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REVIEW

Emerging Role and Function of Th9 Cells in Allergic Inflammation

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Abstract: Th9 cells have emerged as pivotal orchestrators of allergic inflammation across the airway, skin, and nasal mucosa, constituting a mechanistically distinct axis beyond canonical Th2 immunity. This review specifically highlights: (i) the Th9 axis as a unifying driver in asthma, atopic dermatitis, and allergic rhinitis; (ii) key mechanistic programs, including signal transducer and activator of transcription (STAT) 5/STAT6 licensing of the IL9 locus, peroxisome proliferator-activated receptor (PPAR) γ-mammalian target of rapamycin complex (mTORC) 1 metabolic wiring, and the IL-9-monocarboxylate transporter (MCT) 1 feedback loop; (iii) organ-level phenotypes such as eosinophil-independent bronchial hyperresponsiveness (BHR) and variable steroid responsiveness; and (iv) therapeutic implications, including biomarker-guided endotyping, Janus kinase (JAK) inhibition, TNF-like ligand (TL) 1A/death receptor (DR) 3 blockade, and metabolic or airway smooth muscle (ASM) tone modulation. Differentiating under the combined influence of interleukin (IL)-4 and tumor growth factor (TGF)-β, Th9 cells secrete IL-9, a pleiotropic cytokine that drives mast-cell proliferation, goblet cell metaplasia, and airway remodeling. Their transcriptional program is epigenetically licensed by STAT5/STAT6, which opens chromatin at the *IL9* locus and is metabolically sustained by a PPARγ-mechanistic/mTORC1-dependent glycolytic state. This bioenergetic wiring establishes an IL-9-MCT1 feedback loop that reinforces effector function and durability. Clinically, Th9 signatures align with BHR, which can be eosinophil-independent and variably responsive to inhaled corticosteroids; experimental models further demonstrate that Th9-mediated BHR persists in eosinophil-deficient contexts and displays relative glucocorticoid resistance. Within the broader landscape of bronchial asthma, a chronic inflammatory disease marked by reversible airway obstruction, mucus hypersecretion, and BHR, these insights help explain the non-Th2 endotypes that respond poorly to standard anti-inflammatory therapies. Although anti-IL-9 monoclonal antibodies have not improved lung function in unselected asthma cohorts, aggregate evidence argues for biomarker-guided endotyping and upstream pathway intervention, including tumor necrosis factor-like cytokine TL1A/DR3 blockade and metabolic modulation, as more rational strategies to disrupt Th9 pathogenic circuits. Importantly, the Th9 axis also represents one of the non-IgE-mediated hypersensitivity mechanisms pertinent to allergic conditions, a perspective that enhances clinical discoverability and bench-to-bedside translation. This review integrates foundational mechanistic and pharmacologic knowledge with recent advances, positioning Th9 cells as a unifying driver across asthma, atopic dermatitis, and allergic rhinitis, and delineates therapeutic avenues that target epigenetic, metabolic, and cytokine networks sustaining Th9-dependent diseases.

Keywords: allergic rhinitis, asthma, atopic dermatitis, bronchial hyperresponsiveness, non-IgE-mediated hypersensitivity

Introduction

The immunopathology of allergic diseases has evolved beyond the classical Th2 framework, revealing multiple T cell subsets that shape distinct inflammatory circuits. Among these, Th9 cells represent a unique lineage with specialized effector functions.[1,2] Induced by interleukin (IL)-4 in combination with tumor growth factor (TGF)-β, Th9 cells acquire a transcriptional program centered on IL-9 secretion, a cytokine with broad tissue effects, including mast-cell expansion, goblet-cell metaplasia, epithelial remodeling, and modulation of airway smooth-muscle tone.[1,3,4] Unlike Th2 cells, which primarily drive eosinophilic inflammation, Th9 cells contribute to disease phenotypes that are often severe, persistent, and

