ in L from baseline to week 24. $^{*}p < 0.001$. Error bars indicate standard errors.³ d) Relative reduction in asthma exacerbations in two highest dosing regimens. $^{*}p < 0.001$ vs. placebo.³

¹From [N Engl J Med, Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, Silverberg JI, Deleuran M, Kataoka Y, Lacour JP, Kingo K, Worm M, Poulin Y, Wollenberg A, Soo Y, Graham NM, Pirozzi G, Akinlade B, Staudinger H, Mastey V, Eckert L, Gadkari A, Stahl N, Yancopoulos GD, Ardeleanu M; SOLO 1 and SOLO 2 Investigators. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis, 375, 2335–2348. Copyright © (2016) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. ²Reproduced with permission from [JAMA. 2016; 315(5):469–79. Copyright © (2016) American Medical Association. All rights reserved. ³Reprinted from The Lancet, 388, Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, Pirozzi G, Sutherland ER, Evans RR, Joish VN, Eckert L, Graham NM, Stahl N, Yancopoulos GD, Louis-Tisserand M, Teper A. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial, 31–44, Copyright (2015), with permission from Elsevier.

Table 2. Efficacy of dupilumab across three atopic diseases with distinct affected tissues (skin, lung, sinuses, nose).

Organ system	Skin	Lung	Sinuses	Nose
Study population	Moderate-to-severe AD	Moderate-to-severe asthma	Moderate-to-severe CSwNP	Moderate-to-severe CSwNP
Duration of treatment	16 weeks	24 weeks	16 weeks	16 weeks
Efficacy end point ^a	EASI ^b	Exacerbations	Lund-Mackay computed tomography score ^d	Nasal congestion ^f
Change from baseline	-37.6 vs. 72.3 ($p > 0.001$) (SOLO1) -30.9 vs. -67.1 ($p > 0.001$) (SOLO2)	71% (ITT) 81% (high eosinophil group) 60% (low eosinophil group) ^g	Bilateral endoscopic nasal polyp score ^e -0.3 vs. -1.9 ($p > 0.001$)	-0.2 vs. -0.9 ($p > 0.001$)
LS mean difference from placebo	0.16 L		-8.8	-0.7
Reference	[52]	[56]	[57]	[57]

^aData from 300 mg every 2 weeks dose shown for all indications. ^bEASI score assesses the severity and extent of erythema, papulation, and edema; excoriations; and lichenification. EASI scores range from 0 to 72, with higher scores indicating greater severity and extent of atopic dermatitis. ^cFEV₁, forced expiratory volume in 1 s. ^dLund-Mackay computed tomography score: evaluates percentage of maxillary sinus volume occupied by disease. By assessing the patency of each sinus in a 0–2 scale (0 = normal; 2 = total opacification) and has a total score range from 0 to 24 (higher scores indicate more opacification). ^eBilateral endoscopic nasal polyp score is graded based on polyp size (recorded as the sum of the right and left nostril scores with a range of 0–8; higher scores indicate worse status). Range of 0–8 (higher scores indicate worse outcomes). ^fNasal congestion or obstruction in the morning. Symptoms were captured using a categorical scale (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms). Change from baseline averaged over 4 weeks prior to each time. ^gpercent reduction placebo. Study population noted in parentheses. ITT = intent-to-treat population.

those on dupilumab; and, most notably for patients, the severity of itch was significantly and rapidly improved within 2 weeks of dupilumab treatment [54,59]. On the pruritus Numerical Rating Scale (0–10 scale), a patient report of itch severity, nearly 40% of patients receiving dupilumab had at least a 4-point reduction, compared to only 10% on placebo, at Week 16. By Week 2, there was a significant improvement in itch end points favoring patients treated with dupilumab, compared to those receiving placebo [52].

