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Type 2–interferon imbalance in allergic barrier disease: An asthma-centered, cross-disease perspective

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Abstract

Allergic diseases are typically regarded as type 2 inflammatory disorders driven by interleukin-4, interleukin-5, and interleukin-13, which mediate immunoglobulin E class switching, eosinophilic inflammation, mucus hypersecretion, pruritus, tissue remodeling, and epithelial barrier dysfunction. However, type 2 cytokine activity alone does not fully account for variations in exacerbation risk, susceptibility to infections, comorbidities, or responses to biologic therapy. This narrative review proposes an asthma-centered type 2–interferon imbalance framework and discusses its cautious, disease-specific extension to atopic dermatitis, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, and food allergy. The model emphasizes that, particularly in asthma, allergic barrier inflammation arises and persists in injured tissues where excessive type 2 inflammation may coexist with impaired interferon-mediated host defense. Evidence is strongest in asthma, where deficiencies in type I and type III interferon responses are linked to rhinovirus susceptibility, delayed viral clearance, and recurrent exacerbations. In other allergic diseases, interferon dysfunction appears more variable, reflecting differences in tissue context, disease stage, and environmental exposure. In asthma, and potentially in selected allergic barrier diseases, persistent inflammation may result from a cycle of epithelial injury, alarmin release, cytokine amplification, impaired antiviral defense, ongoing exposure, and incomplete tissue repair. These mechanisms provide a rationale for tiered intervention, including blockade of upstream epithelial alarmins, inhibition of downstream type 2 effector pathways, and selected investigational approaches aimed at restoring mucosal host defense.

Key words: Allergic Diseases, Interferons, Type 2 Inflammation, Epithelial Barrier, Biological Therapy, Biomarkers, Immunologic

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Introduction

For many years, allergic diseases were described mainly through the lens of exaggerated type 2 immunity. That model remains valuable, but it is no longer sufficient. Asthma, atopic dermatitis (AD), chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic esophagitis (EoE), and food allergy all contain recognizable type 2 inflammatory programs, yet they vary widely in severity, tissue involvement,

exacerbation frequency, and treatment response.[1-5] These differences point to a broader disorder of barrier-surface homeostasis, in which cytokine excess interacts with epithelial injury, innate immune sensing, microbial ecology, and environmental challenge.[6-15]

IL-4, IL-5, and IL-13 remain central to this biology. They influence IgE class switching, eosinophil maturation and survival, mucus production, airway hyperresponsiveness, remodeling, pruritus, and barrier disruption. However, these cytokines are downstream of a larger tissue response.[1,3,16-18] Their expression is shaped by epithelial damage, alarmin release, dendritic-cell programming, innate lymphoid cell activation, antigen exposure, and disease-specific regulatory circuits.[2,11-15,19]

The added value of the type 2–interferon imbalance model is not to introduce another isolated cytokine pathway, but to integrate two clinically separable dimensions of barrier disease: the magnitude of type 2 inflammation and the competence of epithelial antiviral defense. In this framework, epithelial injury and alarmin release explain inflammatory initiation and amplification, whereas impaired interferon responses help explain why some type 2-high patients remain vulnerable to virus-associated exacerbations or incomplete disease control despite otherwise appropriate anti-inflammatory therapy.

Accordingly, the term type 2–interferon imbalance is used throughout rather than Th2-interferon imbalance, except when referring specifically to T helper 2 cells. This broader terminology reflects the involvement of Th2 cells, group 2 innate lymphoid cells (ILC2s), epithelial cells, dendritic cells, eosinophils, mast cells, basophils, B cells, and interferon-producing innate cells.

Literature Search and Review Scope

This article is a narrative mechanistic review rather than a systematic review. The cited literature was selected to represent major mechanistic studies, clinical trials, consensus statements, and recent reviews on type 2 cytokines, interferon biology, epithelial barrier dysfunction, alarmins, biologic therapy, biomarkers, and endotyping in allergic disorders. Asthma, AD, CRSwNP, EoE, and food allergy were prioritized because they illustrate both the shared type 2 program and the limits of applying a single disease model across organs.