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variably responsive to corticosteroids.[5] This paradigm is particularly relevant to bronchial asthma, a chronic inflammatory disorder affecting over 330 million individuals worldwide and characterized by recurrent wheeze, dyspnea, chest tightness, and physiologic hallmarks of reversible airway obstruction, mucus hypersecretion, and bronchial hyperresponsiveness (BHR).[6] While asthma has long been conceptualized as a Th2-dominant disease, clinical and molecular studies over the past two decades have revealed striking heterogeneity and multiple mechanistic endotypes that better explain variable natural history and treatment response.[7,8] Experimental evidence further demonstrates that Th2-independent pathways, including Th9, can sustain airway inflammation and BHR, even in eosinophil-deficient contexts, underscoring the need for a broader immunologic map to guide therapy.[9] Recent advances have clarified how Th9 cells maintain pathogenicity across tissues. Epigenetically, signal transducer and activator of transcription (STAT) 5 and STAT6 remodel chromatin at the *IL9* locus, enabling bystander IL-9 production in response to paracrine IL-2/IL-4 without T-cell receptor (TCR) restimulation.[10,11] Metabolically, a peroxisome proliferator-activated receptor (PPAR) γ-mechanistic/mammalian target of rapamycin complex (mTORC) 1-driven glycolytic circuit establishes an IL-9-monocarboxylate transporter (MCT) 1 feedback loop that stabilizes effector function.[12,13] These intrinsic programs intersect with extrinsic cues, such as tumor necrosis factor-like cytokine (TL) 1A/death receptor (DR) 3 signaling, which promotes epithelial injury and barrier loss, and Piezo1-mediated mechanotransduction, linking matrix stiffness to Th9 differentiation and airway responsiveness.[14,15]

Therapeutically, the failure of anti-IL-9 monoclonal antibody therapy (MEDI-528) to improve lung function or exacerbation rates in uncontrolled asthma highlights the limitations of cytokine-centric strategies and reinforces the need for biomarker-guided endotyping.[16] Candidate biomarkers include STAT5/6 transcriptional signatures, IL-9$^+$CD4$^+$ frequencies, and PPARγ/MCT1 metabolic modules.[11,12,17] Upstream or parallel interventions, such as Janus kinase (JAK) inhibition, TL1A/DR3 blockade, and airway-smooth-muscle-targeted approaches, offer promising avenues to blunt BHR irrespective of granulocyte burden.[18–20]

In this review, we have integrated foundational and emerging insights into Th9 biology in asthma, atopic dermatitis, and allergic rhinitis through the comprehensive review of recent publications. Inclusion criteria comprised peer-reviewed mechanistic, translational, or clinical studies in English and major guidelines/position statements; we excluded non--peer-reviewed commentaries, single-patient case reports unless mechanistically informative, and duplicate cohorts. When findings conflicted, we prioritized higher-quality evidence and biological plausibility and noted uncertainty explicitly.

We begin by delineating the transcriptional, epigenetic, and metabolic networks governing Th9 differentiation, then examine the organ-level pathobiology and mechanisms of hyperresponsiveness, including the RhoA/Rho-associated coiled-coil containing protein kinase (ROCK)-myosin light chain phosphatase (MLCP) axis, and conclude with a therapeutic and endotyping framework tailored to Th9-high allergic diseases.[1,21] In alignment with the modern nomenclature proposed by the European Academy of Allergy and Clinical Immunology (EAACI) position paper,[22] hypersensitivity mechanisms extend beyond classical IgE-mediated pathways and encompass T-cell-driven and tissue- or metabolism-linked endotypes. Situating Th9-driven inflammation within these non-IgE or mixed mechanisms provides a clearer clinical bridge from bench to bedside and a rationale for biomarker-guided endotyping.

Differentiation and Regulatory Networks of Th9

IL-9 is a pleiotropic cytokine that drives mast-cell proliferation, goblet-cell hyperplasia, induction of IL-13, influx and local maturation of eosinophils, and the emergence of BHR.[5,23,24] Historically, IL-9 has been regarded as a Th2 cytokine and implicated in allergic asthma as well as parasitic infections.[25,26] In 2008, a CD4$^+$ T-helper subset that preferentially produces IL-9 was identified and designated Th9.[3] Th9 cells arise from naïve T cells under the concerted influence of IL-4 and TGF-β.[3,27] Although their full transcriptional circuitry remains incompletely resolved, several signature factors, including STAT6, GATA binding protein (GATA) 3, purine-rich box (PU).1, and interferon regulatory factor (IRF) 4, have been shown to orchestrate Th9 polarization.[1,2,28] IL-4 activates the STAT6 pathway, which in turn induces GATA3, a master regulator of Th2 identity, together with IRF4. In multiple, though not all, studies, GATA3 augments IL-9 production in Th9 cells.[27,29] GATA3 may also antagonize the forkhead transcription factor Foxp3, the lineage determinant of regulatory T (Treg) cells.[30,31] Notably, both Treg and Th9 development require TGF-β; this signaling induces PU.1, which enhances IL-9 during Th9 differentiation and counterbalances GATA3 function.[28,32] TGF-β further induces IRF4, and STAT6, together with IRF4, has been shown to bind directly to the *IL9* promoter.[4,28,33] Although IRF4,

STAT6, and GATA3 are indispensable across several Th lineages, the specific combinations and sequence of cytokine cues that engage this network are crucial for committing cells to a Th9 fate.[2,28,33] The differentiation and regulatory networks of Th9 cells have also been comprehensively depicted in several recent reviews and original articles.[28,33,34]

