



Cytokine-targeting biologics for allergic diseases



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Key Messages

- Multiple approaches have been utilized in the design of biologic drugs that target cytokines.
- New biologic therapies have been approved or are being tested for treatment of eosinophilic allergic diseases.
- Phenotyping of patients is critical for decisions on who to treat with new targeted therapy.
- There is an unmet need for new biologic treatments that target noneosinophilic disorders.

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ABSTRACT

Objective: Asthma and allergic diseases continue to increase in prevalence, creating a financial burden on the health care system and affecting the quality of life for those who have these diseases. Many intrinsic and extrinsic factors are involved in the initiation and maintenance of the allergic response. Cytokines are proteins with growth, differentiation, and activation functions that regulate and direct the nature of immune responses.

Data Sources: clinicaltrials.gov and PubMed.

Study Selections: Relevant clinical trials and recent basic science studies were chosen for discussion.

Results: Many cytokines have been implicated in the development and perpetuation of the allergic response. Biologics have been and are continuing to be developed that target these molecules for use in patients with asthma and atopic dermatitis where standard treatment options fail. The current state of cytokine-targeting therapies is discussed.

Conclusion: This review focused on cytokines involved in the allergic response with an emphasis on those for which therapies are being or have been developed.

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Introduction

Asthma and allergic diseases continue to increase in prevalence, with studies indicating that 8% of the US population has a diagnosis of asthma and 30% to 40% of people have some form of allergic disorder.¹ The use of bronchodilators, corticosteroids, antihistamines, and leukotriene modifiers, as appropriate for the specific condition, does broadly target symptoms or inflammation and for most patients these compounds do provide relief and control of disease. However, a group of individuals remain unresponsive to current treatments and, in the case of asthma, some patients have very poorly controlled disease or severe exacerbations that produce significant morbidity and, rarely, mortality. Therefore, newer

therapies are being developed that target pathways involved in allergy and asthma pathogenesis, including in particular biologics that target cytokines. Cytokines are proteins with growth, differentiation, and activation functions that regulate and direct the nature of immune responses. Understanding the mechanisms of how they work on the molecular and cellular level is leading to new treatments that have the promise of not only inhibiting ongoing inflammation and blocking the progression of the disease but also potentially reversing the damage that has occurred from this inflammation and modifying the natural history of these diseases. The focus of this review is on cytokines that are involved in the initiation and maintenance of the allergic response and a discussion of new treatments aimed at inhibiting their action. In addition, this review explores reasons why some of these therapies have succeeded, whereas others have failed. Specifically, cytokines are discussed that are targeted with currently approved therapeutics or that are in ongoing clinical trials (interleukin [IL]-4/IL-13, IL-5, thymic stromal lymphopoietin [TSLP], IL-33, IL-31) or are likely to be developed in the near future (IL-17, IL-25).

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Overview and Impact of Different Approaches to Targeting Cytokines

There are several approaches to targeting cytokines (and other mediators) and subtle—and not so subtle—differences can affect their efficacy and safety. As such, it is important for the clinician to appreciate distinctions when choosing an optimal biologic. In general, cytokines can be directly targeted through 3 mechanisms: soluble receptors, anticytokine antibodies, and anticytokine receptor antibodies.

Soluble receptors retain the high affinity for their ligand of the native cell surface receptor and thus act as a decoy to capture the cytokine and sequester it in circulation. For example, soluble receptors that target tumor necrosis factor (eg, etanercept) are currently available and are successfully used in rheumatologic conditions.² However, for allergic disorders, soluble receptors have been tried and failed (eg, sIL-4R [altrakcept]) or are being considered but are not yet in development (eg, ST2 [sIL-33R]), so this approach is not be discussed further.

Anticytokine antibodies are currently the mostly widely used approach. These antibodies capture their targeted cytokine, prevent binding to its receptor, and thus can neutralize biological activity. However, several features, including source, immunoglobulin (Ig) subclass, dose, allotype, and glycosylation, can greatly affect efficacy.

Source

All antibodies currently available for allergic disorders are humanized or fully human IgG antibodies. As presented in Table 1, the source of the antibody and the extent to which it is composed of murine as opposed to human components can be readily discerned from the suffix of its generic name. Murine or chimeric antibodies carry the risk of development of antimurine antibodies with subsequent loss of activity and generation of hypersensitivity reactions. Although humanized antibodies use the human Fc and human Fab framework regions, they retain murine amino acids in their cytokine-binding complementarity-determining regions.³ As such, these humanized antibodies could have a remaining tendency to develop antimurine antibodies. In addition, the manipulation required to combine human framework with murine cytokine-binding complementarity-determining regions often produces a molecule with lower affinity for its target.

