International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

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REVIEW

Targeting the Epithelial Alarmin Axis with Biomedical Nanoparticles: A New Frontier in Allergic Asthma Therapy

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Abstract: Allergic asthma is a chronic inflammatory airway disease driven by type 2 immune responses, whose pathogenesis correlates with the release of epithelial alarm proteins—thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25), and interleukin-33 (IL-33)—by airway epithelial cells following barrier injury. This paper systematically reviews the cutting-edge applications of nanoparticles (NPs) in targeting the epithelial alarmin signaling axis and its downstream immune cells, including dendritic cells, macrophages, Th2 cells, and regulatory T cells. By systematically reviewing research progress on nanoparticles in allergic asthma treatment, this review provides crucial theoretical support and technical frameworks for developing precise, efficient, and less-side-effect asthma therapies. It offers forward-looking guidance for advancing asthma treatment from laboratory to clinical translation.

Keywords: nanoparticles, allergic asthma, epithelial alarmins, immunomodulation, MSC-exosomes, DNAzyme nanocapsules

Introduction

Asthma, a chronic noncommunicable disease characterized by airway inflammation, is gradually posing a global threat. According to projections from the 2021 Global Burden of Disease (GBD) study, the number of asthma patients worldwide has reached 260 million and is projected to rise to 275 million by 2050.[1] Its clinical symptoms primarily manifest as chest tightness, shortness of breath, and recurrent wheezing, which can be fatal in severe cases. However, given the complex pathophysiology of this heterogeneous disease, existing treatment regimens can only alleviate rather than cure patients' symptoms. Current clinical asthma management strategies primarily rely on combination therapy with corticosteroids and bronchodilators. Symptoms are controlled through anti-inflammatory responses induced by inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), and leukotriene antagonists. Among these, ICS use is universally recommended in the Global Initiative for Asthma (GINA) guidelines as the first-line treatment for all patients with persistent asthma.[2] In fact, frequent or excessive use of steroids may lead to certain systemic side effects and adverse reactions.[3–5] Therefore, further elucidating the pathogenesis of asthma and developing more precise and effective treatment approaches have become the two primary objectives of current asthma research.

Allergic asthma is the most common asthma phenotype across all studies. Its pathogenesis is primarily driven by a type 2 immune response triggered by inhaled airborne allergens (such as pollen and fungal spores), which produces type 2 helper T (Th2) cytokines leading to airway edema, excessive mucus secretion, and bronchial hyperresponsiveness.[6] Over the past two decades, translational research has identified numerous therapeutic targets for asthma associated with type 2 immune responses, expanding treatment options for asthma management. Furthermore, the recently proposed epithelial barrier hypothesis suggests that many allergens can cause lesions in affected skin and mucosal tissues by disrupting the epithelial barrier, triggering various allergic inflammatory diseases such as asthma.[7] Extensive research demonstrates that in allergic asthma, airway epithelial cells (AECs) respond to compromised barriers by releasing three epithelial cytokines known as "alarm proteins," thereby mediating a complex Type 2 inflammatory

https://doi.org/10.2147/IJN.S588680
Received: 13 December 2025
Accepted: 23 March 2026
Published: 31 March 2026

cascade. This discovery not only clarifies part of the mechanism by which allergens initiate Type 2 immune responses but also provides novel therapeutic targets for asthma treatment.

To date, biologic agents such as human monoclonal antibodies (eg., omalizumab, mepolizumab) have been used to treat moderate-to-severe refractory asthma.[8] However, the significant variation in clinical response to treatment and its limitations have compelled contemporary researchers to seek new avenues for asthma management.[9,10] Today, with the widespread application of nanomedicine and the rapid growth of the nanomedicine market, biomedical nanoparticles (NPs) have garnered significant attention in drug delivery and immunomodulation due to their multifunctionality, high biocompatibility, and potential for advanced therapeutic applications. This paper will focus on discussing the role of epithelial alarmins in type 2 immune responses and the progress of biomedical NPs in their mediation of allergic asthma.

Alarmins

Epithelial alarmins are a class of endogenous danger signaling molecules rapidly released by epithelial cells upon sensing danger signals such as tissue injury, infection, or stress. They constitute an important component of damage-associated molecular patterns (DAMPs). Typical epithelial alarmins include TSLP, IL-25, and IL-33. Produced by healthy activated immune cells and secreted via the endoplasmic reticulum-Golgi pathway or non-classical routes (such as non-programmed cell death), they play crucial roles as initiators and participants in various physiological and pathophysiological processes, including inflammation, infection, and tumor immunity.[11,12] Under steady-state conditions, they are typically confined within cells. However, upon cellular injury, necrosis, or pathogen stimulation, they are actively secreted or passively released into the extracellular environment. There, they bind to receptors to activate downstream inflammatory signaling pathways, recruiting and activating immune effector cells such as dendritic cells, eosinophils, and type 2 innate lymphoid cells, thereby amplifying the local inflammatory response. In allergic asthma, epithelial alarmins serve as crucial mediators, providing distinct tissue-specific signals to innate and adaptive cell populations, making them key therapeutic targets for intervention.

TSLP

TSLP is the earliest clearly identified epithelial alarm protein, holding significant importance in the field of immunology. Its discovery not only revealed a novel mechanism for epithelial-immune cell communication but also established its pivotal role within the core regulatory network of type 2 immune responses. TSLP is an IL-7-like lymphocyte growth factor primarily produced in response to pathogenic stimuli in lung and intestinal epithelial cells and skin keratinocytes. It promotes the adaptive immune system by recruiting and activating antigen-presenting cells such as dendritic cells (DCs) and innate lymphoid cells (ILCs), thereby inducing complex type 2 immune responses at barrier surfaces.[13,14] The functional receptor for TSLP is a heterodimeric complex composed of TSLPR (thymic stromal lymphopoietin receptor) and IL-7Rα.[15] TSLP binds specifically to its receptor, thereby activating downstream signaling pathways. This process constitutes the key molecular basis for its role as a core regulator in type 2 immune responses. Consequently, TSLP is also recognized as a primary modulator of type 2 immune responses.