The central question is how type 2 cytokine excess and epithelial barrier dysfunction interact with impaired interferon-mediated host defense—most clearly demonstrated in asthma—to influence disease persistence, exacerbation risk, and therapeutic response. Rather than cataloguing all immune pathways across allergic barrier diseases, this framework emphasizes mechanisms with direct relevance to disease persistence, exacerbation risk, biomarker development, and therapeutic selection.

Type 2 Cytokines and Effector Networks

Type 2 inflammation is a common feature of many allergic disorders, but it should not be treated as a uniform pathway. In the type 2–interferon imbalance framework, type 2 cytokines define the inflammatory-burden axis that interacts with epithelial injury and antiviral host defense. This axis is shaped by Th2 cells, ILC2s, eosinophils, mast cells, basophils, dendritic cells, B cells, and epithelial cells, but its clinical expression depends on tissue context, disease stage, environmental exposure, and comorbid disease patterns.[1-3]

Among type 2 mediators, IL-4 and IL-13 are most closely linked to epithelial dysfunction, mucus production, airway hyperresponsiveness, remodeling, pruritus, and FeNO-associated epithelial activity. Their shared use of IL-4Rα also explains why IL-4Rα blockade may have cross-organ relevance in asthma, atopic dermatitis, CRSwNP, and eosinophilic esophagitis.[1,3,4,16,20,21] IL-5, in contrast, more directly reflects eosinophilic effector activity and provides the biological rationale for anti-IL-5 and anti-IL-5Rα strategies in eosinophilic disease.[17,18,20] Thus, these mediators are clinically important not because they provide a complete explanation of allergic disease, but because they help define which part of the type 2 axis is dominant in a given patient.[15,20,22]

Overall, type 2 inflammation represents one dimension of allergic barrier disease rather than a complete disease model.[2,3,19]

Interferon Responses in Allergic Diseases

Within the type 2–interferon imbalance framework, type I and type III interferons represent the host-defense axis most directly linked to epithelial antiviral protection, viral clearance, and virus-induced exacerbations. Type I IFNs, including IFN-α and IFN-β, and type III IFNs, including IFN-λ family members, are induced after viral sensing and promote interferon-stimulated gene programs that limit viral replication and epithelial injury.[6-9,19,23]

The three interferon families have overlapping but distinct biological roles. Type I IFNs, mainly IFN-α and IFN-β, act through IFNAR and provide a broad antiviral alarm system that can affect epithelial, dendritic, and circulating immune-cell compartments. Type III IFNs, including IFN-λ family members, signal through IFNLR and are more restricted to epithelial and mucosal barrier sites, making them particularly relevant to localized antiviral defense in the respiratory tract.[24] Type II IFN, represented by IFN-γ, is mainly associated with Th1, cytotoxic, and macrophage-activating responses rather than the primary epithelial antiviral axis, but it can counter-regulate IL-4/IL-13–STAT6-dependent type 2 programs. Therefore, impairment of type I or type III IFN responses may present clinically as recurrent virus-associated airway exacerbations, whereas altered type II IFN activity more often reflects the balance between type 1/type 2 immune polarization, tissue inflammation, and disease context.[6-11,19,23]

The strongest evidence for impaired interferon responses comes from asthma, particularly rhinovirus-associated exacerbations. Airway epithelial cells from patients with asthma have shown reduced or delayed IFN-β, IFN-α, or IFN-λ responses after viral stimulation, which may permit greater viral replication, slower viral clearance, prolonged epithelial stress, and secondary inflammatory amplification. This mechanism helps explain why some patients remain vulnerable to infection-associated exacerbations even when baseline type 2 inflammation appears reasonably controlled.[6,9,25,26]

Mechanistically, type 2 inflammation can suppress antiviral defense at several levels. IL-4 and IL-13 impair rhinovirus-induced IFN-β and IFN-λ1 production by reducing TLR3 expression and IRF3 activation.[27] IL-13 can suppress dsRNA-induced IFN-λ through JAK-dependent mechanisms.[7] Allergen-driven epithelial injury, including house-dust-mite exposure, may further weaken antiviral pattern-recognition receptor signaling.[10] Conversely, interferons can restrain selected type 2 programs through distinct mechanisms. IFN-λ is particularly relevant to epithelial antiviral defense in asthma because IFNLR1 is preferentially expressed on epithelial cells and IFN-λ can reduce respiratory viral replication and spread, although impaired epithelial IFN-λ responses have been reported in asthma.[28] Type I IFNs from plasmacytoid dendritic cells may also limit allergic airway inflammation by suppressing epithelial CCL20, GM-CSF, and IL-33 signals that promote cDC2 and ILC2 recruitment.[29] IFN-γ can counter-regulate IL-4/STAT6-dependent epithelial gene expression.[11]