Immunoglobulin Subclass

All currently available therapeutic antibodies are IgG1 or IgG4. The IgG1 subclass mediates effector functions including complement activation and opsonization of targets, driving antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity.³ These activities take on importance when considering antireceptor antibodies (see below). IgG4 antibodies neither activate the complement nor bind to any of the Fc receptors; hence, although they

can bind and sequester their target, do not actively clear it from the circulation or from the inflammatory milieu.³

Dose

Anticytokine biologics are dosed at a concentration known to neutralize the expression—and typically a biomarker—of that cytokine in the circulation. For example, IL-5–targeting antibodies eliminate circulating eosinophilia. What is not known is the capacity of these high-molecular-weight proteins to access inflamed tissue and neutralize their cytokine target locally. Thus, as one example, it is unknown whether the dose of anti-IL-5 antibody that is sufficient to eliminate circulating eosinophils is sufficient to block the biological activity of IL-5 in an eosinophilic plaque within the central nervous system of a subject with hypereosinophilic syndrome or, indeed, whether that effect can be achieved with higher dosing.

Allotype

Allotype (genetic variability in the sequence of isotype Fc regions) is of theoretical importance because administration of a biologic having a different allotype than that of the recipient could lead to the generation of allotype-specific antibodies and subsequent therapy resistance or conceivably to hypersensitivity reactions. IgG1 has 4 distinct allotypes. This is not an issue for IgG4 for which there is no genetic diversity.

Glycosylation

When considering ADCC (and ADCP), there are 5 activating IgG receptors—FcγRI (CD64), FcγRIIa (CD32a), FcγRIIc (CD32c), FcγRIIIa (CD16a), and FcγRIIIb (CD16b)—and 1 inhibitory receptor (FcγRIIb), with FcγRIIIa being the major receptor driving ADCC. Immunoglobulin subclass and alternative glycosylation of the Fc sequence involved in receptor binding (the CH2 region) can influence the capacity of an antibody to differentially bind these receptors and thereby alter biological functions. This is relevant with antireceptor antibodies in which ADCC of the target cell is a desired outcome. Of note, benralizumab (an anti-IL-5R antibody) is defucosylated at this CH2 region to enhance its ability to mediate ADCC and immune clearance of IL-5R–expressing cells (mainly eosinophils and basophils). Another important concern when considering glycosylation of biologics is the cell line used to produce the biologic and, if produced in a non-human mammalian cell line, the tendency of that cell to add galactose-α-1,3-galactose residues. Although this severely affected the safety of 1 anticancer biologic (cetuximab),⁴ this has not been an issue with biologics available for allergic inflammatory disorders and is assiduously avoided by the pharmaceutical industry.

Anticytokine Receptor Antibodies

In contrast to anticytokine antibodies, antireceptor antibodies mediate their biological activities by binding to the receptor—without inducing activation—and then act to prevent binding of the natural ligand. This distinct mode of action is of much more than theoretical interest because it suggests broader immune efficacy (Table 2). One of the limiting issues with anticytokine antibodies, as noted earlier, is their ability to access the inflammatory space where the cytokines are acting. Although antibodies freely permeate the serum and bone marrow, their access to inflamed tissue, such as bronchoalveolar lavage fluid, the interior of a nasal polyp, or a central nervous system eosinophilic plaque, could be limited. In contrast, an antireceptor antibody will target the cellular target, for example, circulating eosinophils, *before* their egress into the

Table 1
Nomenclature for Monoclonal Antibodies

Antibody source	Nomenclature (suffix)	Example	Function
Mouse	omab	muromomab	anti-CD3 (T cell)
Chimeric	ximab	rituximab	anti-CD20 (B cell)
		infliximab	anti-TNF-α
Humanized	zumab	omalizumab	anti-IgE
		reslizumab	anti-IL-5
		mepolizumab	anti-IL-5
		benralizumab	anti-IL-5R
Fully human	umab	dupilumab	anti-IL-4R (IL-4/IL-13)

Abbreviations: IgE, immunoglobulin E; IL, interleukin; TNF-α, tumor necrosis factor-α.