In allergic asthma, DCs serve as the primary target cell type for TSLP. Under TSLP induction, DCs express OX40 ligand (OX40L), triggering naive CD4+ T cells to produce IL-4, IL-5, and IL-13. This process induces Th2 cell polarization, thereby establishing the Th2-polarized inflammatory environment characteristic of the airway microenvironment in allergic asthma.[16] The latter primarily manifests as elevated levels of cytokines (IL-4, IL-5, IL-13), chemokines (CCL5, CCL11, CXCL2, CXCL12), and growth factors (transforming growth factor-beta (TGF-β); basic fibroblast growth factor (bFGF); vascular endothelial growth factor (VEGF); platelet-derived growth factor-beta (PDGF-β)).[17] These cytokines, chemokines, and growth factors are stored by eosinophils recruited to the site of inflammation and are rapidly released at the inflammatory site to coordinate the Type 2 immune response in an exacerbating or modulating manner. Furthermore, these soluble mediators profoundly affect airway structural cells, directly leading to excessive mucus production, fibrosis, and airway smooth muscle changes, which in turn directly contribute to the manifestation of asthma symptoms.[18,19]

Alveolar macrophages (AM) are also key cellular targets for TSLP-mediated Type 2 immune responses. It is well established that macrophages constitute the most abundant immune cells in the lung. Upon exposure to prototypical cytokines or TLR agonists, they differentiate into two functionally distinct subsets: classically activated (M1)

macrophages and alternatively activated (M2) macrophages, forming a crucial component of the innate immune system. Among these, M2 macrophages are closely associated with asthma pathogenesis. Induced by Th2 cytokines such as IL-4 and IL-13, they express high levels of C-type lectin receptors, chemokines, cytokines, macrophage signaling proteins, and transcription factors that promote airway inflammation, fibrosis, and airway hyperresponsiveness (AHR).[20] Existing research indicates that TSLP can amplify M2 macrophage differentiation. Through TSLP/TSLPR signaling, it participates in M2 cell polarization in mice, inducing M2 macrophages to produce the Th2-inducing cytokine OX40L and the Th2-recruiting chemokines thymus and activation-regulated chemokine (TARC) and macrophage-derived chemokine (MDC), thereby exacerbating allergic inflammatory symptoms.[21] Moreover, TSLP can upregulate *AMFR* (also known as gp78, an endoplasmic reticulum-resident E3 ubiquitin ligase) expression in AMs. By fine-tuning TSLP-STAT5 signaling within AMs, it promotes Th2 responses, thereby driving the progression of allergic airway inflammation.[22]

In summary, TSLP serves not only as a key upstream alarm molecule initiating allergic asthma, but its cascade amplification effect within signaling pathways constitutes the core scientific rationale for therapeutic intervention. TSLP exerts its effects through three primary pathways. First, it directly activates DC-mediated Th2 cell polarization. Second, it drives AM differentiation toward the M2 phenotype. Third, it promotes Th2 immune responses via the TSLP-STAT5 signaling axis. This multi-target regulatory property explains why nanoparticle targeting TSLP demonstrates more pronounced therapeutic advantages compared to other single-target strategies.

IL-25

IL-25 is an upstream protein in immune responses and a key member of the epithelial alerting protein family. Also known as IL-17E, IL-25 was initially defined as a cytokine produced by Th2 cells and is a member of the IL-17 cytokine family.[23] Its receptor is a heterodimeric complex composed of two subunits, IL-17RA and IL-17RB, which is widely expressed across multiple cell types. Its biological effects are distinctly different from those of other members of the IL-17 family.[24] In vivo studies indicate that IL-25 infusion in mice primarily induces a Th2-type immune response across multiple tissues, characterized by enhanced expression of Th2 cytokines, elevated serum immunoglobulin (Ig)E, IgG1, and IgA concentrations, and increased blood eosinophil counts[23] Moreover, studies on the sources of IL-25 indicate that, in addition to Th2 cells, alveolar macrophages (AM), innate lymphoid cells 2 (ILC2), eosinophils, and basophils are all potential sources of IL-25.[25] These findings reveal the intricate mechanisms by which IL-25 mediates Type 2 immune responses. Therefore, elucidating the role of IL-25 in allergic asthma will aid in identifying therapeutic intervention targets (Table 1).

In allergic asthma, the mechanism by which IL-25 triggers Type 2 immune responses largely overlaps with that of TSLP. Specifically, it initiates the recruitment of innate and adaptive immune cells such as eosinophils by inducing excessive production of Th2 cytokines, thereby forming an inflammatory microenvironment that leads to asthma symptoms.[31]

However, among the three typical epithelial alarmin proteins, IL-25 particularly enhances the type 2 immune response and further exacerbates allergic diseases. This effect is attributed to the dependence of the type 2 response on the IL-25

Table 1 Mechanisms of IL-25 in Allergic Asthma

	Cell Target Types	Related Signaling Pathways	Effects on Cell Targets
Innate immune cells	DC	IL-25/IL-17RB	Th2 memory cell activation↑[26]
	AM	PINK1-Parkin	Mitochondrial autophagy, M2 Macrophage↑[27]
	ILC2	Gαq/11-PLCβ-IP3/Ca^{2+}-PKC	IL-4, IL-5, IL-13, IL-6↑[28]
	Eosinophil	IL-25/IL-17RB	HLA-DR, PD-L1 and OX-40L↑[29]
	Basophils	IL-25/IL-17RB	IL-17RB, CCR3↑[30]
Adaptive immune cells	Th2	IL-25/IL-17RB	IL-17RB, IL-4, IL-5, IL-13↑[31]
		STAT6	Th2 cell differentiation, NFATc1, JunB↑[31]
	TH9	IL-25/IL-17RB	IL-9 expression↑[24]
	Treg	Nod2	Treg development↓[32]
	B cell	IL-25/IL-17RB	IGHE, CCL17, CCL22↑[33]

(*Continued*)

https://doi.org/10.2147/IJN.S588680

Table 1 (Continued).

	Cell Target Types	Related Signaling Pathways	Effects on Cell Targets
Structural cell	AEC	PI3K, MEK and NF-κb	VEGF/VEGF Receptor expression, Angiogenesis↑[34]
	Airway smooth muscle cells	TAK1-TPL2-MEK1/2-ERK1/2	Airway smooth muscle contraction, AHR, CCL5, CCL11, GM-CSF↑[35]
	Fibroblasts	AP-1, IL-25/IL-17RB, SMAD2	CXCL8, Collagen deposition↑[36,37]

Abbreviations: AEC, Airway Epithelial Cell; AHR, Airway Hyperresponsiveness; AP-1, Activator protein 1; CCR3, C-C chemokine receptor type 3; CCL5, C-C motif chemokine ligand 5; CCL11, C-C motif chemokine ligand 11; CCL17, C-C motif chemokine ligand 17; CCL22, C-C motif chemokine ligand 22; CXCL8, C-X-C motif chemokine ligand 8; DC, Dendritic Cell; ERK1/2, Extracellular signal-regulated kinase 1/2; ILC2, Group 2 innate lymphoid cell; Gαq/11, G protein subunit alpha q/11; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; HLA-DR, Human Leukocyte Antigen – DR isotype; IGHE, Immunoglobulin Heavy Constant Epsilon; IL-4, Interleukin-4; IL-5, Interleukin-5; IL-6, Interleukin-6; IL-9, Interleukin-9; IL-13, Interleukin-13; IL-25, Interleukin-25; IL-17RB, Interleukin-17 Receptor B; IP3, Inositol trisphosphate; JunB, JunB proto-oncogene, AP-1 transcription factor subunit; MEK, Mitogen-activated protein kinase kinase; MEK1/2, Mitogen-activated protein kinase kinase 1/2; NFATc1, Nuclear factor of activated T-cells, cytoplasmic 1; NF-kb, Nuclear factor kappa-light-chain-enhancer of activated B cells; Nod2, Nucleotide-binding oligomerization domain-containing protein 2; OX-40L, OX-40 ligand; Parkin, Parkin RBR E3 ubiquitin protein ligase; PI3K, Phosphoinositide 3-kinase; PINK1, PTEN-induced putative kinase 1; PLCβ, Phospholipase C beta; PKC, Protein Kinase C; PD-L1, Programmed Death-Ligand 1; Treg, Regulatory T cell; STAT6, Signal Transducer and Activator of Transcription 6; Th2, T helper 2 cell; TH9, T helper 9 cell; TAK1, Transforming growth factor-beta-activated kinase 1; TPL2, Tumor progression locus 2; VEGF, Vascular Endothelial Growth Factor; VEGF Receptor, Vascular Endothelial Growth Factor Receptor.

