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Article

Airway Remodeling: Its Role in the Pathogenesis of Asthma and Ways of Prevention

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Abstract: This article analyzes airway remodeling in bronchial asthma — structural changes in the epithelium, basement membrane, smooth muscles, blood vessels, and extracellular matrix. The main mechanisms of remodeling, including chronic inflammation, growth factor dysregulation, and metalloproteinase activity, are examined in detail along with their clinical significance. The role of remodeling in driving irreversible airway obstruction and bronchial hyperreactivity is discussed comprehensively. Modern strategies for preventing airway remodeling are reviewed, encompassing early-stage inhaled corticosteroid therapy, targeted biologic agents, and emerging anti-fibrotic approaches. The article synthesizes evidence from recent clinical trials and guidelines, including GINA 2024 recommendations, to present a clinically applicable framework for managing airway remodeling in asthma patients.

Keywords: bronchial asthma, airway remodeling, basement membrane thickening, smooth muscle hypertrophy, angiogenesis, TGF-β1, epithelial–mesenchymal transition, anti-remodeling therapy, biologic agents.

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1. Introduction

Bronchial asthma is one of the most prevalent chronic respiratory diseases worldwide, affecting more than 300 million people across all age groups and socioeconomic backgrounds[1]. Traditionally, asthma has been viewed primarily as a disorder of reversible airway obstruction and eosinophilic inflammation driven by Th2 immune responses. However, accumulating evidence over the past two decades has fundamentally shifted this paradigm, revealing that asthma is also characterized by profound structural alterations of the airway wall — a process collectively termed airway remodeling[2].

Airway remodeling refers to persistent, progressive, and partially irreversible changes occurring in all structural components of the airway wall, including the epithelium, basement membrane, lamina propria, airway smooth muscles, and the pulmonary vasculature[3]. These structural changes develop in parallel with chronic inflammation and may, in fact, precede the onset of clinical symptoms — a finding that has been documented even in young children with early-stage atopic disease[4].

The clinical relevance of airway remodeling is considerable. Remodeling contributes to irreversible airway obstruction, progressive decline in forced expiratory volume in one second (FEV_1), and increased resistance to corticosteroid therapy — factors that are collectively associated with worsening disease severity and diminished quality of life[5].

Moreover, the extent of remodeling has been correlated with asthma severity across GINA classification stages, underscoring its pathophysiological centrality[6].

Despite its significance, airway remodeling remains inadequately addressed in clinical practice. Current therapeutic strategies — including inhaled corticosteroids (ICS) and long-acting bronchodilators — primarily target airway inflammation and bronchoconstriction rather than structural remodeling per se. The emergence of biologic agents targeting specific inflammatory pathways has opened new possibilities for modulating remodeling, but significant knowledge gaps persist regarding optimal timing, patient selection, and long-term outcomes[7].

The objective of this review is to systematically analyze the mechanisms underlying airway remodeling in asthma, elucidate its role in disease pathogenesis, and critically evaluate modern strategies for its prevention and management.

2. Materials and Methods

2.1. Study Design

This study was conducted as a structured analytical review of the peer-reviewed literature, synthesizing evidence from experimental studies, clinical trials, systematic reviews, and international clinical guidelines pertaining to airway remodeling in bronchial asthma.

2.2. Literature Search Strategy

A comprehensive search of electronic bibliographic databases was performed, including PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library. Additionally, the Global Initiative for Asthma (GINA) 2024 strategy document was reviewed for evidence-based clinical recommendations[8]. The search was conducted using the following Medical Subject Headings (MeSH) and free-text terms: "airway remodeling," "bronchial asthma," "epithelial–mesenchymal transition," "transforming growth factor-beta," "matrix metalloproteinases," "smooth muscle hypertrophy," "subepithelial fibrosis," and "anti-remodeling therapy."

2.3. Inclusion and Exclusion Criteria

Studies published between 2015 and 2024 were included to ensure contemporaneous relevance. Eligible publications comprised original research articles, meta-analyses, randomized controlled trials, and authoritative clinical guidelines published in English or Russian. Case reports, conference abstracts, and non-peer-reviewed publications were excluded. Studies with sample sizes fewer than 20 participants were also excluded to minimize the risk of bias in estimation.