Table 2
Differences Between Anticytokine and Anticytokine Receptor Antibodies

Function	Anticytokine antibody	Anticytokine receptor antibody
Active in circulation	only if cytokine is present	requires only presence of cellular target
Active in inflamed tissue	only on cytokines acting in an endocrine fashion	requires only presence of cellular target
Active in immune synapse	cannot access synapse	binds and blockades target before synapse has formed
Requirements for cytokine	essential	only requires the cellular target to express the receptor

inflamed tissue. This concern is further apparent insofar as anticytokine antibodies can neutralize only cytokines that are freely diffusing through the inflamed tissue or circulation. Although innate cytokines such as IL-1 and tumor necrosis factor act hormonally, this is much less true for T-helper cell type (T_H)2-derived cytokines, which are present—if at all—only at vanishingly low concentrations in the circulation and diffuse across limited distances even within inflamed tissue. For example, although IL-13 somewhat readily diffuses within the bronchial compartment and acts distally to induce epithelial metaplastic transformation into goblet cells, this is not true for IL-4. IL-4 acts fairly exclusively in a paracrine fashion, being targeted to adjacent cells and even then only after an immune synapse has formed. Because anti-IL-4 antibodies cannot diffuse into an immune synapse, they cannot neutralize IL-4. This contrasts with an IL-4R antibody that can engage receptors before the synapse forms and thus can subsequently antagonize IL-4. Anti-IL-5 has its own unique issue, which is the tendency of eosinophils after they have migrated into the inflammatory tissue to evolve from using IL-5 as their primary survival signal to using autocrine-derived granulocyte-macrophage colony-stimulating factor. Thus, an anti-IL-5 antibody will not shorten survival of eosinophils already present in the airway, in contrast to an anti-IL-5R that will retain its ability to bind to and opsonize tissue eosinophils. This raises the final important difference between anticytokine and antireceptor antibodies, which is the unique ability of the latter to opsonize their targets for ADCC and ADCP. These differences are evidenced by the much greater capacity of anti-IL-5R to eliminate tissue eosinophils in contrast to anti-IL-5 antibodies. (Also, these features underlie the ability of anti-IL-5R to eliminate tissue basophils because, despite the more limited role of IL-5 in driving basophilic inflammation, basophils consistently express IL-5R.)

Biosimilar Products

The US Food and Drug Administration has recently issued guidelines that will streamline the approval process for biological products that are considered “biosimilar” (also termed “interchangeable”) with a product approved by the Food and Drug Administration. In the near future, this could lead to the availability of less expensive counterparts to antibodies currently being used in asthma and allergic

inflammatory disorders. However, it is important to recognize that these guidelines are broadly written and, in the case of monoclonal antibodies (mAbs), the overarching requirements are only to demonstrate a similar capacity to recognize the same target as the approved compound and to have a similar half-life. As such, many of the issues raised in the previous paragraphs regarding differences among mAbs will likely extend to these biosimilar products. This will require the practitioner to recognize the potential for subtle—and perhaps not so subtle—differences in the behaviors of biosimilar antibodies.

Interleukin-4 and -13

Allergic diseases and asthma have been generalized to be a result of the inappropriate production of type 2 immune cytokines. Central to this idea is that production of IL-4 and the homologous cytokine IL-13 are important drivers of this response. These cytokines share many biological activities including the ability to induce the IgE isotype switch, increase mast cell expression of FcεR1, increase inflammatory cytokine and chemokine generation, induce mucin production and goblet cell hyperplasia, promote eosinophil survival, and increase adhesion molecule expression.⁵ Despite their similarity, a few key differences exist between the 2 cytokines. IL-4 is unique in its ability to support T_H 2 differentiation and development from naïve T cells. This is due in part to lack of expression of IL-13Rα1 on all T cells (except those of the T_H 17 lineage⁶). IL-4 also plays an important role in preventing T-lymphocyte apoptosis that can lead to persistence of allergen-specific T_H 2 cells.^{7,8} IL-13 and only to a much lesser extent IL-4 are produced by type 2 innate lymphoid (ILC2) cells, suggesting that IL-13 will have a more important role in the tissue where the ILC2 cells reside. IL-4 receptors are composed of heterodimers of the IL-4Rα chain interacting with the common γ-chain or the IL-13Rα1 chain.⁵ IL-13 receptors are a heterodimer containing the IL-4Rα chain and a unique IL-13Rα chain. Two IL-13Rα chains have been identified that include the active form of the receptor IL-13Rα1 but also IL-13Rα2, which lacks the ability to initiate intracellular signaling and therefore acts as a decoy.⁹ Use of the IL-4Rα chain by IL-4 and IL-13 explains many of the shared biological activities of these 2 cytokines.