receptor. Petersen et al identified a novel neutrophil population expressing IL-25 receptors, termed type 2 myeloid (T2M) cells. These cells serve as the primary source of type 2 cytokines following pulmonary IL-25 administration.[38] Their chronic allergic asthma mouse model demonstrated that when the IL-25-specific receptor is absent, type 2 cytokines associated with T2M cells are significantly reduced, proving that the IL-25 receptor plays a crucial role in mediating innate and adaptive type 2 immune responses in the lungs. Moreover, another experiment surprisingly revealed that mouse T2M cells exhibited resistance to high-dose steroid treatment, and a similar IL-4/IL-13-producing granulocyte population was identified in the peripheral blood of asthma patients. These data establish IL-25 and its receptor as novel targets for both innate and adaptive immune responses in allergic asthma.

Moreover, IL-25 is a major driver of airway remodeling in asthma. As previously mentioned, inhaled airborne allergens damage AECs and trigger the release of epithelial alarm proteins, thereby driving downstream inflammatory processes. The anti-inflammatory repair processes resulting from these abnormal inflammatory responses lead to structural changes in both large and small airways. These changes include epithelial dysfunction, goblet cell hyperplasia and metaplasia, thickening and fibrosis of the subepithelial matrix, increased airway smooth muscle mass, and enhanced angiogenesis—collectively termed airway remodeling.[39] As one of the core characteristics of asthma, airway remodeling not only leads to clinically observable airflow limitation and worsening respiratory symptoms in patients but also triggers multiple adverse consequences such as reduced lung function and diminished responsiveness to medications.

Research indicates that a high IL-25 pattern appears to be associated with poor asthma control.[40] Therefore, the driving mechanism of IL-25 is particularly crucial during airway remodeling. Within AEC itself, IL-25 release induces pro-allergic chemokine production, increased goblet cell and mucus secretion, overall epithelial cell proliferation, and AHR.[31] Research data from Yao et al indicate that IL-25 promotes airway fibrotic remodeling by inducing an epithelial-mesenchymal transition (EMT)-like pro-fibrotic phenotypic shift in bronchial epithelial cells through an autocrine-dependent mechanism.[41] Furthermore, mounting evidence indicates that IL-25 plays a pivotal role in epithelial-mesenchymal crosstalk and local tissue remodeling. Research by Gregory et al demonstrates that IL-25 directly acts on human mesenchymal cells to increase collagen deposition around airways. It enhances bronchial neovascularization by activating the PI3K/Akt and Erk/MAPK pathways, thereby increasing endothelial cell expression of VEGF.[37] Weathington et al demonstrated that IL-25 can maintain a receptor-activated phenotype in human monocytes and macrophages through synergistic stimulation with IL-4. Furthermore, IL-25 induces the expression of specific receptors via feedforward autocrine signaling, thereby establishing a positive feedback loop system capable of perpetuating inflammation.[42]

A deep analysis of IL-25's functional network reveals that its fundamental distinction from other alarmins lies in its receptor dependency and feedback signaling mechanisms. The IL-25/IL-17A-IL-17RB signaling axis is not only essential for initiating Type 2 immune responses but also self-amplifies inflammation through positive feedback loops. This characteristic necessitates that nanoparticle designs targeting IL-25 prioritize signal interruption strategies over simple

ligand blockade. These findings are unique among epithelial alarmin molecules, establishing IL-25 as a potential therapeutic target for cytokine-based therapies.

IL-33

IL-33 is another key alarmin within the epithelial alarmin family. As a dual-function protein derived from the endothelium, IL-33 exhibits multiple characteristics as both a transcriptional repressor and a cytokine.[43] Its gene is located on chromosome 9p24.1, comprising one non-coding exon (exon 1) and seven coding exons (exons 2–8).[44] IL-33 exerts its biological functions through its specific receptor ST2 (IL-33R). The ST2 receptor is widely expressed on the surface of immune cells and serves as a key molecular switch for IL-33-mediated Type 2 immune responses. Current research indicates that among the 61 asthma susceptibility loci identified in recent genome-wide association studies, variants near the IL-33 cytokine and its receptor ST2 gene carry potential significance.[45,46] Experimental data indicate that asthma-associated variants at the *IL-33* locus can mediate allele-specific regulation of activity and *IL-33* expression, thereby elevating IL-33 protein levels. The latter is constitutively and abundantly expressed in numerous human tissues. As a member of the IL-1 cytokine family, it plays a crucial role in many inflammatory processes and diseases.

Unlike the TSLP-DC-OX40L-Th2 axis described above, in allergic asthma, IL-33 operates through a distinct mechanism, directly influencing both innate and adaptive immune cells without requiring DC-mediated Th2 polarization. This divergence in signaling pathways—with IL-33 primarily activating ILC2s while TSLP engages DCs—illustrates the complementary therapeutic targets presented by different alarmins and justifies the development of alarmin-specific nanoparticle strategies. Currently, IL-33 primarily promotes the progression of Type 2 immune responses through two pathways: by interacting with group II ILC2, basophils, and natural killer (NK) cells to induce Th2 cytokine secretion; and by directly inducing Th2 cytokine production in CD4+ T cells.