Improvements in the multidimensional impact of disease (including quality of life, anxiety, and depression) were also assessed in the SOLO studies. Significantly more patients in the two dupilumab groups had improvements in both the Dermatology Life Quality Index (DLQI) and Patient-Oriented Eczema Measure (POEM) measures compared to the placebo group. Of the patients who started the study categorized as depressed or having anxiety on the Hospital Anxiety and Depression Scale (HADS), 40% of dupilumab-treated patients compared with 12% on placebo no longer met the criteria for depression/anxiety after 16 weeks of therapy [52].

In a separate 4-week study, the efficacy of dupilumab was shown to be additive when combined with a TCS. All patients receiving a TCS concomitantly with dupilumab achieved 50% improvement in EASI (EASI-50), compared to 50% of patients receiving TCS alone. There was a 71% reduction in pruritus in patients receiving the dupilumab and TCS combination compared to a 25% reduction observed in patients treated with TCS alone. Patients in the dupilumab group also required 50% less TCS than the placebo group [53]. Adverse events (AEs) occurred with similar frequency in the placebo and dupilumab groups, and most were of mild-to-moderate in severity. Injection site reactions, headache, nasopharyngitis, upper respiratory tract infection and conjunctivitis were the most frequent AEs with dupilumab, while skin infections occurred slightly more frequently with placebo [52–54].

Dupilumab induced a dose-dependent reduction in serum Type 2 biomarkers, corroborating the clinical response measures. Interestingly, the onset of action of dupilumab was independent of the decrease in IgE. Despite very high baseline levels observed in these patients (mean IgE: over 7000 kU/L for a 12-week study), the rate of reduction in IgE lagged behind the improvement in EASI observed as early as 2 weeks [53]. Regardless of baseline IgE and intrinsic or extrinsic status, a similar response to treatment was observed in the 12-week monotherapy study, in which patients were prospectively stratified [53]. In the same study, TARC/CCL17 rapidly reduced with dupilumab treatment: by 40% at Week 2 (Figure 3). In addition, there was a normalizing shift of skin gene expression from lesional toward nonlesional skin after 4 weeks of dupilumab treatment [53,87]. These molecular changes, reduction in itch, and reduced number of skin infections are suggestive of an overall improvement in skin barrier. Experience with dupilumab in AD, which blocks the IL-4/IL-13 pathway, was supported by earlier evidence from the first functional antagonist of IL-4 and IL-13 tested in AD, Aeroderm® (Aerovance), a PEGylated recombinant human IL-4 variant (NCT00676884) [88], in which 30 mg of the subcutaneous formulation of Aeroderm® administered twice a day for 28 days showed trends, but fell short in providing significant improvements in EASI score [48].