Anticytokine and antireceptor approaches have been tested for IL-4 and IL-13 in trials of atopic disease. Dupilumab is currently the only approved biologic that targets the IL-4/13 pathway (Table 3). Dupilumab is a human mAb directed against IL-4Rα (and thereby blocks IL-4 and IL-13). The drug received approval for atopic dermatitis (AD) based on its ability to ameliorate pruritus, decrease signs and symptoms, and improve quality of life in patients whose disease was inadequately controlled by topical treatment.¹⁰ In severe asthma, dupilumab improved forced exhalation volume in 1 second and lowered the asthma exacerbation rate.¹¹ In patients with chronic sinusitis that was refractory to treatment with intranasal steroids, dupilumab demonstrated lower nasal polyp burden, improvement in symptom scores, and an improved sense of smell.¹² Phase 1 safety trials of MEDI 9314, another anti-IL-4Rα antibody, have

Table 3
Approved Drugs in Allergic Inflammatory Disorders

Drug	Source	Subclass	Target	Approved indication	Investigational use
Mepolizumab	humanized	IgG1	IL-5	eosinophilic asthma	ABPA, AD, AERD, ECRS, EGID, EGPA, HES
Reslizumab	humanized	IgG4	IL-5	eosinophilic asthma	EGID, ECRS, EGPA, HES
Benralizumab	humanized	IgG1 ^a	IL-5Rα (CD125)	eosinophilic asthma	CIU, ECRS, EGPA, HES
Dupilumab	human	IgG4	IL-4Rα (IL-4 and IL-13 receptor)	atopic dermatitis	asthma, EGID, NP

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; AD, atopic dermatitis; AERD, aspirin-exacerbated respiratory disease; CIU, chronic idiopathic urticaria; ECRS, eosinophilic chronic rhinosinusitis; EGID, eosinophilic gastrointestinal disease; EGPA, eosinophilic granulomatous polyangiitis (Churg-Strauss syndrome); HES, hypereosinophilic syndrome; Ig, immunoglobulin; IL, interleukin; NP, nasal polyposis.

^aAfucosylated to promote antibody-dependent cellular cytotoxicity.

Table 4
Investigational Drugs

Target	Drug	Investigational use
IL-13	tralokinumab	AD, asthma, alopecia areata
IL-4R	MEDI 9314	AD
TSLP	tezepelumab (AMG 157)	asthma, AD, allergen immunotherapy adjunct (cat)
IL-25	none currently being studied	
IL-33	RG 6149 (formally AMG 282) ANB020	CRSwNP, asthma AD, asthma, immunotherapy adjunct (peanut allergy)
	MEDI 3506	COPD
IL-33R	GSK 3772847 (formally CNTO 7160)	asthma, AD
IL-31R	nemolizumab	AD, pruritic disorders
	lokivetmab	AD (canine)
IL-17	brodalumab	asthma
	secukinumab	ACD, AD

Abbreviations: ACD, allergic contact dermatitis; AD, atopic dermatitis; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin; TSLP, thymic stromal lymphopoietin.

been completed and this drug will be developed as a treatment for AD (Table 4). To date, in contrast to the antireceptor antibodies, all anti-IL-4 and anti-IL-13 anticytokine antibodies (and soluble receptors) have failed to meet their primary end points in asthma; the reasons for each are unclear but some possibilities have been discussed earlier. Despite their failure in asthma, tralokinumab and lebrikizumab, which are anti-IL-13 antibodies, are still in active studies for treatment of AD.