In the innate immune pathway, pulmonary ILC2s, which are abundant in mucosal tissues and barrier surfaces, serve as the primary targets for IL-33.[47,48] Research indicates that the IL-33/ST2 axis is a key factor driving the extrusion and transport of bone marrow-derived ILC2 lineage cells to the lungs. It effectively induces rapid expansion of ILC2s in the lungs, thereby enhancing airway constriction capacity.[49,50] Its significance in allergic airway inflammation has been demonstrated in numerous experiments.[51–55]

In the adaptive immune pathway, IL-33 induces distinct types of effector CD4+ T cells, influencing various aspects of the Type 2 immune response through Type 2 cytokine production, airway eosinophilia, mucus hyperplasia, and IgE antibody production.[56]

Moreover, IL-33 participates in regulating adaptive immune responses and maintaining homeostasis. Research by Chen et al indicates that IL-33 directly activates regulatory T cells (Tregs) by enhancing the expression of their surface receptor ST2. This process causes Tregs to lose their ability to suppress effector T cells and instead produce Th2 cytokines, thereby compromising the immune tolerance established in the lungs following prior antigen exposure. Consequently, IL-33 promotes the progression of airway inflammation.[57] IL-33 exhibits the broadest spectrum of actions among the three alarmins, capable of both activating ILC2 and regulating adaptive immunity (Th2, Treg). This dual regulatory capacity makes it the most promising therapeutic target. Notably, IL-33's bidirectional regulation of Treg cells —activating ST2+ Tregs while suppressing conventional Tregs—reveals the complexity of immune regulatory networks. These findings indicate that IL-33 is a central mediator in triggering Type 2 immune responses.

Synergistic Effects of TSLP, IL-25, and IL-33

As described above, TSLP, IL-25, and IL-33 are potent inducers of airway inflammation, receptors and target cells were detailed in Table 2. Although their cellular functions overlap, in allergic asthma, these three molecules drive Type 2 immune responses through distinct tissue-specific signaling pathways, thereby synergistically promoting the development of airway inflammation. Studies indicate that in a mouse model of innate allergic airway inflammation induced by Alternaria extract (Alt-Ext), TSLPR and ST2 signaling pathways mutually enhance the expression and release of their respective ligands in the lungs.[58] In TSLP-DC-activated human Th2 memory cells, IL-25 maintains Th2 transcription factor expression independently of IL-4, enhancing Th2 memory cell polarization and cytokine production.[26] In an ovalbumin (OVA)-induced mouse model, TSLP, IL-25, and IL-33 act synergistically to promote cell migration and ILC2

Table 2 Alarmins and Their Target Cells

Alarmins	Receptor	Target cells	Reference
TSLP	TSLPR-IL-7Rα Complex	DC, AM	[15, 16, 20]
IL-25	IL-17RA- IL-17RB Complex	T2M cells, eosinophils, basophils	[24, 38]
IL-33	ST2 (IL-33R)	ILC2, Treg, alveolar macrophages	[46, 47, 50, 58]

Abbreviations: AM, Alveolar macrophages; DC, Dendritic cells; ILC2, Group 2 innate lymphoid cells; IL-17RB, Interleukin-17 Receptor B; IL-25, Interleukin-25; IL-33, Interleukin-33; Treg, Regulatory T cells; T2M, Type 2 myeloid cells.

activation.[59] Although studies by Vannella et al have found that the combined use of antibodies targeting TSLP, IL-25, and IL-33 does not further reduce established pulmonary inflammation or fibrosis in certain circumstances, indicating partial redundancy among these three molecules in maintaining type 2 pathology.[60] During the early inflammatory phase preceding chronicity, combined targeting of these mediators is essential for alleviating subsequent allergic airway manifestations. The central role of epithelial alarmins in initiating type 2 immune responses and the corresponding nanoparticle-based intervention strategies are schematically summarized in Figure 1, which serves as a visual roadmap for the following sections.

Application of Biomedical Nanoparticles in Targeting Epithelial Alarmin-Producing Cells

NPs, ie., functional NPs applied in the biomedical field, represent one of the most promising frontier research hotspots in recent years. Their unique physicochemical properties enable precise control over the biodistribution of drug payloads and the rate of drug release, facilitating site-specific delivery, deposition, and cellular uptake. This achieves targeted drug delivery, thereby enhancing drug efficacy and therapeutic outcomes.[61,62] Therefore, biomedical nanoparticles are frequently developed as drug delivery systems to overcome the limitations of traditional delivery methods. Currently, with the continuous

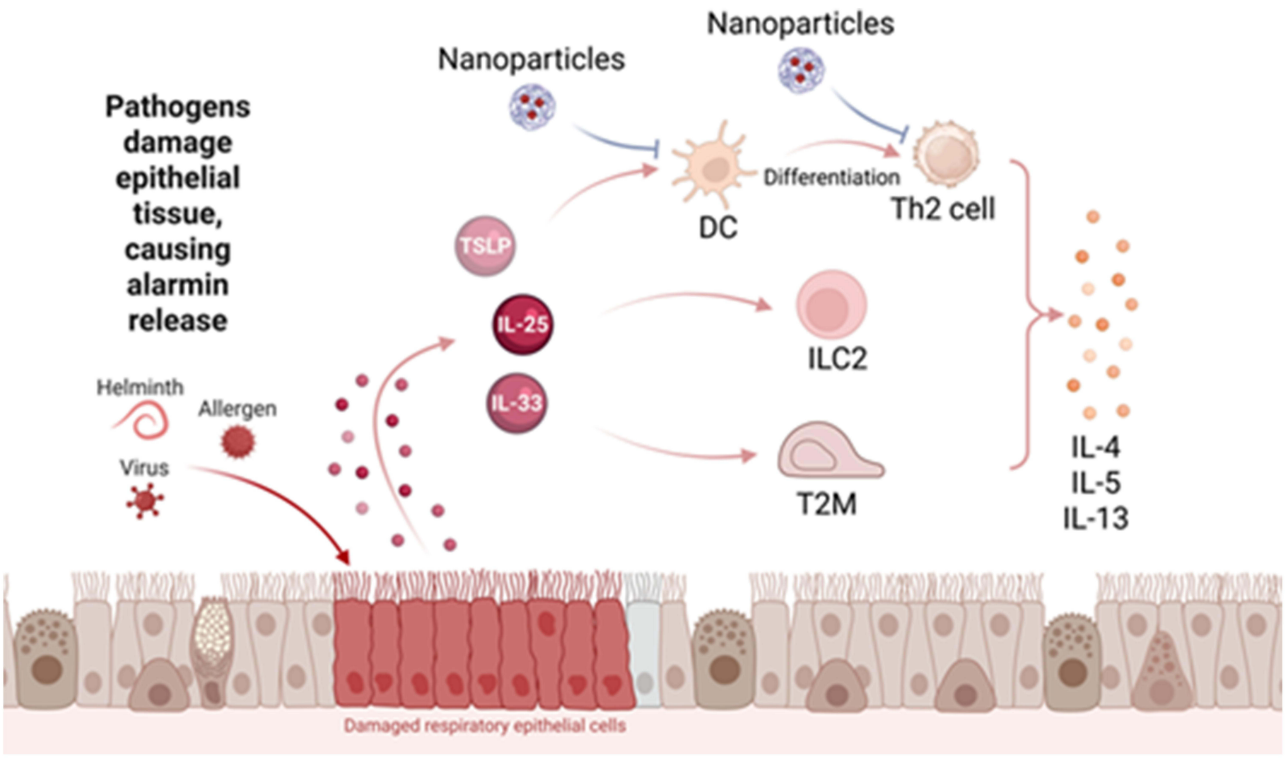

Figure 1 Schematic overview of the epithelial alarmin axis and nanoparticle-based intervention strategies in allergic asthma.

advancement of nanomedicine technology, the structural design of nanoparticle drug delivery systems has become increasingly complex. They exhibit high diversity in chemical composition, size, morphology, electrostatic charge, hydrophobicity, surface chemistry, and other properties, aiming to leverage biomaterials and biomedical engineering innovations to overcome biological barriers and patient heterogeneity.[63] Among these, NPs with immunomodulatory properties represent emerging tools for developing anti-infective therapies, inducing immune tolerance, and regulating inflammation, offering significant therapeutic potential. Since the introduction of the epithelial barrier hypothesis, the pathophysiological mechanisms of allergic asthma have been further refined. Immunomodulatory NPs targeting epithelial alarmin cells have consequently emerged as a promising new generation of asthma treatment strategies.