Th9 cells have been linked to a spectrum of conditions, including autoimmunity and pathogen-mediated immunomodulatory disorders, while multiple studies have suggested that Th9 cells play a prominent role in anti-tumor immunity.[35,36] Purwar et al. demonstrated that Th9 cells elicit stronger anti-tumor activity than Th1 or Th17 cells in adoptive-transfer mouse models.[37] Th9 cells potentiate adaptive anti-tumor responses via IL-9, which activates mast cells endowed with tumor growth-suppressive functions.[37,38] Lu et al. reported that Th9 cells promote robust host $CD8^+$ cytotoxic T-lymphocyte (CTL) responses by recruiting dendritic cells (DCs) to tumor sites through C-C motif chemokine ligand (CCL) 20/C-C motif chemokine receptor (CCR) 6-dependent pathways.[38,39]

Although the capacity of Th9 cells to kill cancer cells directly remains debated, Purwar et al. showed that OT-II-derived Th9 cells killed ovalbumin (OVA)-expressing tumor cells and expressed high levels of granzyme B; down--regulating granzyme B diminished their anti-melanoma efficacy.[37] Beyond STAT6, IRF4, and PU.1, cooperative Ets factors (E26 transformation-specific (ETS) transcription factors-related gene (ERG)/ETS variant 5 (ETV5)) together with the Dual-specificity phosphatase (DUSP) 8-Pur-α axis further refine IL-9 transcriptional control; critically, STAT5 is required for enhancer accessibility and for Basic leucine zipper transcription factor, ATF-like (BATF)-mediated activation.[28,40]

Organ-Level Pathobiology: Asthma, Dermatitis, and Rhinitis

Bronchial Asthma

Bronchial asthma is a chronic inflammatory airway disease characterized by reversible obstruction, mucus hypersecretion, and BHR.[6] Traditionally, type 2 cytokines, IL-4, IL-5, and IL-13, have been considered central to its pathogenesis, driving IgE class switching, eosinophil recruitment, and airway remodeling (Table 1).[5,53,54] IL-4 promotes IgE production and mast cell activation,[53,55] while IL-13 induces goblet cell hyperplasia and airway smooth muscle changes.[54,56] IL-5 is essential for eosinophil maturation and survival, and eosinophil-derived mediators contribute to tissue damage and BHR.[57–60] Eosinophil levels often correlate with disease severity and exacerbation frequency.[61] However, studies using eosinophil-deficient mice have shown that BHR can occur independently of eosinophils, indicating heterogeneity in asthma mechanisms.[5,62,63] In addition to Th2 pathways, Th1 and Th17 cells can also induce BHR, often associated with neutrophilic inflammation and steroid resistance.[9,64–66] These findings support the concept of asthma as a spectrum of endotypes, with variable contributions from Th2, Th1, and Th17 cells, and highlight the need for tailored therapeutic

Table 1 Th9 Axis Across Allergic Diseases: Pathobiology, Biomarkers, and Therapeutic Implications

Disease	Primary Th9 Effector / Targets	Pathobiology Highlights	Candidate Biomarkers	Therapeutic Implications (Examples)
Bronchial asthma	IL-9 → mast cells, goblet cells, ASM[1,5,23]	BHR, mucus hypersecretion, and remodeling; Th9-high endotypes may show ICS refractoriness[5,41]	IL-9^+CD4^+ frequency; STAT5/6 signatures; PPARγ/MCT1 module[11,12]	JAK inhibition; TL1A/DR3 blockade; metabolic modulators; ASM tone control (ROCK2/MLCP)[11,13,14,20]
Atopic dermatitis	IL-9 → mast cells, keratinocytes[42,43]	Amplifies itch/barrier dysfunction; metabolic (PPARγ–mTORC1) dependency[44,45]	Serum IL-9, Th9 signatures, metabolic indicators[45–47]	PPARγ modulators; adjunct IL-9–axis interventions[45,47]
Allergic rhinitis	IL-9 → nasal mast cells and goblet cells[48,49]	NHR and secretory responses; partial dexamethasone sensitivity in nasal compartment[48,49]	IL-9 in nasal secretions; increased peripheral Th9 cells[49–51]	Combine IL-9/upstream (TL1A/DR3) targeting with standard intranasal therapies[14,52]

Abbreviations: ASM, airway smooth muscle; BHR, bronchial hyperresponsiveness; DR3, death receptor 3; JAK, Janus kinase; MCT1, monocarboxylate transporter 1; MLCP, myosin light chain phosphatase; mTORC1, mechanistic/mammalian target of rapamycin complex 1; PPARγ, peroxisome proliferator-activated receptor γ; ROCK2, Rho-associated coiled-coil containing protein kinase 2; STAT, signal transducer and activator of transcription; TL1A, tumor necrosis factor-like cytokine 1A.

approaches.[7,8,67] Beyond these traditional and recently proposed pathophysiological mechanisms, the pivotal role of the Th9-IL-9 axis in asthma pathogenesis, particularly in the development of BHR, is discussed in the following section.