Together, these data support interferon competence as a disease- and tissue-dependent modifier rather than a universal signature across allergic disorders. Impaired type III IFN activity is expected to present mainly as defective mucosal epithelial antiviral defense, whereas broader type I IFN alterations may involve both epithelial and systemic immune compartments; altered IFN-γ activity more often reflects immune polarization than a primary epithelial antiviral defect.

Defining the Type 2–Interferon Imbalance Model

Type 2–interferon imbalance denotes a barrier-surface immune state in which excessive or insufficiently restrained type 2 inflammation interacts with impaired, delayed, or contextually dysregulated interferon-mediated host defense. This interaction is best established in asthma and virus-associated airway exacerbations; in other allergic barrier diseases, the interferon component should be regarded as variable and disease-specific. These two processes may reinforce one another through tissue injury: environmental or viral insults promote alarmin release, while type 2 inflammation and weak antiviral defense prolong epithelial stress and delay repair.

This model differs from earlier barrier-alarmin or virus-exacerbation paradigms by treating interferon competence as a modifying axis rather than merely a downstream consequence of infection. It should therefore be used to stratify mechanisms and generate disease-specific hypotheses, not to unify all allergic diseases under one pathway. The key components, evidence gradient, and feedback relationships of this model are summarized in **Figure 1**.

Clinically, this distinction is important because patients with similar baseline symptom burden may differ substantially in their risk of virus-associated exacerbations. A patient may report moderate day-to-day symptoms but remain highly vulnerable to viral attacks if antiviral defense is weak. Conversely, a patient may show marked improvement in eosinophilia after type 2–directed therapy but continue to have mucus plugging, epithelial fragility, or infection-related flares.[7,8,25,30]

Disease-Specific Evidence and Limits of Generalization

A recurring source of overstatement in this area is the tendency to treat all allergic diseases as if they share the same interferon biology. Type 2 inflammation is well supported across several disorders, but interferon impairment is not equally proven in each. **Table 1** summarizes the relative maturity of evidence and the main clinical implication of applying the type 2–interferon imbalance model to different disease areas.

Asthma is the disease in which the model is most directly supported. Viral infection can initiate epithelial injury, a weak interferon response can delay viral control, and type 2 cytokines can amplify mucus production and eosinophilic inflammation. Together, these processes contribute to recurrent exacerbations and incomplete disease control.[7-9,17]

In CRSwNP, AD, EoE, and food allergy, type 2 inflammation is also central, but the interferon component is less consistently defined. These diseases involve barrier dysfunction, altered microbial interactions, epithelial stress, and tissue remodeling, yet they do not necessarily reproduce the same antiviral-deficiency phenotype seen in asthma. Therefore, extension of the model beyond asthma should remain cautious, disease-specific, and supported by organ- and region-specific evidence.

Regional context is particularly relevant when applying the type 2–interferon imbalance model to Asian settings, particularly East Asian populations for which current regional evidence is available. In China, recent asthma guidelines and severe asthma consensus documents emphasize that type 2 airway inflammation, reflected by blood or sputum eosinophilia, FeNO, atopy, and elevated IgE, is a major treatable endotype in severe asthma and can guide the use of type 2-targeted biologics.[31,32] However, regional interpretation should not rely on type 2 biomarkers alone.