Innate Immune Cells

Dendritic Cells

DCs are key players in Type 2 immune responses. As professional antigen-presenting cells (APCs) bridging innate and adaptive immunity, DCs bear significant responsibility in initiating and regulating the dynamic process of Type 2 immune responses. Extensive research analyses indicate that most airborne allergens can directly or indirectly activate DC sensitization via epithelial alarmins, amplifying Th2 cell-mediated airway inflammation during the effector phase of allergic asthma.[64–66] These findings have positioned tolerance-inducing nanoparticles (tNPs) that induce DC differentiation into tolerogenic DCs as promising candidates for allergic asthma treatment. It is well established that DCs differentiate into either immunogenic DCs or tolerogenic DCs based on the regulation of different microenvironmental signals. The former phagocytose exogenous antigens and present them to naive CD4+ T cells to initiate a Th2 immune response, while the latter maintain immune tolerance, preventing excessive immune reactions to self-antigens or harmless antigens. Based on this, tNPs that can precisely target DCs and induce tolerogenic DC differentiation, while exhibiting good stability, biocompatibility, and immunomodulatory properties, have become a hotspot for development in asthma treatment strategies.

tNPs, which carry allergens or self-antigens, can target APCs and deliver tolerance-coordinating signals to promote antigen-specific immune responses, demonstrating significant potential in inducing tolerance-inducing immunity. Over the past decades, researchers have explored three distinct delivery strategies for tNPs. Among these, tNPs simultaneously carrying both allergens and immunomodulators have been demonstrated to induce antigen-specific tolerance by delivering allergens to APCs, thereby inducing the differentiation of tolerogenic APCs.[67] This form of treatment, also known as allergen-specific immunotherapy (AIT), has yielded encouraging results in treating inflammatory conditions such as allergies and autoimmune diseases, representing a potential curative approach for asthma.[68]

In recent years, Zhao et al have developed biodegradable tNPs loaded with the allergen OVA and the immunomodulator rapamycin.[69] These tNPs can be loaded onto microneedle tips via centrifugation to form sustained-release microneedles for transdermal delivery of tNPs. The PLGA@OVA-Rapa formulation exhibits sustained release within the skin for over 96 hours, inducing the generation of allergen-specific Treg cells. This reduces pulmonary inflammation, mucus, and collagen accumulation, ultimately providing effective relief from allergic symptoms. Research indicates that these nanoscale needles can overcome the skin barrier to deliver drugs non-invasively and painlessly into the epidermis and dermis, significantly enhancing the transdermal delivery efficiency of biopharmaceuticals.[70] Following successful co-delivery of OVA and rapamycin to the dorsal skin of mice via microneedles, expression of DC co-stimulatory molecules was significantly downregulated, effectively inducing antigen-specific immune tolerance and alleviating asthma symptoms.

Additionally, sublingual delivery represents a promising therapeutic strategy. Sadeghi et al engineered Exo-Ova composite tNPs decorated with DC-specific aptamers, combining the allergen OVA with mesenchymal stem cell-derived exosomes (MSC-exos) for targeted delivery to DCs. Their therapeutic efficacy was evaluated via sublingual immunotherapy in a mouse model of allergic asthma.[71] Experimental results demonstrate that this complex precisely delivers allergens to dendritic cells within the sublingual mucosa, significantly reducing the allergen dose required for sublingual immunotherapy and effectively minimizing adverse reactions associated with AIT. Moreover, these tNPs exhibit outstanding immunomodulatory capabilities. MSC-exos, a subtype of naturally occurring extracellular vesicular nanoparticles, possess inherent stability, biocompatibility, minimal immunogenicity, and leverage the potent immunomodulatory and regenerative properties of MSCs. They play a crucial role in diverse therapeutic fields including drug delivery and immune regulation.[72]

Extensive research has demonstrated its immunomodulatory capacity in inflammatory airway diseases.[73–76] Undoubtedly, MSC-exos are emerging as a highly promising therapeutic vehicle for allergic asthma. Administration results in mouse models further corroborate this finding. Data indicate that tNPs can enhance the therapeutic efficacy of sublingual immunotherapy, significantly inducing Treg cell immune responses to alleviate airway and pulmonary inflammation.[77] This offers a novel strategy for applying MSC-exos in the immunotherapy of allergic asthma.

DCs, serving as a bridge between innate and adaptive immunity, act as both early respo410nders to alarmins and key initiators of Th2 polarization in TSLP-driven asthma inflammation. Current DC-targeted NP strategies have evolved into three major technical pathways: transdermal microneedle sustained-release systems, sublingual aptamer-targeted delivery, and exosome-based drug-loading platforms. The core rationale behind these designs is to precisely modulate the expression of DC co-stimulatory molecules, redirecting immune responses from pathogenic Th2 to tolerogenic Treg pathways, thereby achieving a paradigm shift from "anti-inflammatory" to "tolerogenic" effects.