Atopic Dermatitis

Atopic dermatitis (AD) represents a chronic, relapsing inflammatory skin disorder characterized by epidermal barrier dysfunction, pruritus, and heightened susceptibility to microbial colonization.[68,69] While traditionally associated with type 2 cytokines such as IL-4 and IL-13, emerging evidence implicates Th9 cells as critical amplifiers of cutaneous inflammation (Table 1).[46,47] Th9 cells, through robust IL-9 secretion, exert pleiotropic effects on mast cells, keratinocytes, and resident immune cells, fostering a microenvironment conducive to chronic allergic inflammation.[42,43] IL-9 promotes mast-cell proliferation and activation, enhancing histamine release and protease secretion, which aggravate pruritus and tissue remodeling.[70–72] Furthermore, IL-9 synergizes with IL-4 and IL-13 to reinforce epithelial barrier disruption and mucus-like glycoprotein deposition, features increasingly recognized in severe AD phenotypes.[44,73]

Recent mechanistic studies revealed that the Th9 effector function in the skin is metabolically gated by the PPARγ-mTORC1 axis, which drives glycolytic reprogramming and selectively augments IL-9 expression without proportionally increasing IL-13.[12,13] This metabolic dependency is further stabilized by an IL-9-MCT1 feedback loop, enabling sustained lactate flux and proliferation under nutrient-variable conditions typical of inflamed dermis.[13,74] Clinically, elevated Th9 signatures and serum IL-9 correlate with disease severity, and microbial cues, such as Staphylococcus aureus superantigens, can potentiate Th9 polarization, linking dysbiosis to immune amplification.[46,47,75]

These insights suggest that metabolic and cytokine-targeted interventions, including PPARγ modulators and IL-9 pathway inhibitors, are promising adjuncts to conventional barrier-restorative and biological therapies in AD.[45,76]

Allergic Rhinitis

Allergic rhinitis (AR) is a prevalent upper-airway disorder marked by nasal congestion, rhinorrhea, sneezing, and mucosal hyperreactivity.[77,78] Historically attributed to IgE-mediated mast-cell activation and type 2 cytokines, AR pathogenesis is now understood to involve a broader T-helper repertoire, including Th9 cells.[77,79] Experimental transfer models demonstrate that Th9 cells can induce nasal hyperresponsiveness (NHR) independent of eosinophilic infiltration, underscoring their capacity to modulate airway tone through noncanonical pathways.[80,81] IL-9 produced by Th9 cells amplifies mast-cell density within nasal mucosa, augments local histamine release, and promotes goblet-cell hyperplasia, collectively intensifying secretory responses and mucosal edema (Table 1).[48,49,82] Mechanistically, IL-9 acts in concert with epithelial-derived alarmins and type 2 cytokines to sustain chronic inflammation, while epigenetic and metabolic programs, STAT5/STAT6-mediated chromatin licensing, and PPARγ-driven glycolysis, mirror those observed in lower-airway disease.[11–13,82] Notably, NHR exhibits tissue-specific pharmacodynamics: whereas bronchial Th9-driven BHR often resists corticosteroid suppression, nasal models reveal partial dexamethasone responsiveness, suggesting differential glucocorticoid sensitivity across airway compartments.[41,80,81] This heterogeneity likely reflects variations in local cytokine gradients, vascular permeability, and stromal cell composition.[83]

Clinically, elevated IL-9 levels in nasal secretions and increased Th9 frequency in peripheral blood have been documented in patients with AR, correlating with symptom burden.[49–51] These findings advocate for endotype-driven strategies that integrate IL-9 blockade or upstream modulators (eg, TL1A/DR3 antagonists) with established intranasal corticosteroids and allergen immunotherapy to achieve durable disease control.[14,52]

Mechanisms of Hyperresponsiveness and Tissue Mechanics

Th9-linked BHR: Clinical and Experimental Lines of Evidence

In addition to their anti-tumor activity, Th9 cells also play a substantial role in allergic diseases. Like Th2 cells, Th9 cells can provoke airway eosinophilic inflammation accompanied by BHR, yet the routes by which Th9 cells drive BHR are multifactorial (Table 2).[5,87] In an original mouse transfer model, allergen challenge of Th9-recipient mice induced both BHR and eosinophil infiltration, mirroring the phenotype seen after transfer of in vitro-differentiated allergen-specific Th2 cells.[9,41] Upstream drivers are diverse: tumor necrosis factor receptor superfamily, member 4 (TNFRSF4/OX40)