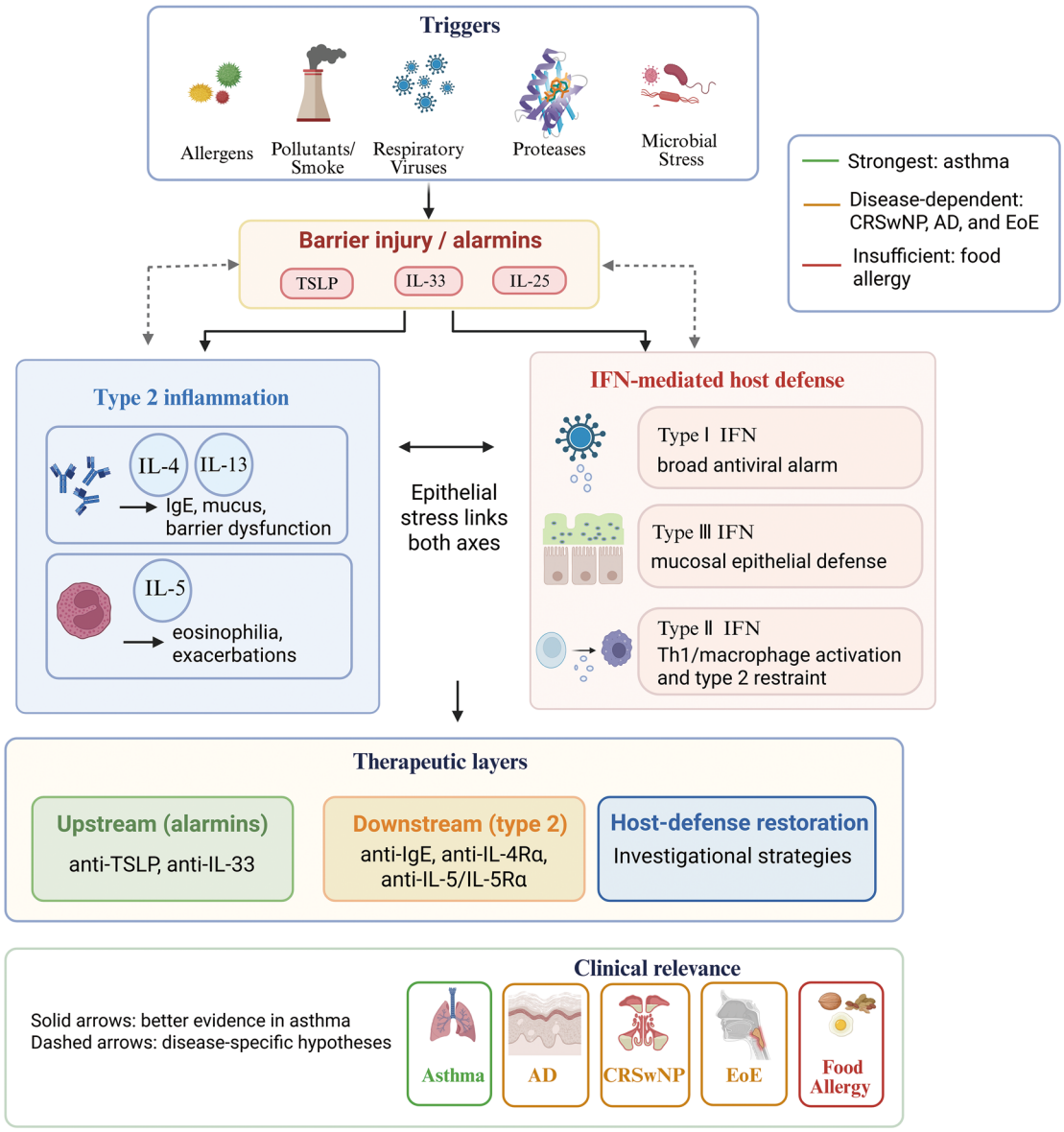

Figure 1. Conceptual and clinical framework of type 2–interferon imbalance across allergic barrier diseases.
Environmental triggers, including allergens, pollutants or smoke, respiratory viruses, proteases, and microbial stress, can induce epithelial barrier injury and the release of alarmins such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-33, and IL-25. These signals amplify type 2 inflammation through IL-4-, IL-5-, and IL-13-mediated pathways, promoting immunoglobulin E production, mucus hypersecretion, epithelial dysfunction, eosinophilia, and exacerbations. In parallel, impaired or delayed interferon-mediated host defense, particularly involving type I and type III interferons, may compromise antiviral protection, while type II interferon contributes mainly to T helper 1/macrophage activation and counter-regulation of type 2 responses. Epithelial stress links the inflammatory and host-defense axes and may sustain a feed-forward cycle of barrier injury and immune dysregulation. Therapeutic strategies can therefore be considered at three levels: upstream alarmin blockade, downstream type 2 pathway inhibition, and investigational restoration of host defense. Solid arrows indicate better-supported pathways in asthma, whereas dashed arrows denote isease-specific extensions. The evidence is strongest in asthma, disease-dependent in CRSwNP, AD, and EoE, and currently insufficient in food allergy.