2.4. Data Extraction and Analysis

Data were extracted independently and organized thematically according to the principal components of airway remodeling: structural changes, molecular mechanisms, pathophysiological consequences, and therapeutic strategies. The analytical approach included separate assessment of each structural component of remodeling, evaluation of the roles of specific cytokines and growth factors, and critical appraisal of pharmacological and biologic anti-remodeling interventions, including their reported efficacy levels and mechanisms of action.

3. Results

3.1. Structural Components of Airway Remodeling

Airway remodeling in asthma encompasses a spectrum of structural alterations affecting every layer of the bronchial wall. These changes are not uniform across patients and may vary depending on disease severity, phenotype, age of onset, and individual genetic predisposition[9]. The principal structural components and their clinical significance are summarized in Table 1.

Table 1. Structural Components of Airway Remodeling in Bronchial Asthma.

Structure	Observed Change	Clinical Significance
Epithelium	Desquamation, goblet cell metaplasia, mucous hypersecretion	Impaired mucociliary clearance, barrier dysfunction, increased cytokine release
Basement membrane	Subepithelial fibrosis, collagen deposition, thickening	Bronchial hyperreactivity, irreversible obstruction
Airway smooth muscle	Hypertrophy and hyperplasia of smooth muscle bundles	Increased propensity to bronchoconstriction, airflow limitation
Pulmonary vasculature	Angiogenesis, vessel wall thickening, increased permeability	Mucosal edema, plasma exudation, airway narrowing
Extracellular matrix (ECM)	Accumulation of collagen I/III, fibronectin, proteoglycans	Structural basis for irreversible remodeling

The epithelial layer is among the first to be affected. Goblet cell metaplasia and mucous hypersecretion increase airway resistance and reduce mucociliary clearance efficiency[10]. Subepithelial fibrosis — characterized by the deposition of collagen types I, III, and V, as well as fibronectin and tenascin — is a hallmark feature detectable even in mild asthma and correlates with disease severity[11]. Smooth muscle mass has been reported to be increased by up to 200% in fatal asthma cases compared to non-asthmatic controls, with hypertrophied and hyperplastic smooth muscle bundles contributing substantially to fixed airflow limitation.

3.2. Molecular Mechanisms of Airway Remodeling

The molecular architecture underlying airway remodeling involves a complex interplay of pro-inflammatory cytokines, growth factors, and proteolytic enzymes operating across multiple cellular compartments[12].

Among inflammatory mediators, interleukin (IL)-4, IL-5, and IL-13 play central roles in Th2-driven remodeling by activating fibroblasts and promoting collagen synthesis. IL-13, in particular, is a potent inducer of goblet cell metaplasia and mucus production. IL-17, produced predominantly by Th17 lymphocytes, drives neutrophilic inflammation and contributes to matrix degradation through upregulation of matrix metalloproteinases (MMPs). Tumor necrosis factor-alpha (TNF-α) further amplifies MMP activity and activates nuclear factor-kappa B (NF-κB) signaling pathways[13].

Transforming growth factor-beta 1 (TGF-β1) is the most potent and extensively studied pro-fibrotic mediator in asthmatic airways. It promotes basement membrane thickening, stimulates fibroblast-to-myofibroblast differentiation, and inhibits metalloproteinase activity, thereby favoring ECM accumulation[14]. Vascular endothelial growth factor (VEGF) drives angiogenesis and increases vascular permeability, while platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) promote smooth muscle proliferation.

A critically important mechanism is the epithelial–mesenchymal transition (EMT), whereby bronchial epithelial cells acquire a mesenchymal phenotype characterized by loss of E-cadherin, gain of N-cadherin and vimentin expression, and acquisition of migratory and fibrogenic properties. EMT is induced principally by TGF-β1 and represents a major source of subepithelial myofibroblasts contributing to fibrosis[15].

3.3. The Role of Remodeling in Asthma Pathogenesis

Airway remodeling contributes to asthma pathogenesis through multiple interdependent mechanisms that progressively worsen lung function and increase disease

severity over time. The temporal evolution of remodeling across disease stages is presented in Table 2.

Table 2. Temporal Progression of Airway Remodeling in Bronchial Asthma.