Interleukin-5

Interleukin-5 is critical for eosinophil maturation, proliferation, and activation and can enhance basophil differentiation.^{13,14} IL-5 promotes tissue accumulation of eosinophils through its ability to upregulate expression of adhesion molecules on eosinophils, thereby promoting their adherence to and transmigration across endothelial cells.¹⁴ In addition, IL-5 prolongs eosinophil survival by blocking apoptosis.¹⁵ The major cellular sources of IL-5 are T_H2 cells, ILC2, and, to a lesser extent, mast cells and natural killer T cells.¹³ The IL-5R is a heterodimer of the cytokine-binding α -chain (CD125) and the signal-transducing common β -chain (CD131), which is shared by the receptors for granulocyte-macrophage colony-stimulating factor and IL-3.¹³

Anticytokine and antireceptor drugs targeting IL-5 are currently approved for use in eosinophilic asthma (Table 3). Mepolizumab is a humanized IgG1 mAb that targets free IL-5. It is approved for use in patients at least 12 years old and leads to improved quality of life and lower asthma exacerbation rates. Studies have been inconsistent but generally do support symptom improvement and increases in forced exhalation volume in 1 second.¹⁶ Clinical efficacy primarily occurs in patients with asthma and a threshold blood absolute eosinophil count of at least 150 cells/ μ L,¹⁷ explaining why initial trials in patients with mild to moderate asthma, who were not selected for eosinophilia, were disappointing. One study reported decreased airway wall thickness after 1 year of treatment, suggesting potential for reversing airway remodeling.¹⁸ Reslizumab also is directed against free IL-5 and, like mepolizumab, has been shown to lower the asthma exacerbation rate, improve quality of life, and ameliorate asthma symptoms.^{19,20} Although they target the IL-5 cytokine, some important differences between mepolizumab and reslizumab include the age for which the drug is approved (18 and 12 years, respectively); the threshold absolute eosinophil count used in trials (150 and 400 cells/ μ L, respectively); the route of administration (subcutaneous vs intravenous); and dosing (fixed vs weight based). Benralizumab is a recently approved afucosylated IgG1 mAb directed against

IL-5R α that induces elimination of its target cells by ADCC.^{21,22} In addition to being the only antireceptor antibody targeting the IL-5 pathway, it is unique in demonstrating efficacy even in patients without eosinophilia²³ (although maximal effects are seen in those patients with increased peripheral eosinophilia) and in producing much greater depletion of tissue eosinophils.²⁴ Although no head-to-head comparative study has been performed of mepolizumab, reslizumab, and benralizumab, a recent meta-analysis of 10 trials suggested no clear superiority of any one of these drugs.²⁵ Whether the molecular and biological differences between these drugs outlined previously will lead to differing clinical efficacy in particular diseases or subgroups remains to be determined.

Although not currently approved for use other than for asthma, small studies have been completed for other eosinophilic diseases. Mepolizumab and reslizumab have been tested in patients with eosinophilic esophagitis or gastrointestinal disease and significantly decreased peripheral blood and tissue eosinophilia, although there have been variable reports in clinical outcomes and, as such, their use in these conditions is still under investigation.^{26–29} One published trial explored the use of mepolizumab in adults with AD with no significant clinical improvement demonstrated.³⁰ This is perhaps not surprising given our understanding that AD is not primarily an eosinophil-mediated disease. Mepolizumab has been evaluated in hypereosinophilic syndrome and 84% of subjects demonstrated a significant decrease in their daily prednisone dose.³¹ Other smaller uncontrolled studies have studied the use of mepolizumab and reslizumab for hypereosinophilic syndrome and have had mostly favorable results; studies are in progress for benralizumab. Mepolizumab has demonstrated efficacy in eosinophilic granulomatous polyangiitis (formerly known as Churg-Strauss syndrome), although it induced remission in only approximately half the patients in the largest multicenter trial published to date.³² Studies are underway for benralizumab in eosinophilic granulomatous polyangiitis (NCT03010436). Mepolizumab was shown in a small trial to reduce the mass of polyp tissue significantly in patients with chronic rhinosinusitis³³ and has more recently been shown to prevent requirement for revision endoscopic surgery.³⁴ Chronic rhinosinusitis studies are ongoing for benralizumab. Mepolizumab in combination with the anti-IgE drug omalizumab has been used successfully in steroid-dependent treatment-resistant allergic bronchopulmonary aspergillosis.³⁵ It is important to note that the use of combination biologic therapy has not been tested in large case series or clinical trials and could have unforeseen risks or consequences compared with the use of single biologic agents.