Abbreviations: AD, atopic dermatitis; CRSwNP, chronic rhinosinusitis with nasal polyps; EoE, eosinophilic esophagitis; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; TSLP, thymic stromal lymphopoietin.

Table 1. Disease-specific evidence strength for type 2–interferon imbalance.

Disease area	Type 2 inflammation	Interferon impairment	Evidence level	Clinical implication
Asthma	Strong; supported by type 2 cytokines, eosinophilia, FeNO, IgE, and biologic responsiveness.[15,17,22,27,67,68]	Impaired type I/III IFN responses are linked to viral susceptibility and exacerbations.[6,7,9,17,58]	Strong	Explains virus-triggered exacerbations and partial response to type 2 biologics.
CRSwNP	Strong: type 2 inflammation, eosinophilia, epithelial alarmins, and biologic responsiveness are prominent.[37,44,49,52-54,69,70]	IFN-specific defects are less consistent than in asthma and may depend on tissue context and disease stage	Moderate	Supports integrated assessment of upper and lower airway disease and biologic selection.
Atopic dermatitis	Strong; IL-4/IL-13 pathways, barrier dysfunction, itch, and dupilumab response support type 2 biology.[1,21,56,57]	Infection susceptibility and dysbiosis are important, but IFN defects vary by lesion context.	Limited	Emphasizes barrier repair, microbial ecology, and type 2 blockade rather than a simple IFN-deficiency model.
Eosinophilic esophagitis	Strong; type 2 inflammation, epithelial remodeling, and IL-13 signatures are central.[4,45,55]	Clinically actionable IFN impairment remains insufficiently defined.	Limited	Avoids direct extrapolation of airway IFN biology to esophageal disease.
Food allergy	Strong; IgE sensitization and type 2 immunity are central, with barrier and tolerance mechanisms variably involved.[2,5]	IFN biology is not yet a dominant clinical framework.	Insufficient	Prioritizes barrier integrity, sensitization routes, IgE, and tolerance mechanisms.

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; FeNO, fractional exhaled nitric oxide; IFN, interferon; IgE, immunoglobulin E; IL, interleukin.

Asia has heterogeneous patterns of urbanization, air pollution, viral exposure, microbial ecology, healthcare access, and biologic availability, all of which may influence exacerbation risk and treatment response.[31,33] In CRSwNP, East–West differences appear especially important: Asian CRS cohorts have been reported to show less eosinophilic/type 2 inflammation and more non-type 2 inflammation than Western cohorts, although type 2-biased CRSwNP remains clinically relevant in selected patients.[34,35] Therefore, in Asian settings, this model should be used as a cautious endotyping framework that integrates type 2 biomarkers, viral-exacerbation history, epithelial or microbial context, comorbid asthma/CRSwNP, and local treatment accessibility rather than as a fixed universal mechanism.[36]

Upstream Regulators of the Imbalance

Epithelial barrier dysfunction and environmental triggers

Barrier tissues actively sense injury and shape innate and adaptive immunity. Across the airway, skin, and gut, epithelial disruption increases exposure to allergens, microbes, irritants, pollutants, and proteases, thereby promoting alarmin release and chronic immune activation. Protease-containing allergens, smoke, and pollution may further impair epithelial junctions and amplify inflammatory responses.[2,10-15,33]

Epithelial alarmins

TSLP, IL-33, and IL-25 are epithelial-derived alarmins released after tissue injury. They activate ILC2s, dendritic cells, eosinophils, mast cells, and Th2 cells, placing them upstream of many type 2 cytokine programs.[10-14,37-39] This upstream position is the reason alarmin blockade may have broader effects than inhibition of a single downstream cytokine.