Disease Stage	Predominant Remodeling Process
Early (childhood onset)	Subepithelial fibrosis, goblet cell hyperplasia, early basement membrane thickening
Intermediate (adult asthma)	Smooth muscle hypertrophy, progressive basement membrane thickening, angiogenesis
Late (severe/refractory asthma)	Irreversible obstruction, marked FEV_1 decline, steroid resistance, extensive ECM deposition

A pivotal clinical correlation has been established between the thickness of the reticular basement membrane and the annual rate of FEV_1 decline ($r = 0.72$, $p < 0.001$), highlighting the direct functional consequences of structural remodeling. Furthermore, smooth muscle mass has been shown to correlate significantly with GINA severity stage, establishing structural quantification as a potential biomarker for disease assessment. Notably, remodeling begins in childhood, prior to the onset of atopic sensitization in some cohorts, challenging the traditional assumption that inflammation invariably precedes structural changes.

3.4. Prevention and Treatment Strategies

Given the irreversibility of established airway remodeling, prevention through early and sustained therapeutic intervention represents the most effective strategy for preserving lung function. Table 3 provides a comprehensive summary of current and emerging anti-remodeling approaches.

Table 3. Anti-Remodeling Strategies in Bronchial Asthma: Mechanisms and Efficacy Levels.

Strategy / Agent	Mechanism of Action	Evidence Level
Early ICS initiation	Suppression of eosinophilic inflammation; reduction of TGF-β1 secretion	High — GINA Grade A
ICS + LABA combination	Synergistic anti-inflammatory and bronchodilatory effects; reduced smooth muscle hypertrophy	High
Anti-IgE (Omalizumab)	IgE blockade; reduced mast cell degranulation and Th2 cytokine release	Moderate (T2-high phenotype)
Anti-IL-5 (Mepolizumab)	Eosinophil depletion; secondary reduction in TGF-β1 production	Moderate (eosinophilic asthma)
Anti-IL-4/13 (Dupilumab)	Dual Th2 cytokine blockade; reduction of goblet cell metaplasia and fibrosis	High (T2-high phenotype)

Strategy / Agent	Mechanism of Action	Evidence Level
Anti-TSLP (Tezepelumab)	Upstream epithelial cytokine blockade; broad anti-inflammatory action	High — all phenotypes
Macrolides (Azithromycin)	MMP inhibition; immunomodulation of neutrophilic airway inflammation	Low–moderate (neutrophilic phenotype)
Anti-TGF-β agents	Direct attenuation of pro-fibrotic signaling and ECM deposition	Experimental (clinical trials ongoing)
Mesenchymal stromal cell (MSC) therapy	Anti-fibrotic paracrine effects; modulation of inflammatory microenvironment	Research stage (preclinical evidence)

4. Discussion

4.1. The Causal Relationship Between Inflammation and Remodeling

The traditional conceptualization of asthma pathogenesis posited a linear causal sequence in which chronic allergic inflammation invariably precedes and drives structural airway remodeling. However, this model has been substantially revised in light of evidence demonstrating that remodeling and inflammation develop concurrently and may, in certain contexts, proceed independently [1]. Basement membrane thickening and subepithelial fibrosis have been documented in children as young as 6 years of age, prior to the emergence of atopic sensitization or clinical asthma symptoms. This temporal uncoupling implies that remodeling may be, in part, a primary response to environmental stimuli — including respiratory pathogens, allergens, and air pollutants — rather than solely a downstream consequence of allergic inflammation.

This paradigm shift carries important therapeutic implications: targeting inflammation alone may be insufficient to halt remodeling, and early structural intervention may be necessary to prevent long-term functional decline. The evidence reviewed here supports a dual-strategy approach that simultaneously addresses inflammatory and structural components of asthma from the earliest stages of disease.

4.2. Clinical Consequences and the Case for Early Intervention

The progressive, irreversible nature of established airway remodeling underscores the critical importance of early therapeutic intervention. Once significant smooth muscle hypertrophy, subepithelial fibrosis, and vascular remodeling have occurred, currently available biologic agents can only arrest further progression rather than reverse pre-existing structural changes. This therapeutic ceiling emphasizes that prevention — rather than reversal — is the primary achievable goal, reinforcing the need for proactive identification and treatment of at-risk patients.

The relationship between remodeling severity and clinical outcomes is well-established: patients with greater degrees of subepithelial fibrosis and smooth muscle mass demonstrate accelerated FEV_1 decline, more frequent exacerbations, and greater dependence on systemic corticosteroids. Furthermore, remodeling-associated steroid resistance constitutes a major clinical challenge, as it reduces the efficacy of the most widely used anti-inflammatory agents and contributes to difficult-to-treat asthma.