Thymic Stromal Lymphopoietin

Thymic stromal lymphopoietin is a key cytokine expressed early in the immune response and is important in orchestrating T_H2 immune deviation. TSLP exists in 2 isoforms that differ by 63 amino acids in length, each with its own promoter.³⁶ The short form is constitutively expressed and the long form is induced under inflammatory conditions. Little is known concerning the differences in biological activity of these 2 isoforms; however, developing antibodies to target this molecule need to take this into account because removal of the short form could have unwanted side effects. Many stimuli including chemicals, microbes (bacterial and viral), and allergens induce TSLP production. TSLP is primarily expressed by epithelial cells of the skin, gut, and lung and this leads to the priming of resident dendritic cells to promote T_H2 cytokine immune deviation. TSLP also enhances production of the T_H2-attracting chemokines CCL17 (thymus and activation regulated chemokine) and CCL22 (macrophage-derived chemokine). TSLP signals through a heterodimeric receptor composed of a unique TSLP-specific receptor and the IL-7R α chain (CD127). TSLP receptors are primarily

expressed by dendritic cells, but expression on mast and ILC2 cells promotes their secretion of type 2 cytokines, serving to amplify the allergic response.

Tezepelumab is currently the only an anti-TSLP antibody that is in human trials and it is being developed for asthma and AD (Table 4). In an early study, treatment with tezepelumab decreased allergen-induced bronchoconstriction and markers of airway inflammation before and after an allergen challenge.³⁷ This study was followed up with a controlled trial that demonstrated significantly fewer asthma exacerbations and improved forced exhalation volume in 1 second and, of note, this was independent of blood eosinophil counts.³⁸ Trials in AD are ongoing and no results have been reported.

Interleukin-33

Interleukin-33 is an IL-1 superfamily member that signals through the IL-1 receptor-related protein (originally termed ST2) and its coreceptor IL-1RAP.³⁹ These receptors for IL-33 are expressed on many cells involved in the allergic response, including T_H2 cells, ILC2 cells, macrophages, hematopoietic stem cells, eosinophils, basophils, mast cells, and fibroblasts. Similar to TSLP, IL-33 induces IL-5 and IL-13 secretion by ILC2 cells. IL-33 differs from most cytokines in that it exists as a nuclear and a secreted protein with differing functions depending on location. Nuclear IL-33 is believed to act as a transcription factor, enhancing the inflammatory response by stimulating gene expression. The model for secreted IL-33 is that it is released from cells undergoing programmed cell necrosis (“pyroptosis”) in response to infection or inflammation. Once released from the cell, it acts to enhance cytokine secretion from T_H2 cells, in addition to being a chemoattractant for T_H2 cells. IL-33 is expressed by multiple cell types, but bronchial epithelial cells are believed to be the primary source.

Three drugs are in development or trials that target soluble IL-33: ANB020, MEDI 3560, and AMG 283 (RG 6149; Table 4). ANB020 is being investigated for use in asthma, AD, and peanut allergy. In the latter study, subjects are being enrolled in a phase 2 trial that will examine safety and, secondarily, changes in clinical scores after oral peanut challenges. MEDI 3506 is undergoing testing in ongoing phase 1 studies for chronic obstructive pulmonary disease. Phase 1 studies with AMG 282 (RG 6149) for asthma and chronic rhinosinusitis with nasal polyps have been completed, but no results have been reported. Trials for GSK 3772847 (formally CNTO 716) targeting the IL-33R (ST2) are ongoing in asthma and AD and no results have been reported.

Future Cytokine Targets

Interleukin-25

Interleukin-25 (or IL-17E) is produced by a specific type of epithelial cell that, based on its appearance, is termed the “tuft” cell. Tuft cells have been demonstrated in the gastrointestinal tract, lung, and sinus tissue. Additional sources include T_H2 cells, mast cells, eosinophils, and basophils. As with TSLP and IL-33, IL-25 has a central role in driving type 2 inflammation. The IL-25 receptor is a heterodimer composed of IL-17RB and IL-17RA.⁴⁰ In response to IL-25, T_H2 lymphocytes release IL-4, IL-5, and IL-13 and ILC2 cells release IL-5 and IL-13, thus underlying an important mechanism driving IgE synthesis and eosinophilic inflammation in response to airway epithelial injury. Therefore, IL-25 is an intriguing potential therapeutic target for allergic asthma⁴¹ and chronic rhinosinusitis.⁴² A patent application for the use of anti-IL-25 antibodies in different disorders including asthma, AD, and eosinophilic granulomatous polyangiitis has been filed (Regeneron Pharmaceuticals, Tarrytown, New York), but no clinical studies have been initiated.