TSLP biology is further complicated by isoform-specific functions. In humans, short-form TSLP (sfTSLP) and long-form TSLP (lfTSLP) appear to have distinct biological effects in allergic airway disease. Experimental studies suggest that lfTSLP is more closely linked to airway epithelial barrier disruption and allergic inflammation, whereas sfTSLP may help preserve epithelial barrier integrity. In a house-dust-mite-induced asthma model, HDM and lfTSLP impaired airway epithelial barrier function, while sfTSLP prevented HDM-induced barrier disruption and ameliorated asthma-like inflammation.[40] This isoform-specific biology highlights a potential precision-medicine consideration, although current therapeutic TSLP blockade is not clinically selected on the basis of TSLP isoform profiling.

Among these targets, TSLP has advanced furthest clinically. Tezepelumab has shown that epithelial-targeted therapy can benefit patients beyond the narrowest eosinophilic or allergic phenotype.[12,41] IL-33-directed strategies are promising, particularly for exacerbation-prone disease and epithelial inflammatory signatures, but candidate selection and long-term effects remain under study.[13,14,39] IL-25 remains biologically plausible but less mature as a therapeutic target.

Innate sensing, antigen presentation, and microbial context

Innate sensing determines whether epithelial injury leads to tolerance, short-lived inflammation, or persistent type 2 immunity. Pattern-recognition receptors, including Toll-like receptors and RIG-I-like receptors, activate IRF3/IRF7-dependent interferon production, followed by IFN receptor–JAK-STAT signaling that induces antiviral interferon-stimulated genes.[19] Dendritic-cell programming and antigen presentation then influence whether adaptive immunity becomes regulatory, type 1, type 2, type 17, or mixed.[19,23]

The microbiome adds another layer of control. Gut-skin and gut-lung interactions, microbial metabolites, bacterial colonization, and dysbiosis can affect epithelial permeability, immune tolerance, interferon tone, and type 2 inflammation.[2] These pathways are increasingly important conceptually, although clinical translation remains less mature than cytokine-directed treatment.

Therapeutic Implications

Therapeutic strategies can be grouped into upstream alarmin blockade, downstream type 2 targeting, and investigational host-defense restoration. As summarized in **Table 2**, these therapeutic strategies differ in clinical maturity, potential advantages, and key limitations.[4,5,11-15,17,20,21,42]

Clinical use of the model for biologic selection

Compared with the traditional type 2-high approach, the type 2–interferon imbalance model asks two linked clinical questions: first, which type 2 effector pathway is dominant; and second, whether epithelial injury, viral susceptibility, mucus plugging, or impaired host defense contributes to persistent exacerbations despite type 2-directed therapy. In routine practice, biologic selection should therefore integrate exacerbation history, blood eosinophils, FeNO, IgE sensitization, oral corticosteroid exposure, comorbid type 2 diseases, epithelial or mucus-related features, prior biologic response, local access, and patient preference.[15,20,30,31,38,43] However, this framework is conceptual and does not yet constitute a prospectively validated treatment algorithm or replace guideline-based biologic selection.

Tezepelumab may be considered when exacerbations remain frequent despite optimized inhaled therapy, particularly when conventional type 2 biomarkers are discordant or do not fully explain disease burden. Environmental or viral-triggered worsening, mucus plugging, airway hyperresponsiveness, persistent airflow limitation, and mixed biomarker patterns may provide a mechanistic rationale for considering an upstream strategy, but these features are not yet validated as independent predictors of response to tezepelumab.[12,15,39,41] Dupilumab is more directly aligned with IL-4/IL-13 biology and may be favored when FeNO is high, IL-13-associated epithelial activity is prominent, mucus or barrier features are present, or when asthma coexists with AD, CRSwNP, or EoE.[15,21,44-47] Anti-IL-5 or anti-IL-5Rα therapy remains most appropriate when blood or sputum eosinophilia, eosinophilic exacerbations, oral corticosteroid dependence, or eosinophilic comorbidities dominate the clinical picture.[18,46,48-50] Omalizumab is most relevant when allergic sensitization and IgE-mediated mechanisms are central.[50,51] Host-defense restoration is discussed below as an investigational adjunctive strategy.