4.3. Biologic Therapies as Precision Anti-Remodeling Agents

The advent of targeted biologic therapies has transformed the management of severe asthma and opened new avenues for addressing airway remodeling. Tezepelumab, an anti-TSLP monoclonal antibody, is particularly noteworthy for its broad applicability across asthma phenotypes, including those with low eosinophil counts and non-T2

inflammation. Clinical trial data from the PATHWAY and NAVIGATOR studies have demonstrated significant reductions in annualized exacerbation rates and improvements in lung function and quality of life, with emerging data suggesting attenuation of remodeling biomarkers.

Dupilumab, by simultaneously blocking IL-4 and IL-13 signaling, addresses two of the most potent drivers of goblet cell metaplasia, basement membrane thickening, and fibroblast activation. Anti-IL-5 therapies, particularly mepolizumab and benralizumab, reduce eosinophil-derived TGF-β1 and other fibrogenic mediators, with evidence of histological improvements in airway biopsy specimens following sustained treatment.

4.4. Emerging Therapies and Future Research Directions

Several promising therapeutic targets are currently under investigation for their anti-remodeling potential. Direct anti-TGF-β strategies — including anti-TGF-β1 monoclonal antibodies and small molecule inhibitors of TGF-β receptor signaling — have demonstrated efficacy in experimental models of asthmatic remodeling, though clinical translation remains at an early stage. Anti-fibrotic agents established in other fibrotic lung diseases (pirfenidone, nintedanib) are being explored for potential applicability in severe asthmatic remodeling.

Mesenchymal stromal cell (MSC) therapy represents a conceptually distinct approach, leveraging the anti-fibrotic and immunomodulatory paracrine effects of MSCs to create a local microenvironment that disfavors remodeling. Novel molecular targets, including the Wnt/β-catenin and YAP/TAZ signaling pathways — which regulate fibroblast activation and ECM production — are being explored in preclinical models.

Future research should prioritize the development and validation of accessible, non-invasive remodeling biomarkers. Serum periostin, MMP-9, and TGF-β1 levels have demonstrated preliminary utility as surrogates of remodeling activity, but require prospective validation in large, phenotypically well-characterized cohorts. Pharmacogenomic approaches targeting ADAM33 and TGFB1 polymorphisms associated with accelerated remodeling may ultimately enable individualized prevention strategies.

4.5. Clinical Recommendations Based on GINA 2024

Based on the evidence synthesized in this review and current GINA 2024 guidance, the following clinical recommendations are proposed for the management of airway remodeling in bronchial asthma. Early initiation of ICS therapy (GINA Grade A recommendation) remains the most effective single strategy for slowing remodeling in mild-to-moderate asthma. In patients with severe, phenotype-defined asthma, biological therapies should be selected based on endotype: anti-IL-5/5R agents (mepolizumab, benralizumab) for the eosinophilic phenotype; anti-IgE therapy (omalizumab) for the allergic phenotype; anti-IL-4/13 therapy (dupilumab) for broad Th2-high disease; and anti-TSLP therapy (tezepelumab) as an option for all phenotypes, including those with inadequate response to other biologics [14]. Macrolide therapy (azithromycin) may be considered in patients with a confirmed neutrophilic phenotype (GINA Grade B recommendation).

5. Conclusion

Airway remodeling constitutes a central and clinically significant mechanism in the pathogenesis of bronchial asthma, encompassing structural changes in the epithelium, basement membrane, airway smooth muscle, pulmonary vasculature, and extracellular matrix. The principal molecular drivers of remodeling — TGF-β1, VEGF, metalloproteinases, and epithelial–mesenchymal transition — act through interconnected signaling networks that are amenable to pharmacological modulation.

Critically, airway remodeling begins early in life, often preceding overt clinical symptoms, and progresses to irreversible airway obstruction if left unaddressed. The prevention and early treatment of remodeling, rather than its reversal, represent the most

attainable therapeutic goals with currently available agents. Inhaled corticosteroids initiated early in the disease course remain the cornerstone of anti-remodeling therapy, while biologic agents targeting specific cytokine axes offer important additional benefits in patients with severe or difficult-to-control asthma.

The emergence of novel therapeutic targets — including anti-TGF-β strategies, MSC therapy, and Wnt/YAP pathway modulators — holds promise for future expansion of the anti-remodeling therapeutic arsenal. The parallel development of validated, non-invasive biomarkers of remodeling activity will be essential for enabling individualized treatment strategies, monitoring therapeutic responses, and ultimately transforming the long-term management of asthma.

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