Interleukin-31

Interleukin-31³ is another type 2-derived cytokine that is identified in allergic inflammation such as the asthmatic lung but, in particular, it is produced by the T_H2 lymphocytes infiltrating the skin in AD that express the skin-homing molecular cutaneous lymphocyte antigen.^{43,44} Other sources include mast cells, macrophages, and dendritic cells. Signaling occurs through a heterodimer consisting of the IL-31RA and a second chain that also is used by the related IL-6 superfamily member oncostatin M. Biological activities of IL-31 include activation of epithelial cells, neutrophils, eosinophils, basophils, monocytes, and T cells, but its primary function is believed to be facilitation of cell-mediated immunity against pathogens. What makes developing biologics to target IL-31 particularly intriguing is that IL-31 receptors also are expressed by sensory neurons, specifically within the dorsal root ganglia, where the “itch” sensation is believed to originate.^{45,46} It is considered the most important cause of itch in AD and other pruritic inflammatory cutaneous disorders. Overexpression of IL-31 in a murine model induced skin lesions and pruritus similar to what is observed in AD.⁴⁷ In addition to AD, IL-31 is important in other allergic inflammatory diseases such as asthma in which its induction of CCL17 (thymus and activation regulated chemokine) and CCL22 (macrophage-derived chemokine) is, as noted earlier, important in the recruitment of T_H2 effector cells. An anti-IL-31R antibody (nemolizumab) is currently being investigated for its anti-inflammatory and antipruritic efficacy in AD and, in a phase II study, was recently demonstrated to dramatically decrease pruritus.⁴⁸ Of note, an anti-IL-31R antibody (lokivetmab) is currently available as a treatment for canine AD.

Interleukin-17

The IL-17 family is composed of 6 proteins (IL17A–F) with overlapping, but not identical, biologic activities. IL-17A is mainly expressed by CD4⁺ T cells and to a lesser extent by neutrophils, eosinophils, and CD8⁺ T cells. Closely structurally related to IL-17A, IL-17F also is expressed by activated CD4⁺ T cells but can be produced by activated basophils and cord blood-derived mast cells.⁴⁹ IL-17A plays an important role in the activation of fibroblasts and expression of the pro-fibrotic cytokines IL-6 and IL-11, whereas IL-17F induces transforming growth factor- β expression, a cytokine also associated with fibrosis. Thus, IL-17 is recognized to have an important role in autoimmune diseases involving tissue fibrosis and remodeling such as inflammatory bowel disease and multiple sclerosis.⁵⁰ Given their ability to induce neutrophil, but not eosinophil, migration and to induce goblet cell hyperplasia and mucus hypersecretion, it is speculated that IL-17A and IL-17F play a role in severe neutrophilic asthma and, therefore, could be reasonable therapeutic targets.⁵¹ IL-17A, IL-17F, and IL-25 (IL-17E) bind to the heteromeric IL-17R A chain (IL-17RA), making this a potent target for receptor blockade.

Most clinical trials for anti-IL-17–targeting drugs have been performed in ankylosing spondylitis, psoriatic and other inflammatory arthritides, and plaque psoriasis. However, a limited number of trials have focused on atopic disease.⁵² Brodalumab is a human IgG2 anti-IL-17RA mAb. A phase 2 trial of brodalumab in subjects with moderate to severe asthma failed to demonstrate a treatment effect.⁵³ However, study subjects were not selected for neutrophilic airway inflammation and no further studies are ongoing in asthma. Similarly, a preliminary study of secukinumab, a human IgG1 anti-IL-17A mAb, in asthma was prematurely terminated, presumably because of lack of efficacy ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01478360) identifier NCT01478360). Secukinumab is currently being investigated as a treatment for allergic contact dermatitis ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02778711) identifier NCT02778711) and AD ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02594098) identifier NCT02594098).

Summary

The pathophysiology of allergic disorders is multifactorial, with genetic and environmental components being important. These factors result in activation of the immune system and release of cytokines that ultimately produce the allergic inflammatory response. The challenging aspect of these diseases is that no single cytokine is responsible for driving these processes in any given disease or, indeed, even within a given affected individual. Key targets in select groups have been identified that promote the disease process and biologicals have been developed to inhibit these molecules. With correct selection of patients, these new drugs show the promise of decreasing disease morbidity and improving clinical outcomes where previous treatments have failed.

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