Alveolar Macrophages

AM are the most abundant immune cells in the lungs. As mentioned earlier, AM exposed to prototypical cytokines or TLR agonists can differentiate into two functionally distinct subsets: pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages. The former exhibit potent antibacterial and anticancer activity, aiding in pathogen clearance during infections. The latter participate in Th2 responses, parasite clearance, and inflammation suppression, promoting tissue repair, wound healing, angiogenesis, and fibrosis. Both are alternately activated during inflammatory processes, maintaining homeostasis through a balanced ratio. Epithelial alarmin proteins like TSLP activate AMs through signaling pathways and induce their polarization toward M2 macrophages, thereby activating Th2 cells and driving the development of allergic asthma. Consequently, targeting signaling pathways that promote M2 macrophage polarization to remodel AM polarization and restore pulmonary homeostasis may represent a potential strategy for immunomodulatory NP-based therapies against allergic asthma. Increasing research supports the feasibility of this approach. Recently, Pei et al developed a biomimetic NP (EM-PLGA@Dnmt3aos $^{\text{smart silencer}}$) that leverages the "homing" properties of AMs to precisely deliver small nucleic acid drugs to lung and airway inflammatory tissues by coating M2 macrophage exosome membranes to modify siRNA-loaded poly(lactic-co-glycolic acid) (PLGA) NPs, enhancing PLGA targeting to pulmonary M2 macrophages. This enables efficient delivery of therapeutic Dnmt3aos$^{\text{smart silencer}}$ to suppress M2 polarization, effectively treating allergic airway inflammation in mice.[78] Wu et al developed cationic liposomes loaded with *Mbd2* siRNA that specifically target AMs via macrophage phagocytosis. By reducing *Mbd2* expression in AMs, this approach eliminates M2 macrophage polarization, significantly reversing OVA-induced allergic asthma symptoms in mice, including airway inflammation and excessive mucus secretion.[79] Xin et al purified extracellular vesicles containing *Emu-miR-10a-5p* from the scolex of *Echinococcus multilocularis*, which can interfere with leukemic factors and JAK1-STAT3 signaling in the lungs of allergic asthma mice. Through a cross-species approach, it targets and binds to leukemic pathogenic factors to inhibit M2 macrophage polarization, thereby alleviating OVA-induced allergic asthma.[80] These findings demonstrate that inhibiting M2 macrophage polarization through diverse mechanisms suggests that developing NP delivery strategies targeting M2 macrophages represents a promising therapeutic approach for asthma. Notably, distinct NPs exhibit markedly different mechanisms for inhibiting M2 polarization, encompassing focused epigenetic regulation, gene targeting, and cross-species regulatory pathways. Intervention through these diverse pathways consistently demonstrates superior efficacy compared to conventional asthma medications while providing a foundation for mechanistic research.

Adaptive Immune Cells

Th2 Cells

Th2 cells are central participants in the pathogenesis of allergic asthma and the ultimate targets for epithelial alarmins in inducing inflammation. They mediate IgE production and inflammatory cell recruitment by secreting multiple cytokines, triggering immediate allergic reactions and exacerbating airway inflammation.[81] It is well established that IgE serves as the primary initiator of immediate allergic reactions. Upon allergen exposure, IgE cross-links with its specific allergen, rapidly activating bound mast cells and basophils to release inflammatory mediators such as histamine and leukotrienes.

This triggers immediate-phase asthma responses including bronchospasm and mucosal edema. Concurrently, inflammatory cells such as eosinophils—targeted by Th2 cytokines—accumulate in the airways. These cells release inflammatory mediators like granule proteins, damaging AECs and disrupting airway structure. This triggers late-phase asthma responses including AHR and airway remodeling, transforming asthma from acute episodes into a chronic, difficult-to-treat condition requiring long-term management. Therefore, drug delivery and immunomodulation targeting Th2 cell differentiation and function have become primary strategies for asthma treatment in nanomedicine. Based on different mechanisms of action, NPs can be categorized into the following two types.

First are NPs that suppress Th2 cell differentiation. In allergic asthma, an imbalance in the Th1/Th2 cell ratio has long been recognized as the root cause of airway inflammation. Therefore, shifting the immune response from the disease-promoting Th2 type to the non-pathogenic Th1 type—thereby bringing the immune system into a more balanced state—may help alleviate asthma symptoms. In recent years, novel NP delivery systems designed to modulate the Th1/Th2 response balance have proliferated.

Cell membrane-coated nanoparticles (CNPs) are one such example. As the name suggests, these are bio-inspired nanoparticles synthesized by modifying cell membranes from natural sources. They possess dual characteristics of both the original nanoparticles and the biological interface of cell membranes, demonstrating therapeutic potential in multiple fields including drug delivery, immunotherapy, and tumor targeting.[82] In allergic asthma, Jin et al designed a bioinspired nanoparticle delivery system, PM@Ber-NPs, coated with platelet membranes. They loaded the natural herbal compound berberine into the nanomaterial PLGA and administered it intranasally to target delivery to the airways and inflammatory regions of the lungs, thereby suppressing the inflammatory response.[83] Berberine is a benzoisoquinoline alkaloid extracted from the Chinese medicinal plant Berberis, which effectively suppresses T-selectin-like protein (TSLP) expression. It downregulates Th2 cells and their cytokine levels, thereby inhibiting asthma progression.[84] However, its low water solubility and bioavailability significantly limit its therapeutic efficacy. To harness its anti-inflammatory effects, researchers developed a nanoscale membrane vesicle platform derived from platelets. This platform shields the encapsulated mimetic NPs from phagocytic uptake by macrophages, enabling precise targeting and retention at inflammatory sites.[85] Studies demonstrate that these bio-inspired NPs exhibit enhanced cellular uptake and targeted retention within inflammatory microenvironments. This cell membrane-coated biomimetic drug delivery system enhances the stability and active targeting capabilities of NPs by coating extracellular vesicles onto existing biocompatible NPs like PLGA. This approach significantly improves drug efficacy in airway inflammatory diseases such as allergic asthma, offering a promising platform for advancing asthma treatment.

Beyond this, novel nanocarrier systems for delivering bioactive proteins and peptides represent an exciting avenue of research. Song et al proposed a novel cathepsin B-activated nanocarrier MPP-Trp for asthma immunotherapy. This involved obtaining the cathepsin B-reactive peptide fragment Fmoc-IALLIPF-GFLG-W via solid-phase synthesis and combining it with the anti-inflammatory agent tryptophan (Trp), and hydrophilic-modified copolymer polyethylene glycol (PEG). This PEG, which exhibits excellent biocompatibility, water dispersibility, and stability, demonstrates remarkable sensitivity and selectivity toward cathepsin B, a key enzyme in asthma-related inflammation.[86] Research indicates that MPP-Trp exerts immunomodulatory effects on Th1/Th2 cell populations, significantly alleviating OVA-induced allergic asthma by shifting the immune response toward Th1 dominance. This approach may offer a safer, more sustainable solution for asthma management.

Rochman et al encapsulated nucleoside-modified allergen-encoding mRNA vaccines for allergy prevention and treatment within lipid nanoparticles (LNPs) exhibiting adjuvant properties, forming allergen-specific mRNA-LNPs. This enabled mRNA to shape $CD4^+$ and $CD8^+$ T cell responses and induce allergen-specific IgG1 and IgG2 antibodies at lower doses, block Th2 cell activation, and generate anti-allergic environments to prevent allergic manifestations such as experimental asthma. This demonstrates a promising approach for preventing and treating allergic diseases.[87]