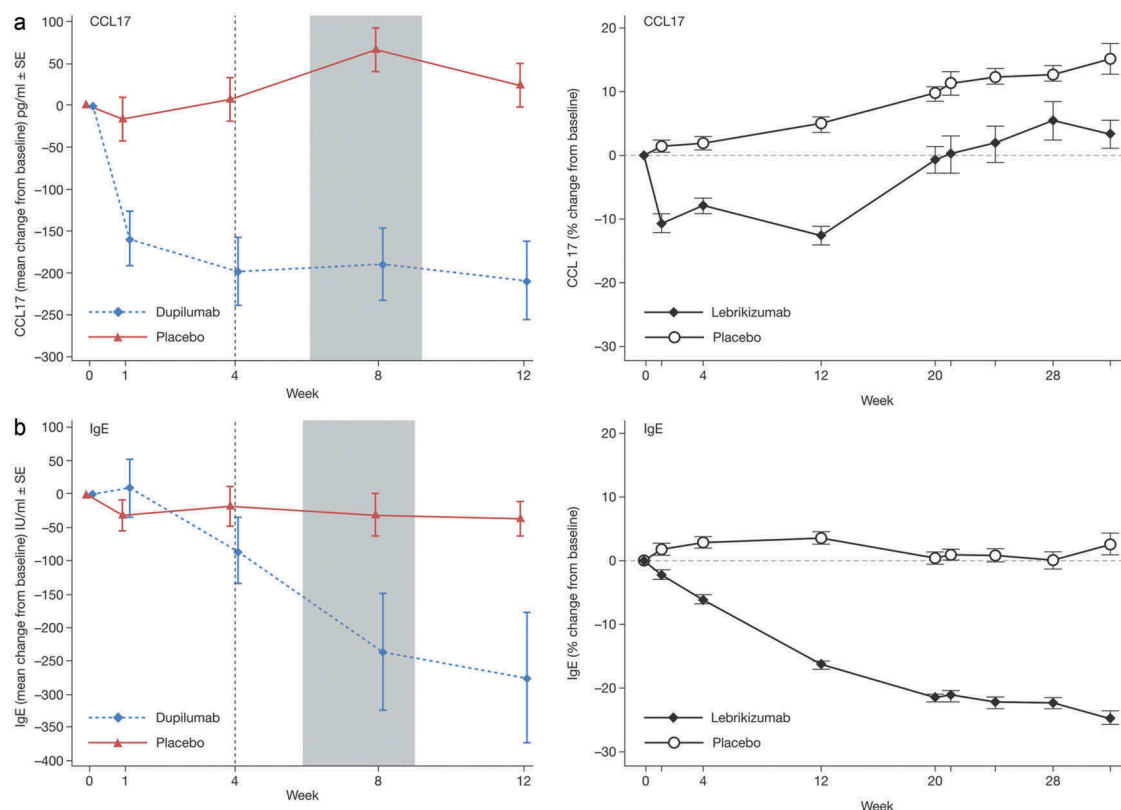


Figure 3. Effect anti-IL-4 and/or IL-13 inhibition on biomarkers of Type 2 activation in asthma.

a) Percent change in TARC (CCL17) with dupilumab in patients with asthma¹ and percent change in TARC (CCL17) with lebrikizumab in patients with asthma²; b) mean change in total IgE with dupilumab in patients with asthma¹ and percent change in total IgE with lebrikizumab in patients with asthma².

¹From [N Engl J Med, Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, Wang L, Kirkesseli S, Rocklin R, Bock B, Hamilton J, Ming JE, Radin A, Stahl N, Yancopoulos GD, Graham N, and Pirozzi G. Dupilumab in Persistent Asthma with Elevated Eosinophil Levels, 368, 2455–66. Copyright © (2013) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. ²From [N Engl J Med. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, Harris JM, Scheerens H, Wu LC, Su Z, Mosesova S, Eisner MD, Bohnen SP, and Matthews JG. Lebrikizumab treatment in adults with asthma, 365, 1088–98. Copyright © (2011) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

As dupilumab trials have confirmed the key role of both IL-4 and IL-13 in AD, recent studies have investigated the specific contribution of IL-13. Clinical studies in AD were performed using the single cytokine blockers tralokinumab (AstraZeneca) and lebrikizumab (Roche) – monoclonal antibodies that bind to IL-13 and neutralize its activity with different binding properties; tralokinumab binds IL-13 at a site that prevents the ligand from binding both IL-13Rα1 and IL-13Rα2 [89] whereas lebrikizumab binds IL-13 blocking the epitope required for IL-4R binding but allowing the ligand to bind IL-13Rα2 [43,89]. Top-line results conclude that tralokinumab demonstrated a significant improvement in EASI score at the two highest doses compared to placebo after 12 weeks of treatment [90]. A Phase 2 trial with lebrikizumab (TREBLE) tested three doses of lebrikizumab against placebo in moderate-to-severe AD patients (N = 209) receiving intensive TCS regimens over 12 weeks. In this study, 82% of patients achieved EASI-50, the primary end point with lebrikizumab treatment, compared to 62% of patients in the placebo arm. However, only one treatment dose, 125 mg every 4 weeks (q4w), demonstrated statistical significance compared to placebo. In addition, lebrikizumab treatment did not produce a significant difference from placebo on any other key end points, IGA, or reduction in itch, given the high placebo response due to intensive concomitant background topical medication [91]. Biomarker

changes were not reported in either study. Studies with lebrikizumab in other indications showed that initial suppression of TARC with anti-IL-13 therapy alone is not sustained after 12 weeks (Figure 3) [44], suggesting an incomplete inhibition of a biomarker associated with treatment response [78]. Taken together, these results suggest that IL-13 is a contributor to the immunopathogenesis of AD, but is not the only disease driver; blocking IL-13 did not provide the same magnitude of clinical benefit as targeting both IL-4 and IL-13 with dupilumab. And further, these results highlight the importance of IL-4 as a key pathogenic cytokine in AD.