Table 2 Th-Subset–Driven Hyperresponsiveness Across Airway Compartments: Dependency, Steroid Response, Bronchoactive/ASM Pathways

Th subset	Dominant cytokines	BHR (bronchi)	Eosinophil Dependency (BHR)	Steroid Responsiveness (BHR)	NHR (nasal)	Eosinophil Dependency (NHR)	Steroid Responsiveness (NHR)	Candidate Bronchoactive / ASM pathways
Th1	IFN-γ	Can induce BHR with neutrophilia; Th1 transfer fails to blunt Th2-BHR and may exacerbate inflammation[64]	Independent of eosinophils (neutrophilic route)[64]	Often steroid-refractory in these settings[5]	Induces NHR in mice[84]	Independent (upper airway)[84]	Undetermined	CXC chemokines; T-cell bronchoactive mediators; RhoA/ROCK axis engagement[7,20]
Th2	IL-4 IL-5 IL-13	Robust; mucus hypersecretion and remodeling common[9,64]	Often dependent; but can be strain/setting-dependent[9]	Generally steroid-responsive in transfer/immunization models[41,66]	Present in transfer models[80,84]	Largely independent (upper airway)[84]	Suppressed by dexamethasone in Th2-transfer nasal models[80]	CysLTs–ASM constriction; IL-13–induced Ca^{2+} sensitization via RhoA/ROCK–MLCP[20,54,85]
Th9	IL-9	Present; can persist when eosinophils are absent[9]	Frequently independent or variable vs Th2[9]	Relative resistance (migration not curtailed by steroids)[9,41]	Induces NHR and secretory responses[81]	Undetermined	Partial sensitivity reported depending on site[81]	T-cell–derived bronchoactive factors; Piezo1 tuning; ASM Ca^{2+} sensitization interface[15,20]
Th17	IL-17A IL-17F IL-22	Induces BHR with robust neutrophilia and minimal eosinophilia[66]	Independent (neutrophilic pathway)[66]	Frequently steroid-refractory; dexamethasone can worsen neutrophilia in models[66]	Induces NHR in mice[84,86]	Independent (upper airway)[84,86]	Undetermined/variable; tissue-dependent[66,86]	IL-17A effects on epithelium/ASM; Ca^{2+} sensitization; RhoA/ROCK–MLCP modulation[20,67]

Abbreviations: ASM, airway smooth muscle; BHR, bronchial hyperresponsiveness; MLCP, myosin light chain phosphatase; NHR, nasal hyperresponsiveness; ROCK, Rho-associated coiled-coil containing protein kinase.

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signaling in T cells promotes Th9 differentiation and airway inflammation,[88] and chronic exposure to Aspergillus fumigatus augments Th9 development in murine lungs.[89] Clinically, peripheral blood from patients with allergic asthma contains higher Th9 frequencies and elevated IL-9 relative to healthy subjects.[90,91] Against this background, a randomized, placebo-controlled, double-blind, multicenter trial of an anti-IL-9 monoclonal antibody in uncontrolled moderate-to-severe asthma (2013) failed to improve predicted forced expiratory volume 1 (FEV_1), underscoring that IL-9 neutralization alone is insufficient in an unselected cohort.[16] Organ-level pathways linking Th9 programs to bronchial and nasal hyperresponsiveness (including chemokine-guided trafficking and airway-smooth-muscle tone interfaces) are summarized in previously published figures and reviews.[92,93]

Consistent with these findings, our mouse study showed Th9-mediated BHR was not abrogated by IL-9 blockade; IL-10 was dispensable, as IL-10-deficient Th9 cells still induced BHR; and, notably, Th9-dependent BHR was markedly increased in eosinophil-deficient mice, contrasting with the eosinophil requirement observed in Th2-mediated BHR.[9] Although previous studies by Kung et al and Cheng et al demonstrated that anti-IL-9 antibody treatment reduced airway inflammation and BHR in allergic mouse models, differences in experimental design, such as mouse strain and allergen challenge duration, may account for the heightened IL-9 dependency observed in those settings.[94,95] In parallel, steroid responses diverge by lineage: despite similar glucocorticoid-receptor expression and dexamethasone-sensitive cytokine output in vitro, dexamethasone suppressed allergen-induced eosinophilia and BHR in Th2-transfer mice but not in Th9-transfer mice.[41] Tracking allergen--specific cells revealed dexamethasone curtailed Th2, but not Th9, migration into the lung, suggesting steroid efficacy in Th2-driven BHR may stem from reductions in Th2 cell trafficking rather than direct eosinophil depletion.[96]