Next are NPs that suppress Th2 cytokine expression. In allergic asthma, the transcription factor *GATA-binding protein 3 (GATA-3)* is a key regulator of Th2-specific cytokine transcription. It directly binds to the promoter and enhancer regions of the IL-4, IL-5, and IL-13 genes to initiate their transcription, thereby inducing cytokine expression.[88] It is evident that the expression of these Th2 cytokines is the direct cause of allergic airway inflammation. Consequently, NP delivery systems targeting *GATA-3* expression to suppress Th2 cytokine production have emerged. In recent years, Gavitt et al attempted to

cross-link matrix metalloproteinase-9 (MMP-9)-specific peptide substrates with DNAzyme-functionalized nucleic acid nanocapsules (DNAzyme-NAN) to achieve *GATA-3*-specific gene regulation in allergic asthma.[89] Previously, their group had demonstrated that DNAzyme-NAN is a promising therapeutic nucleic acid delivery vehicle capable of achieving up to 60% *GATA-3* mRNA knockdown in MCF-7 cells without the use of toxic transfection agents.[90] Based on this, they hypothesized that increased MMP-9 during airway inflammation could enhance the degradation specificity of the peptide-crosslinked *GATA-3* DNAzyme-NAN, enabling its rapid breakdown in the lungs to specifically knock down *GATA-3*. Experimental results demonstrate that peptide-conjugated *GATA3* DNAzyme-NANs effectively deliver *GATA-3*-specific DNA enzymes to immune cells and regulate eosinophil levels in asthmatic mice, potentially reducing the severity of asthma symptoms in human patients. Furthermore, Jürgens et al engineered transferrin-conjugated lipid nanoparticles (Tf-LNPs) for Th2 cell targeting in allergic asthma. Leveraging the abundant expression of transferrin receptors (TfRs) on Th2 cell surfaces, they achieved specific delivery of therapeutic siRNA to Th2 cells, enhancing Tf-dependent cellular uptake and therapeutic efficacy of *GATA-3*.[91] Tf-LNP enhances the efficiency and recovery rate of *GATA-3* knockdown in the NP delivery system. In summary, by precisely regulating Th2 cell differentiation and function, nanomedicine has opened new avenues for treating allergic asthma. These innovative therapeutic approaches not only improve drug targeting and efficacy but also lay the foundation for developing safer, more effective asthma management strategies.

Regulatory T Cells

Treg cells are a subset of T cells with immunosuppressive functions that play a crucial role in maintaining immune homeostasis and tolerance to harmless antigens. In allergic asthma, Treg cells precisely downregulate Th2 cells through three mechanisms: directly inhibiting Th2 cell activation, secreting anti-inflammatory factors to neutralize Th2 effects, and depleting essential cytokines for Th2 cells, thereby blocking the Th2-mediated Type 2 immune response.[92–95] However, extensive research indicates that both the number and function of Treg cells are significantly suppressed by epithelial alarmins.[32,57,96] To this end, researchers customized nanoparticles capable of reducing epithelial alarmin expression while promoting Treg cell differentiation and survival, thereby restoring immune homeostasis and tolerance within the body. In recent years, Liu et al designed tNPs surface-modified with apolipoprotein B peptide sequences or mannan oligosaccharides. By targeting scavenger or mannose receptors, these nanoparticles selectively delivered the allergen OVA to naturally tolerant APCs—hepatic sinusoidal endothelial cells—thereby inducing Treg cell production.[97] In vitro and in vivo experiments demonstrated that these tNPs effectively enhanced the uptake of OVA by hepatic sinusoidal endothelial cells and the production of anti-inflammatory cytokines IL-10 and transforming growth factor TGF-β. Through tissue infiltration of Treg cells, they significantly suppressed OVA-induced allergic airway inflammation.[97] Furthermore, Li et al encapsulated IL-10 within AM-membrane-coated PLGA particles. Leveraging the biological properties of the AM membrane, this approach enabled efficient delivery of the therapeutic cytokine to the lungs, substantially increasing IL-10 bioavailability. This intervention improved the Th2/Treg response balance and alleviated airway inflammation.[98] These findings suggest that using nanoparticles to induce Treg cell generation represents a promising strategy for asthma management. Liver-targeted tNPs and AM-membrane-coated NPs may form complementary strategies. The former induces Tregs by enhancing antigen presentation capacity in hepatic sinusoidal endothelial cells, while the latter leverages the innate homing properties of macrophages to improve pulmonary targeting efficiency, potentially enabling synergistic regulation of the "liver-lung axis."

In summary, the application of biomedical nanoparticles in epithelial alarmin cell targeting demonstrates a multi-level precision treatment strategy: at the innate immune level, DC-targeted tNPs reshape the Th1/Th2 balance, while AM-membrane-modified bionic NPs target macrophage polarization pathways; At the adaptive immune level, they employ dual pathways of inhibiting Th2 cell differentiation and blocking cytokine expression, while simultaneously restoring immune tolerance through Treg cell induction and functional recovery. These NPs not only address the issues of low bioavailability and poor targeting inherent in traditional drugs but also achieve multi-targeted intervention from the cellular to the molecular level through their unique physicochemical properties, offering novel solutions to overcome drug resistance and side effects in asthma treatment. Additionally, beyond the aforementioned NPs specifically targeting the epithelial alarmin signaling pathway, various NPs have emerged in recent years that suppress allergic airway inflammation through different mechanisms (Table 3). These nanocarriers validate the broad application potential of NPs in asthma treatment from multiple perspectives.

Table 3 Details of NPs Suppressing Allergic Airway Inflammation

Nanocarrier	Functional Components	Target Molecule	Reference
PEG-LNP	antimiR-145	mmu-miR-145a-5p	[96]
PEG Microspheres/Nanospheres	Clonazepam	TMEM16A	[97]
LNP	siGAPDH	GAPDH gene	[98]
Chitosan-Tripolyphosphate Microspheres	Naringin and Doxorubicin	PDE3, PDE4	[99]
β-glucan	β-glucan	GPx4, SOD and CAT	[100]
PAMAM-B-NS	B-NS	cfDNA, NET, RONS	[101]

Abbreviations: B-NS, Boron nanosheets; CAT, Catalase; cfDNA, Cell-free DNA; GAPDH, Glyceraldehyde-3-phosphate dehydrogenase; GPx4, Glutathione peroxidase 4; LNP, Lipid nanoparticle; mmu-miR-145a-5p, Mus musculus microRNA 145a-5p; NET, Neutrophil extracellular traps; PDE3, Phosphodiesterase 3; PDE4, Phosphodiesterase 4; PEG, Polyethylene glycol; PAMAM, Polyamidoamine; RONS, Reactive oxygen and nitrogen species; siGAPDH, Small interfering RNA targeting glyceraldehyde-3-phosphate dehydrogenase; SOD, Superoxide dismutase; TMEM16A, Transmembrane member 16A.