Additionally, IL-4 and IL-13 have also been implicated in other atopic disease such as asthma. AD is a significant risk factor for the development of asthma; 30% of children with AD will progress to asthma [92,93]. It is not well understood how these seemingly different diseases are related. Therefore, understanding how drugs that are effective in AD perform in other atopic diseases could help to unravel key mechanistic commonalities between atopic diseases.

3. Asthma

Asthma is a prevalent, chronic respiratory disease characterized by airway obstruction, airway inflammation, and hyper-responsiveness. More than 25 million people (8% of the US

population) are afflicted with asthma [94] and over 4% of the population worldwide [95]. Symptoms of asthma include cough, wheezing, chest tightness, and shortness of breath. In addition, patients can experience an exacerbation, which is an episodic worsening of asthma symptoms associated with decline in lung function and need for more intense treatment [96]. Mild asthma is managed by inhaled corticosteroids (ICS) and treats airway inflammation. Patients with more severe disease are treated with higher doses of ICS and the stepwise addition of bronchodilators, such as long-acting β_2 agonists (LABAs), or other immune-targeting drugs (e.g. leukotriene modifiers, cromolyn sodium, and/or immune modulators such as anti-IgE and anti-IL-5) [96]. However, 5–10% of asthma patients have severe or refractory asthma that is prone to frequent and severe exacerbations requiring extensive disease management [97]; hence, this patient segment is in the greatest need of new therapies.

The pathophysiology of asthma is multifactorial. Many immune cell types that span innate and adaptive immunity and Type 1 and Type 2 immunity, such as mast cells, eosinophils, ILC2s, T-lymphocytes, neutrophils, and epithelial cells are found in the lung of asthmatics [98,99]. Their biological products, immune mediators and growth factors (e.g. leukotrienes, PDE4, IL-9, thymic stromal lymphopoietins, IL-33, transforming growth factor- β , fibroblasts, or epidermal growth factors), can modulate the activity of epithelial cells, fibroblasts, smooth muscle cells, and vascular endothelial cells and contribute to airway alterations [[100–102]. The presence of both peripheral and lung eosinophilic and TH2 cellular infiltrates based on histology has implicated a role for IL-4 and IL-13 as disease drivers [98,99]. These cytokines may also mediate the smooth muscle contraction, basement membrane thickening, goblet cell hyperplasia, and mucus secretion that lead to airway obstruction, propagating this atopic disease. Numerous *in vivo* studies of allergen-induced lung inflammation were attenuated by a lack of IL-4 and/or IL-13 [88,103,104].

Several therapies targeting IL-4, IL-13 or both cytokine with different molecular properties were tested in asthma [Table 1]. Two IL-4 inhibitors (altrakinecept [Immunex] [40,105] and pascolizumab [GSK]) [106], several anti-IL-13 monoclonal antibodies, including anrukinzumab (Wyeth/Pfizer) [42], and one dual cytokine blocker, AMG317 (Amgen) [50], all showed promising results in early studies that did not persist in later studies. These unexpected negative results led to skepticism about the importance of these cytokines in asthma [107], and highlighted the heterogeneous nature of the disease.