Upstream alarmin targeting

Upstream alarmins, including TSLP, IL-33, and IL-25, are released early after epithelial injury and may amplify multiple downstream type 2 pathways. Tezepelumab provides the strongest clinical validation of this strategy by extending treatment benefit beyond narrowly eosinophilic severe asthma, although IL-33- and IL-25-directed approaches remain less mature.[12-15,37,39,41]

Table 2. Therapeutic levels, maturity, advantages, and limitations.

Intervention level	Representative targets or agents	Clinical maturity	Potential advantages	Key limitations
Upstream epithelial alarmins	TSLP; IL-33; IL-25 pathways	TSLP blockade is established in severe asthma; IL-33 and IL-25 strategies remain investigational.[12-14, 41]	May modulate multiple downstream type 2 pathways and epithelial-driven exacerbation biology.	Optimal patient selection and long-term benefits remain uncertain.
IgE pathway	Omalizumab	Established in allergic asthma and selected IgE-mediated diseases.[5,50,51]	Targets IgE-driven sensitization and allergic comorbidities.	Limited value in non-IgE-mediated disease.
IL-5/IL-5Rα pathway	Mepolizumab, reslizumab, benralizumab	Established in eosinophilic severe asthma and related eosinophilic comorbidities.[17,18,48,49,53]	Reduces eosinophilic inflammation, exacerbations, and corticosteroid burden.	May not fully address epithelial injury, mucus plugging, or interferon impairment.
IL-4Rα pathway	Dupilumab	Established across asthma, AD, CRSwNP, and EoE.[4,15,21,44,45,56,57]	Blocks both IL-4 and IL-13 signaling with cross-organ relevance.	Partial response occurs, and symptom, remodeling, and comorbidity outcomes may diverge.
Host-defense restoration	Interferon therapy and immune-training strategies	Exploratory and less mature than biologic cytokine blockade.[6,7,9,58-60]	Aims to improve antiviral defense as an adjunct to anti-inflammatory therapy.	Dose, timing, safety, phenotype selection, and durable benefit remain unresolved.

Abbreviations: AD, atopic dermatitis; CRSwNP, chronic rhinosinusitis with nasal polyps; EoE, eosinophilic esophagitis; IgE, immunoglobulin E; IL, interleukin; IL-4Rα, interleukin-4 receptor alpha; IL-5Rα, interleukin-5 receptor alpha; TSLP, thymic stromal lymphopoietin.

Downstream type 2 biologics

Downstream type 2 biologics, including anti-IgE, anti-IL-5/IL-5Rα, and anti-IL-4Rα therapies, remain the most established precision treatments. Their differing effects confirm that type 2 disease is mechanistically heterogeneous. Although these agents reduce exacerbations and pathway-specific inflammation, they do not uniformly resolve epithelial injury, mucus plugging, remodeling, infection susceptibility, or cross-organ disease activity. Partial response therefore remains common, and direct comparative evidence is limited.[4,5,15,17,18,21,44,45,48,49,52-57]

Restoring interferon responses and host defense

Host-defense restoration remains investigational rather than routine care and should complement, not replace, established anti-inflammatory treatment and approved biologics.

Direct interferon augmentation has mainly been studied in asthma. Inhaled IFN-β after cold onset did not meet its primary endpoint in the overall asthma population, although lung-function and difficult-to-treat asthma signals were reported; the INEXAS trial of on-demand inhaled IFN-β1a in severe asthma was stopped early because of a low exacerbation rate and did not reduce severe exacerbations, despite pharmacodynamic IFN-response and peak-flow signals. Accordingly, IFN therapy, PRR modulation, bacterial lysates, and immune-training strategies remain investigational and phenotype-dependent.[6,7,25,26,58-60]