Application of Biomedical Nanoparticles in Conventional Asthma Therapies

Beyond immunomodulation, delivering conventional asthma medications such as steroids using biomedical nanoparticles is also a common approach to asthma management in the field of nanomedicine.[99] Budesonide (BUD) is a commonly used ICS medication for asthma that effectively suppresses type 2 inflammatory responses and repairs airway epithelium, reducing the release of epithelial alarmin. The SMART (Single Maintenance and Reliever Therapy) regimen combining budesonide with the long-acting bronchodilator formoterol is currently prioritized in asthma management guidelines by the National Asthma Education and Prevention Program Coordinating Committee and the GINA for sustained maintenance and rapid relief of asthma symptoms.[100,101] However, inhalers have drawbacks such as medical-legal issues, high drug costs, and poor patient compliance.[102,103] Therefore, there is an urgent need for novel therapeutic interventions to enhance the bioavailability of budesonide in the lungs, thereby improving its therapeutic efficacy to control symptoms and exacerbations in asthma patients. To address this, Zuo et al developed BUD-LNPs by incorporating budesonide into LNP systems via thin-film hydration. This approach leverages the LNP's ability to encapsulate hydrophobic substances, thereby improving budesonide's bioavailability, preventing premature degradation, and ensuring controlled-release delivery. The study demonstrated that BUD-LNPs exhibit excellent biocompatibility both in vitro and in vivo, along with superior therapeutic efficacy compared to free BUD. This approach holds great promise for the development of novel drugs for future asthma treatment.[104] Moreover, the hydrophilic/hydrophobic surface properties of LNP enhance drug delivery by prolonging retention time and boosting systemic absorption. In an OVA-induced allergic asthma mouse model, Liu et al designed a highly hydrophilic LN loaded with BUD.[105] Mechanistic studies indicate that this LNP prolongs the pulmonary residence time of BUD by reducing alveolar epithelial transport and avoiding clearance by alveolar macrophages, thereby decreasing dosing frequency and significantly alleviating asthma symptoms.

Additionally, numerous natural products such as curcumin and quercetin exhibit anti-inflammatory effects. However, they typically suffer from poor water solubility, rapid metabolism, and low bioavailability, hindering their optimal therapeutic efficacy. Research indicates that curcumin nanoformulations can significantly enhance its bioavailability and drug stability.[106]

In the field of traditional asthma treatment, biomedical nanoparticles have significantly enhanced the therapeutic efficacy of existing drugs through innovative delivery strategies. Addressing issues such as low bioavailability, poor patient compliance, unstable formulations, unclear targeting, and inappropriate delivery timing, researchers have developed nanoparticle drug delivery systems. These systems improve the bioavailability of hydrophobic drugs while enabling controlled-release administration to prevent premature degradation. These studies confirm that by rationally designing nanoparticle surface properties and drug-loading mechanisms, the delivery efficiency and clinical efficacy of traditional asthma medications can be improved, providing crucial technical support for developing next-generation asthma treatment solutions.

Beyond these preclinical and formulation-based advances, several nanoparticle-based therapies have entered clinical trials for asthma and allergic diseases, marking a critical step toward clinical translation. These include AZD-1419 (TLR9 agonist-conjugated nanoparticles; NCT02898662) for moderate-to-severe asthma, which completed Phase II evaluation with time to first loss of asthma control as the primary endpoint; Inflamax TSLP-siRNA (siRNA-loaded lipid

nanoparticles; NCT05243550), a Phase I/IIa study assessing safety and *TSLP* knockdown in mild-to-moderate asthma; and AllerT (liposomal allergen peptides; NCT04072796), a Phase IIb trial in house dust mite-allergic patients that met its primary endpoint of improved Combined Symptom and Medication Score. These ongoing studies provide critical proof-of-concept for the translational potential of the strategies discussed throughout this review and highlight the growing maturity of nanomedicine approaches for respiratory diseases.[107–109]

Conclusion and Prospect

This review has systematically examined the emerging frontier of biomedical nanoparticles designed to intercept the epithelial alarmin axis in allergic asthma. The reviewed studies demonstrate quantifiable therapeutic advances that transcend generic claims: DNAzyme-functionalized nucleic acid nanocapsules achieve up to 60% *GATA-3* mRNA knockdown in immune cells, offering a precision gene-regulation platform inaccessible to antibody-based biologics; MSC-exosome-based tolerogenic nanoparticles reduce the required allergen dose for sublingual immunotherapy by approximately 5-fold while maintaining efficacy, addressing a critical safety limitation of conventional allergen-specific immunotherapy; and budesonide-loaded lipid nanoparticles prolong pulmonary residence time from 4 hours to 24 hours by avoiding macrophage clearance, transforming a standard-of-care corticosteroid into a sustained-release formulation with reduced dosing frequency.

These advances must be contextualized within the evolving therapeutic landscape. Compared to biologic agents requiring subcutaneous administration every 2–4 weeks at an annual cost of $20,000–40,000 per patient with variable response rates of 50–70%, NP-based approaches offer the potential for inhaled or transdermal delivery, targeting of intracellular transcription factors, and enhanced patient adherence through reduced dosing frequency. With approximately 26 million patients globally suffering from severe asthma inadequately controlled by current therapies, even modest improvements in efficacy or accessibility could yield substantial clinical and economic impact. The path forward requires scalable GMP manufacturing, biomarker-driven patient stratification, and rigorous head-to-head trials against standard-of-care biologics to establish the clinical superiority and cost-effectiveness that will ultimately determine whether these platforms fulfill their transformative potential.

Abbreviations

AECs, Airway epithelial cells; AHR, Airway hyperresponsiveness; AIT, Allergen-specific immunotherapy; AM, Alveolar macrophages; APCs, Antigen-presenting cells; bFGF, Basic fibroblast growth factor; BUD, Budesonide; CNPs, Cell membrane-coated nanoparticles; DAMPs, Damage-associated molecular patterns; DCs, Dendritic cells; DNAzyme-NAN, DNAzyme-functionalized nucleic acid nanocapsules; EMT, Epithelial-mesenchymal transition; GATA-3, GATA-binding protein 3; GBD, Global Burden of Disease; GINA, Global Initiative for Asthma; ICS, Inhaled corticosteroids; ILCs, Innate lymphoid cells; IL-25, Interleukin-25; IL-33, Interleukin-33; LNP, Lipid nanoparticle; LABA, Long-acting beta-agonists; MDC, Macrophage-derived chemokine; MSC-exos, Mesenchymal stem cell-derived exosomes; MMP-9, Metalloproteinase-9; NPs, Nanoparticles; NK, Natural killer; OVA, Ovalbumin; OX40L, OX40 ligand; PDGF-β, Platelet-derived growth factor-beta; PEG, Polyethylene glycol; TARC, Thymus and activation-regulated chemokine; TGF-β, Transforming growth factor-beta; Tregs, Regulatory T cells; TSLP, Thymic stromal lymphopoietin; tNPs, Tolerance-inducing nanoparticles; TfRs, Transferrin receptors; Tf-LNPs, Transferrin-conjugated lipid nanoparticles; Trp, Tryptophan; TSLP, T-selectin-like protein; Th2, Type 2 helper T; T2M, Type 2 myeloid; VEGF, Vascular endothelial growth factor.

Acknowledgments

Neither ChatGPT nor other generative language models were used for the ideation or writing process.

Disclosure

The author reports no conflicts of interest in this work.

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