The next advancement in the field sought to address this heterogeneity by focusing on more severe forms of asthma, and identifying patient subsets based on pathological phenotypes that would respond more uniformly when paired with therapy with a relevant mechanism. Employing cross-disciplinary learnings from phenotypic cluster analysis, molecular profiling with empirical clinical research, a subset of asthma that was otherwise clinically indistinguishable, was defined based on inflammatory patterns. A cluster analysis of various demographic and clinical variables of asthmatics revealed a subset of patients with elevations of eosinophils in sputum or blood shared several disease characteristics: frequent exacerbations,

degrees of response to corticosteroids and elevations in markers of Type 2 pathway activation such as serum IgE, increased mucus production, and airway structural changes compared to a non-eosinophilic phenotype [108,109]. Further supporting the existence of this inflammatory phenotype, gene expression analysis of airway epithelial cells from asthmatics showed by clustering on three IL-4 and/or IL-13 inducible genes (POSTN [perisotin], CLCA1, SERPINB2), a distinct TH2-high gene expression profile existed in 50% of the patients, while the other half had low-TH2 gene expression similar to healthy controls [110]. This suggested that selectively targeting this pathway, in this subset, could provide more consistent clinical benefit than in an unselected population. Positive results from two clinical studies, using an eosinophil-targeting therapy, mepolizumab (anti-IL-5) in patients with severe asthma with predominant eosinophilic inflammation, reinforced the findings from clinical and molecular cluster analyses [111,112]. The success of anti-IL-5 inhibitors in asthma pivoted on these studies that characterized the eosinophilic phenotype of asthma [111,112].

In addition to investigating the use of eosinophils to enrich treatment response, lebrikizumab studies explored the potential of periostin, a biomarker of IL-13 activity. Periostin is an extracellular matrix protein made by epithelial cells and expressed by fibroblasts and is implicated in subepithelial fibrosis [113,114]. A Phase 2 lebrikizumab study (MILLY) enrolled patients with moderate-to-severe asthma not controlled with standard ICS and LABA therapy. After 12 weeks of therapy with lebrikizumab added to stable ICS+LABA, the subset of patients with elevated serum periostin or elevated Type 2 biomarkers (i.e. IgE and blood eosinophils) derived the most benefit on the improvement in lung function as evaluated by forced expiratory volume 1 (FEV₁) [44]. In Phase 2b lebrikizumab trials (LUTE and VERSE), pooled analysis of these replicate studies also confirmed a greater magnitude of reduction in exacerbations in patients with high periostin levels [115]. Interestingly, there was not a clear dose-response relationship on this end point; the highest dose (250 mg q4w) showed a 22% reduction in exacerbations, while the lower-dose groups (37.5 mg q4w and 125 mg q4w) had a reduction in exacerbations of 81% and 77%, respectively [115]. The largest and most recent studies of lebrikizumab in asthma, two identical, randomized, double-blind, placebo-controlled Phase 3 studies (LAVOLTA 1 and 2, N = 2148), explored the efficacy of 2 doses, 37.5 and 125 mg q4w, of lebrikizumab versus placebo on the rate of exacerbations in a period of 52 weeks. Since only one of the two studies met its primary end point, the asthma program was subsequently discontinued [116] (Sponsor press 29 February 2016).

Tralokinumab is the second IL-13 inhibitor to proceed to Phase 3 studies, despite some equivocal findings in Phase 2. The Phase 2a trial in patients with moderate-to-severe asthma did not meet the primary end point, which was the change in mean Asthma Control Questionnaire (ACQ-6), a composite measure six items: short-acting β_2 -agonist use and five asthma symptoms (e.g. nighttime waking, symptoms upon waking, activity limitation, shortness of breath, wheezing) after 13 weeks of treatment. Mean ACQ change in pooled tralokinumab treatment groups was –0.76, compared to –0.61 in the

placebo arm ($p = 0.375$) [117], in which a 0.50-point change is considered a clinically meaningful difference on this end point [118]. However, improvement in FEV_1 and reduction in the use of short-acting β_2 -agonists in tralokinumab-treated subjects were suggestive of a treatment effect [117]. These results were supported by a second Phase 2 study, in which patients treated with tralokinumab q2w had 7% improvement, corresponding to an FEV_1 change of 0.13 L from placebo ($p = 0.003$). However, the study did not reach the primary end point of reduction in annual asthma exacerbation rate over 52 weeks [45].