Together, these data suggest that Th9 cells can sustain BHR through pathways that do not strictly rely on IL-9 or eosinophils and respond variably to steroids, reinforcing the need for endotype-aware interventions.[5,9,41]

Eosinophil-T-cell Crosstalk, Bronchoactive Mediators, and the Airway Smooth Muscle (ASM) Contractile Set-point

T cells and their cytokines, especially IL-5, are necessary for eosinophil accumulation in allergic lungs, yet eosinophils themselves shape T-cell dynamics.[97,98] Beyond canonical $CCR3^+$/Siglec-F^+ profiles, functionally distinct eosinophil subsets have been identified; Siglec-F^+Gr1^{hi} cells accumulate after allergen challenge and maintain T-cell-active cytokines.[99] In eosinophil-deficient mice, adoptive transfer of eosinophils plus CCL11 instillation rescued BHR and T-cell infiltration, and independent work showed that accumulated T cells contribute to eosinophil-dependent BHR.[5,100] Differences in BHR steroid-responsiveness between Th2 and Th9 contexts may therefore reflect subset-specific chemotaxis and cellular choreography within inflamed tissue.[5] Importantly, BHR can also arise without eosinophils: transfer models using Th1, Th9, or Th17 cells each produced eosinophil-independent BHR, implying the presence of shared bronchoactive factors released by T cells (Table 2).[9,64,66]

T cells can synthesize acetylcholine, and we identified a high-molecular-weight T-cell-derived activity that contracts bronchial smooth muscle.[101,102] Moreover, allergen-induced late-phase airway obstruction occurred after transfer of OVA-reactive T-cell clones.[103] In parallel, mechanotransduction via Piezo1 links matrix stiffness to Th9 output and airway responsiveness, providing a physical cue that complements RhoA/ROCK-MLCP-mediated Ca^{2+} sensitization.[15,20] These convergent routes place the T cell, not solely the eosinophil, at the center of dynamic tone control in the allergic airway.[5,15,64,66]

Tissue Specificity and Nasal Hyperresponsiveness: Physiology, Pharmacology, and Mechanics

With respect to hyperresponsiveness and commonality across Th subsets, allergen-induced NHR, quantified by increased sneezing responses to non-specific stimuli, was elicited not only by Th2 transfer but also by Th1 and Th17 transfer in mice (Table 2).[84] In striking contrast to the eosinophil requirement typical of Th2-mediated BHR, eosinophils were dispensable for NHR even in Th2-transfer models, indicating that upper-airway hyperreactivity can be sustained by T-cell programs independent of granulocyte burden.[84] In immunized and Th2- or Th17-transferred mice, allergen-induced NHR was suppressed by dexamethasone, though the impact on Th1-driven NHR remains to be determined.[81,84,86] These

observations argue for a tissue-specific lens: bronchial smooth-muscle contraction and the sneeze reflex are distinct physiological outputs with overlapping but non-identical upstream controllers.[83,104]

Mapping these outputs onto local mechanics clarifies the picture: Piezo1-based sensing of matrix stiffness can tune Th9 effector output and airway responsiveness, while the RhoA/ROCK-MLCP axis modulates Ca^{2+} sensitivity at the myocyte level, together defining a dual control system in which immune programming and tissue biomechanics co-produce the hyperresponsive state.[15,20] This framework helps explain differential steroid responsiveness between bronchi and nose and supports endotype- and site-specific strategies for intervention.[5,80,84]

Therapeutics and Endotyping

Guideline Backbone and Modulators of the Th2 Cascade

The foundation of asthma management remains the Global Initiative for Asthma (GINA) stepwise/track-based approach, centered on inhaled corticosteroids (ICS) and, as needed, add-on therapies such as long-acting beta-agonists (LABA), leukotriene receptor antagonists (LTRA), and theophylline. Recent updates emphasize ICS-containing reliever regimens to minimize short-acting beta-agonist (SABA)-only exposure.[6] From a systems perspective, cysteinyl leukotrienes (CysLTs) are potent endogenous bronchoconstrictors, and $CysLT_1$ antagonists (eg, montelukast) have demonstrated efficacy in randomized trials, serving as adjuncts in mild-to-moderate or non-type 2 asthma.[85,105] Building on this standard, endotype-driven biologic therapies have become established. The IL-5/IL-5 receptor (IL-5R) axis is particularly effective in type 2-high phenotypes, marked by elevated blood/sputum eosinophils or oral corticosteroid (OCS) dependence. Mepolizumab and benralizumab show robust OCS-sparing effects and sustained efficacy in real-world and extension studies.[106–108] However, IL-5-independent endotypes also exist, necessitating careful stratification.[106] Targeting IL-4/IL-13 has proven more nuanced.[109] While single-cytokine blockade yielded inconsistent results, dual inhibition via IL-4 receptor (IL-4R) α (dupilumab) suppresses both IL-4 and IL-13 signaling, delivering reproducible reductions in exacerbations and sustained lung function improvements, especially in type 2-high patients identified by fractional exhaled nitric oxide (FeNO) and blood eosinophils. These biomarkers have proven useful for predicting and stratifying dupilumab responses in both clinical trials and real-world practice.[110–112]