Biomarkers and Precision Medicine

Precision medicine depends on biomarkers that reflect mechanism, predict response, and can be measured reproducibly. Current tools are helpful but incomplete. Blood eosinophils are practical indicators of eosinophilic inflammation and often guide anti-IL-5 or anti-IL-5Rα therapy, but they do not reliably quantify tissue eosinophilia or mucus-plug burden.[18,20,38,43] FeNO reflects IL-13-associated epithelial activity in the airway, yet it is influenced by inhaled corticosteroids, smoking, infection, adherence, and measurement technique.[20,38,43] Total and allergen-specific IgE support assessment of sensitization and anti-IgE candidacy, but IgE does not define all type 2 disease.[5,51] Periostin has mechanistic value as an IL-13-associated marker, although its clinical standardization and availability remain limited.[61]

Interferon-related biomarkers remain investigational, but several measurable candidates may help define IFN-deficient or IFN-dysregulated endotypes, particularly in asthma and airway disease. Transcriptomic approaches could assess baseline or inducible expression of IFN-related genes and interferon-stimulated genes, including IFNB1, IFNL1, IFNL2/3, ISG15, MX1, OAS1, IFIT1, IFIT3, and CXCL10, especially before and after rhinovirus or poly(I:C) stimulation.[6,7,23,62] Airway epithelial ISG signatures, and in some settings blood ISG signatures, may be informative.[62] Nasal epithelial sampling may offer a less invasive approach to functional endotyping, although evidence from small asthma cohorts remains preliminary.[63] Functional assays may measure ex vivo rhinovirus-induced IFN-α, IFN-β, or IFN-λ production in epithelial cells, PBMCs, or plasmacytoid dendritic cells, whereas clinical or virologic surrogates may include recurrent virus-associated exacerbations, delayed viral clearance, or viral-load persistence.[6-9,25,26,58] However, these approaches remain limited by timing dependence, compartment discordance, corticosteroid and infection effects, lack of validated thresholds, and absence of treatment algorithms. Thus, IFN-related markers should be regarded as research endotyping tools rather than routine clinical biomarkers or stand-alone guides for selecting approved type 2 biologics.

Future endotyping will likely combine inflammatory biomarkers, epithelial signatures, imaging, exacerbation history, comorbidities, and functional immune assays to identify the dominant active mechanism rather than rely on static type 2-high or type 2-low labels.[20,25,41,43,45]

Discussion and Future Directions

Several barriers limit clinical translation of the type 2–interferon imbalance framework. First, currently available biomarkers do not fully define mechanism-level endotypes across tissues or over time.[20,22,43,64] Second, remission remains inconsistently defined, and inflammatory improvement may not parallel symptom or functional recovery, particularly in united airway disease and EoE.[65,66] Third, type 2-low, steroid-resistant, neutrophilic, and mixed inflammatory states remain outside the main scope of this model. Fourth, whether biologics restore durable barrier homeostasis, prevent remodeling, or modify disease progression remains uncertain.[64] Finally, cost, access, and reimbursement continue to influence real-world treatment selection. Future studies should prioritize validated predictive biomarkers, longitudinal tissue-specific endotyping, rational biologic sequencing, and trials designed to assess disease modification rather than short-term control alone.[15,30,42]

Conclusions

The allergic disorders considered in this review can be understood as disturbances of epithelial-immune homeostasis at barrier surfaces. Type 2 inflammation remains central, but it operates within a larger system shaped by epithelial injury, alarmin release, innate sensing, microbial ecology, environmental exposure, and host-defense capacity.[2,15,16,19] Interferon impairment, particularly in airway disease, adds an important explanatory layer by linking allergic inflammation to viral susceptibility, exacerbation risk, and incomplete therapeutic response.[6,7,9,17,58]

The type 2–interferon imbalance model is therefore useful, but it should be applied with discipline. Its strongest evidence lies in asthma, while its relevance to CRSwNP, AD, EoE, and food allergy requires more disease-specific study. Therapeutically, the model supports layered intervention: upstream alarmin blockade, downstream type 2 cytokine biologics, and selected strategies aimed at restoring host defense. Future progress will depend less on adding another cytokine target to an already crowded list and more on integrating epithelial biology, immune regulation, antiviral defense, and environmental exposure into a practical form of precision medicine.

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Conflicts of Interest

The authors declare no conflict of interest.

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- Writing—original draft preparation: S.R.
- Writing—review and editing: S.R., S.L., H.S. and T.J.
- All authors reviewed and approved the final version of the manuscript.

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