The potential of dual cytokine blockade has also been explored using different types of antagonists: a combination of IL-4 and IL-13 antibodies, recombinant human IL-4 variant and two anti-IL-4R monoclonal antibodies, which provided disparate results in the clinical setting. QBX258 [Novartis], a combination of two antibodies raised to the sister cytokines, IL-4 and IL-13, showed a significant change in ACQ after 12 weeks in patients with asthma that were inadequately controlled with ICS and LABA. There was a -0.513 point change and 0.001 point change on the primary end point of ACQ and 0.076 L and 0.050 L improvement on FEV_1 with QBX258 treatment and placebo, respectively (NCT01479595). In contrast, 12 weeks of AMG317 treatment failed to improve ACQ (the primary end point) in a placebo controlled study, in patients with moderate-to-severe atopic asthma. AMG317 demonstrated a reduction of serum IgE of 7%, 14%, and 34% for doses of 75, 150, and 300 mg, respectively, and was relatively rapidly cleared in comparison to other fully human monoclonal antibodies, suggesting a suboptimal activity in reducing systemic Type 2 biomarkers [51]. The initial signal that this mechanism could have robust efficacy came from a subset analysis of a Phase 2 study with pitrakinra, using baseline elevated blood eosinophilia to predict patient response. In this study, ICS and LABA were tapered over a 12-week treatment period to destabilize asthma control and accelerate the detection of a treatment effect. While at 12 weeks there was no statistically significant reduction in the primary end point of exacerbations in the intention-to-treat (ITT) population ($n = 534$), the high-dose group in the eosinophil-high subset had a 74% relative reduction in exacerbation frequency; 50% of patients on placebo experienced exacerbations compared to only 13% of treated patients [49]. Building upon these conclusions, dupilumab was prospectively studied in patients with the eosinophilic phenotype of asthma using a similar ICS and LABA taper study design.

In a proof-of-concept study (Phase 2a), dupilumab resulted in significant improvements in loss of asthma control (as assessed by an exacerbations index) by 87%. The 300 mg dose of dupilumab administered weekly by subcutaneous injection also significantly improved FEV_1 ; an 11% relative improvement with placebo, or a 0.27 L difference between dupilumab and placebo, was observed at 12 weeks [55]. These results were followed up by a larger study in a broader population, with 24 week treatment duration. This Phase 2b study examined dose response and efficacy in a broader patient segment, with blood eosinophil levels at baseline above and below 300 μ L, stratified across four dose groups. In this double-blind, placebo-controlled study, significant improvements were observed, in a dose-dependent manner, for several end

points in the overall patient population, not selected by eosinophil levels. Patients treated with the two highest doses of dupilumab, 200 or 300 mg q2w (twice a week), achieved around 12% improvement in FEV_1 , corresponding to a 0.16–0.2 L difference from placebo ($p > 0.001$) (Figure 2; Table 2). In turn, patients in the high eosinophil group (>300 eosinophils/ μ L) had a more pronounced improvement in FEV_1 , the primary end point of the study – around 16%, corresponding to a 0.21–0.26 L difference from placebo. Regardless of eosinophil strata, the exacerbation data showed robust reduction in exacerbation rates; 71%, 81%, or 60% reduction relative to placebo in the ITT, high eosinophil and low eosinophil (<300 eosinophils/ μ L), respectively. Significant improvement in ACQ-5 was also observed in the ITT population with dupilumab treatment. The frequency of AEs was similar with dupilumab in both asthma studies. Overall, patients in the placebo and dupilumab groups experienced similar rates of AEs. The most common AEs in dupilumab-treated patients were injection-site reactions, nasopharyngitis, and headache, with a slightly higher rate of upper respiratory infections in the placebo group, compared to the dupilumab group [55,56]. These data indicate that the simultaneous inhibition of the IL-4 and IL-13 pathways with dupilumab resulted in improved efficacy in a broad population of asthmatics. This shows that the Type 2 pathway is broadly relevant across the severe asthma population. The 200 and 300 mg q2w doses of dupilumab are currently being investigated in Phase 3 clinical studies.