Beyond Th2: Th9-axis Strategies and an Endotype-guided Roadmap

Anti-IL-9 monoclonal antibody therapy did not improve outcomes in uncontrolled asthma, indicating that downstream neutralization may be insufficient without endotype enrichment (Table 3).[16] In contrast, the STAT5/STAT6-licensed bystander IL-9 program in Th9 cells, together with patient data, positions JAK inhibition as a rational option for Th9-high endotypes.[11] Upstream interference with the TL1A/DR3 pathway and metabolic modulation of Th9 biology (PPARγ/mTORC1; acetyl-CoA carboxylase (ACC) 1) are similarly compelling avenues,[12–14,113] while ROCK2 inhibition or MLCP activation offers endotype-agnostic control of airway tone by attenuating Ca^{2+} sensitization in airway smooth muscle.[20,21]

Practically, an endotyping framework would integrate (i) clinical markers (exacerbation pattern, steroid responsiveness), (ii) cellular/molecular readouts (blood and airway Th2/Th9 signatures; IL-5/IL-13/IL-9 axes; STAT5/STAT6 gene sets), and (iii) physiologic surrogates (FeNO, sputum eosinophils, bronchial hyperresponsiveness) to match patients to IL-5/IL-5R, IL-4Rα, or JAK/TL1A-targeted approaches, adding ASM-directed therapy when tone dysregulation predominates.[8,18,114,115] Notably, a subset of patients with asthma, rhinitis, or atopic dermatitis exhibit “intrinsic” (non-IgE-mediated) allergic phenotypes, which may be overlooked by conventional IgE-based diagnostics. The application of the leukocyte adherence inhibition test and related assays has enabled the identification of non-IgE-mediated immunoreactivity in such patients, reinforcing the need for endotype-driven approaches in allergy diagnosis and management.[116] This layered strategy leverages type 2 successes, acknowledges IL-5-independent diseases, and incorporates Th9-specific circuitry to personalize control across the asthma spectrum.[8,114]

Table 3 Therapeutic Targets Related to Th9 Biology (Candidate Agents, Endotypes, and Safety)

Target Pathway	Rationale in Th9 Disease	Representative Agents	Candidate Endotype / Biomarker	Expected eFfect	Key Safety Notes
IL-9 / IL-9R	Core to mast cells, mucus, and barrier disruption[23,24,73]	Anti–IL-9 / anti–IL-9R mAbs (clinical/ early trials)[16]	IL-9-high; mast cell–dominant; mucus phenotype[23,73]	Reduce exacerbations and mucus; improve BHR (endotype-selected)[73,94,95]	Monitor host defense (parasites/tumor surveillance)[16]
TL1A / DR3	Sustains Th9 survival/ polyfunctionality in tissues[14]	Anti-TL1A mAbs (investigational)[19,52]	DR3/IL-9 co-expression; skin/ gut involvement[14,19,52]	Shrink tissue Th9 pools; ease chronicity[14,19,52]	Gastrointestinal-related adverse events; disease-specific risks[19,52]
JAK–STAT (JAK1/3 → STAT5/6)	Licenses IL-9 locus; bystander IL-9 bursts[11]	JAK inhibitors (eg, tofacitinib)[18]	High IL-9 / STAT signatures[11,18]	Suppress Th9 expansion and rapid responses; restore steroid control (combination)[11,18]	Infections, venous thromboembolism, lipids[18]
ROCK2 / STAT3 (ASM tone)	ASM Ca^{2+} sensitization and contractility in BHR[20,21]	ROCK2 or STAT3 inhibitors[20,21]	BHR-dominant, non-eosinophilic[20,21]	Lower ASM contractility and BHR[20,21]	
Epigenetic modulation (BET / HDAC)	Exploit IL-9 locus plasticity; durable suppression[10,11]	BET/HDAC modulators (preclinical)[10,11]	Epigenomic signatures / Th9 chromatin accessibility[10,11]	Sustain IL-9 downregulation[10,11]	

Abbreviations: ASM, airway smooth muscle; BET, bromodomain and extraterminal; BHR, bronchial hyperresponsiveness; DR3, death receptor 3; HDAC, histone deacetylases; IL-9R, IL-9 receptor; JAK, Janus kinase; mAbs, monoclonal antibodies; ROCK2, Rho-associated coiled-coil containing protein kinase 2; STAT, signal transducer and activator of transcription; TL1A, tumor necrosis factor-like cytokine 1A.

Safety and Tolerability

From a safety perspective, downstream IL-9 neutralization has shown neutral efficacy signals without new major safety concerns in unselected asthma cohorts;[16] in contrast, JAK inhibition warrants infection, lipid, and thromboembolism monitoring,[18] and investigational TL1A/DR3 blockade has reported gastrointestinal-related adverse events in disease--specific contexts.[19,52] Epigenetic modulators (BET/HDAC) and ASM-tone targeted approaches (eg, ROCK2/STAT3 axis) carry class-typical risks and remain under active evaluation. These safety considerations are summarized alongside putative endotypes in Table 3.

Clinical Translation and Decision-Making

A pragmatic pathway links (i) suspected endotype features (exacerbation pattern, eosinophil-independence, variable steroid responsiveness; bronchial vs nasal compartment) with (ii) molecular readouts (blood/airway Th9 signatures; IL-$9^{+}CD4^{+}$ frequencies; STAT5/STAT6 gene sets; metabolic modules) and (iii) therapeutic choices (IL-5/IL-5R or IL-4Rα for type 2-high; JAK or TL1A/DR3 targeting for Th9-high; ASM-tone modulation when Ca^{2+} sensitization predominates). This bench-to-bedside mapping is intended to guide trial enrichment and individualized care.

Limitations

The evidence base for Th9-axis interventions remains heterogeneous across tissues (bronchus versus nose) and disease endotypes; downstream IL-9 neutralization has yielded inconsistent benefits in unselected cohorts, underscoring the need for biomarker-enriched trial designs. Mechanistic inferences drawn from preclinical models may not fully capture human tissue pharmacodynamics, and standardized readouts for Th9 signatures require further validation across platforms.

Conclusions and Future Directions

In summary, while type 2-eosinophilic inflammation remains a central mechanism of asthma, non-type 2 endotypes are common and clinically consequential. Therefore, we posit novel, eosinophil-independent BHR mechanisms in which various Th subsets, particularly Th9, drive hyperresponsiveness through immune-metabolic-mechanical crosstalk. Aligning endotyping, upstream targeting (STAT/JAK, TL1A/DR3), metabolic control (PPARγ/mTORC1, ACC1), and ASM-directed modulation (ROCK2/MLCP) offers a coherent, precision-ready strategy to expand benefits across the full spectrum of allergic airway diseases.

Future studies should integrate single-cell epigenomics under steroid and JAK inhibitor exposure, map nutrient and stiffness gradients that set IL-9 thresholds (PPARγ/MCT1; Piezo1), and prospectively test biomarker-enriched cohorts for JAK or TL1A/DR3 blockade combined with ASM-directed therapy.

Abbreviations

ACC1, acetyl-CoA carboxylase 1; ASM, airway smooth muscle; BATF, basic leucine zipper transcription factor, ATF-like; BHR, bronchial hyperresponsiveness; DR3, death receptor 3; EAACI, European Academy of Allergy and Clinical Immunology; ECAR, extracellular acidification rate; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; HDAC, histone deacetylase; IL, interleukin; IL-9R, interleukin-9 receptor; IRF4, interferon regulatory factor 4; JAK, Janus kinase; mAb, monoclonal antibody; MLCP, myosin light chain phosphatase; MCT1, monocarboxylate transporter 1; mTORC1, mechanistic/mammalian target of rapamycin complex 1; NHR, nasal hyperresponsiveness; OCS, oral corticosteroid; TNFRSF4/OX40, tumor necrosis factor receptor superfamily, member 4 ; PPARγ, peroxisome proliferator-activated receptor gamma; ROCK2, Rho-associated coiled-coil containing protein kinase 2; STAT, signal transducer and activator of transcription; TL1A, TNF-like ligand 1A; Treg, regulatory T cell.

Data Sharing Statement

Data availability is not applicable as no new data was generated for this paper.

Author Contributions

Osamu Kaminuma: Conceptualization, Writing – original draft, Funding acquisition, Investigation, Project administration, Visualization. Noriko Kitamura: Writing – review and editing, Funding acquisition, Validation. Minoru Gotoh: Conceptualization, Writing – review and editing, Supervision.

All authors gave final approval of the version to be published; approved on the journal to which this article was submitted; and agree to be accountable to the content of this article.

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Disclosure

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be considered potential conflicts of interest.

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