4. Chronic sinusitis with nasal polyposis

CSwNP is a prevalent and persistent disease characterized by inflammation of the paranasal sinuses and the occurrence of bilateral polyps located in the upper nasal cavity. The nasal/paranasal sinus inflammation plus the outgrowth of the mucosa originating from the ostiomeatal sinus complex that forms the polyps lead to symptoms of facial pain, pressure, congestion and loss of smell that last more than 12 weeks [119]. The estimated prevalence of CSwNP is 2–4% in Europe and in the US [119–121] with 40–50% of patients have comorbid asthma [120,122]. Pharmacological treatment options include nasal corticosteroids or short-term courses of oral corticosteroids [123]; when these are insufficient, functional endoscopic sinus surgery is used to mechanically remove obstructions improving ventilation and sinus function. However, polyps tend to recur even after surgery [124].

Intense eosinophilia and elevation in IgE are two hallmarks that implicate Type 2 activation in disease pathogenesis of CSwNP [125]. Histological analysis of sino-nasal mucosa and polyp tissue from patients with CSwNP shows an increase in the inflammatory cellular infiltrate with notable tissue eosinophilia [126]. In addition to eosinophils, IL-5, a differentiation and survival factor for eosinophils, and nasal IgE levels have been found to be elevated in patients with CSwNP [127]. The pathogenic role of these biomarkers of Type 2 immune activation was validated in clinical studies with anti-IL-5 and anti-IgE therapies. Both therapies have demonstrated efficacy in CSwNP [128,129]. Expanding on these investigations, IL-4/IL-13 cytokine blockade with dupilumab was studied in

combination with mometasone furoate nasal spray. After 16 weeks of therapy, patients on dupilumab had a significant reduction in nasal polyp size and improvement in several other disease assessments [57]. Based on endoscopy evaluation, a 1.6-point reduction in polyps score was observed compared to a 0.3-point change with placebo ($p < 0.001$; Figure 2; Table 2). In addition, there was 50% improvement in the patency of the sinus by computerized tomography scan and 44% improvement in patient-reported symptoms (i.e. sense of smell, congestion, postnasal drip, runny nose, sleep disturbance) with dupilumab treatment. Half of the patients enrolled in this study had comorbid asthma. The change in polyp size was more pronounced in this subset, with -2.3- and 0.02-point changes with dupilumab and placebo, respectively. Interestingly, patients on dupilumab in this subset also saw a 0.2 L volume improvement in FEV₁ and meaningful improvement in ACQ score, suggesting that CSwNP and asthma are manifestations of the same aberrant immune pathway. Safety findings in this study were consistent with previous dupilumab studies; the most common AEs with dupilumab were injection site reactions, nasopharyngitis, oropharyngeal pain, epistaxis, headache, and dizziness [57]. Together, these data show that the Type 2 inflammation is the driver pathway in this subset of chronic sinusitis patients.

5. Expert commentary

Allergy is the result of an overactive Type 2 inflammatory response that leads to diverse symptoms affecting multiple tissues, individually or concomitantly. Atopic dermatitis is associated with inflamed skin and an unrelenting itch that significantly impairs daily living; asthma is characterized by airway inflammation, airway hyperresponsiveness, and episodic bronchoconstriction that lead to cough, wheezing, and potentially life-threatening episodic worsening of asthma symptoms; the obtrusive polyps and sinus inflammation can cause facial pain/pressure, congestion, and scent impairment in patients with CSwNP. These diseases are commonly treated with daily topical administration of corticosteroids to the affected organ by creams, inhalers, or sprays to control symptoms. However, these treatments are often inadequate in severe atopic conditions or insufficient to address the causative underlying systemic inflammation.

The canonical Type 2 cytokines, IL-4 and IL-13, have been implicated in driving the aberrant Type 2 response that perpetuates atopic diseases. However, historical observations of mixed and non-TH2 inflammatory patterns of AD and early failures of agents targeting these Type 2 pathway mediators in asthma underestimated the significance and generalizability of this pathway in atopic diseases like AD and asthma until recently, when IL-4/IL-13 pathway inhibition by dupilumab demonstrated robust efficacy across these diseases. This validates the existence of Type 2 pathway activation in AD and asthma seen by molecular profiling in AD and physiological characterization in asthma, and clarifies the role of these cytokines in atopic disease.

The allergy burden is growing in prevalence and diversity, with a growing list of allergens. Worldwide epidemiological

studies highlight the steady and sequential rise in prevalence of initially rhinitis, then asthma, and now food allergy [94,130,131]. The list of allergens that provoke an allergic response is also broadening in food (peanut, alpha-galactose, wheat) and in the environment (molds, pollens, dust mites) [132]. Environmental factors are blamed for the changes in allergy epidemiology, especially in developed countries, where improved hygiene, industrialization of food, and widespread vaccination may lead to epigenetic modification that could unleash the regulated Type 2 response [133,134]. Since these societal factors are not easily alterable, development of new therapies or improvement to existing treatment strategies for atopic disease are needed to address the growing epidemic.

6. Five-year view

Moving forward, pathway-focused therapies could have paradigm shifting implications for treatment of atopic diseases. First, clinical discoveries with targeting IL-4 and/or IL-13 serve to advance and transform treatment options for patients. Secondly, they provide evidence of a unifying pathological mechanism in diseases originally thought to be distinct entities because of their different tissue manifestations. The fact that these diseases which often occur comorbidly and are responsive to the same therapy supports the concept of a 'common driver pathway.' Targeting individual components of the Type 2 pathway (e.g. IgE, IL-5 or IL-4, or IL-13 alone) is effective on certain diseases and fallen short to extend to multiple diseases. For instance, anti-IL-5 therapies are effective in treating eosinophilic phenotype of asthma, but are not effective in treating AD.

In contrast, positive results from clinical studies investigating dupilumab in AD, asthma and CSwNP supports that IL-4 and IL-13 are, indeed, central pathogenic cytokines in these atopic diseases. The power to identify and target central disease pathways in allergy could have the potential to provide disease-modifying benefits across multiple diseases, treat comorbidities, and potentially prevent disease progression such as the atopic march.

Key issues

- Type 2 inflammation results from a complex interaction between the innate and adaptive immune system evolved to effectively purge parasites from the body. Immune cells (e.g. TH2, ILC2, eosinophils, mast cells, basophils) and mediators (e.g. Type 2 cytokines, IgE, histamine) activate a broad scope of physiological responses that include mucus production, cell hyperplasia, itch, constriction, sneezing, coughing, vomiting, and diarrhea.
- Allergy is a misdirection of these responses towards allergens. Heterogeneity in severity, tissue manifestations and types of allergens are salient; allergic symptoms can range from mild to life-threatening, limited to one organ or present comorbidities depending on the environmental trigger and patient genetic predisposition.
- Biological therapies selectively targeting this pathway have been investigated for efficacy in atopic diseases. The varying degrees of success of these precedent agents could be

explained by target selection or the molecular characteristics of the inhibitor. Anti-IgE and anti-IL-5 agents that target downstream mediators of the Type 2 pathway are effective in treating asthma and CSwNP, but not AD. Several agents with varying molecular properties targeting IL-4 and/or IL-13, key potentiators of the Type 2 process, failed in clinical trials in asthma, whereas, dual blockade of IL-4 and IL-13 with dupilumab demonstrated significant efficacy across the three allergic diseases – asthma, AD, and CSwNP. With this potent blocker to the shared IL-4 receptor moiety, it was revealed that the IL-4/IL-13 pathway is a common pinch-point among these seemingly disparate atopic diseases.

- Elucidating and inhibiting the central disease pathways in allergy holds a potential for new therapies to provide more than temporary symptomatic relief, but a potential to investigate if disease-modification and benefits of treating comorbidities is achievable.

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