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The Role of Airway Remodeling in the Pathophysiology and Treatment of Severe Asthma

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Abstract

Asthma is a highly prevalent chronic inflammatory airway disease, affecting more than 358 million individuals globally, and its prevalence is increasing in many countries. Asthma manifests with respiratory symptoms such as cough, wheezing, dyspnea, and chest tightness that vary over time and in intensity and with variable airflow limitation. Airflow obstruction in patients with asthma is due to airway inflammation, Airway Hyperresponsiveness (AHR), and remodeling which lead to bronchoconstriction in response to allergens, respiratory infections, pollutants, and environmental smoke. Severe asthma is characterized by airway remodeling due to thickening and shedding of the airway epithelium, deposition of Extracellular Matrix (ECM) proteins, subepithelial fibrosis, and Airway Smooth Muscle (ASM) cells hyperplasia and hypertrophy. Immune cells, such as T helper type 2 lymphocytes (Th2), Th17 cells, and innate lymphoid group two cells release multiple cytokines, chemokines, and growth factors which orchestrate airway inflammation, AHR, and activation of structural cells, such as fibroblasts, myofibroblasts, and ASM cells. Structural cells are proliferative and highly secretory. Upon activation, they release a myriad of cytokines, chemokines, adhesion molecules, enzymes, and growth factors, which further promote AHR, and remodeling. Fibroblasts, myofibroblasts, and ASM cells produce ECM proteins which lead to thickening of the reticular basement membrane, and subepithelial fibrosis cells. Hyperplasia and hypertrophy of the ASM cells result in increase in ASM mass which aggravates airway narrowing and bronchoconstriction. The airway structural changes result in persistent airflow obstruction, and severe asthma. The standard of care treatment, including most of the biologics do not ameliorate airway remodeling. The therapeutic option for severe asthma associated with airway remodeling is to use biologics which target the IL-4/IL-13 and IL-4Rα immune pathway, alarmin cytokines blockers, or bronchial thermoplasty to remove excessive ASM mass.

Keywords: Severe asthma; Airway smooth muscle; Airway remodeling; Biologics; Bronchial thermoplasty

Introduction

Asthma is a highly prevalent chronic inflammatory airway disease, affecting more than 358 million individuals globally, and its prevalence is rising in many counties. The Global Initiative for Asthma (GINA) defines asthma as a heterogenous disease usually characterized by chronic airway inflammation [1]. It manifests with respiratory symptoms such as cough, wheezing, dyspnoea, and chest tightness that vary over time and in intensity and with variable airflow limitation [1]. The variable airflow limitation in patients with asthma is mainly due to

contraction of the hypertrophic and hypercontractile Airway Smooth Muscle (ASM) cells leading to bronchoconstriction in response to allergens, respiratory infections, pollutants, environmental tobacco smoke, and chemical irritants.

Airway obstruction in asthmatics is also due to thickening of the reticular basement membrane and subepithelial fibrosis; deposition of Extracellular Matrix (ECM) proteins; goblet cells hyperplasia and mucus hypersecretion, angiogenesis, vascular congestion, and mucosal oedema. The complex structural change which occurs in severe asthmatic airways is termed airway remodeling [2,3]. Table 1 lists the pathophysiological mechanisms of airway obstruction in patients with severe asthma.

Table 1: Mechanisms of airway remodeling in patients with severe asthma

Epithelial injury due to allergen proteases, pollutants, and respiratory viral infections
Release of cytokines, chemokines, growth factors, and adhesion molecules
Airway epithelial thickening, and shedding
Epithelial cell apoptosis, and release of "alarmin" cytokines
Submucous glands and goblet cell hyperplasia, and mucus hypersecretion
Activation of myofibroblasts, and fibroblasts
Deposition of extracellular matrix proteins
Reticular basement membrane thickening and subepithelial fibrosis
Mast cell infiltration of airway smooth muscle cells
Airway smooth muscle hyperplasia, and hypertrophy
Neoangiogenesis, and exaggerated vasodilatation
Airway hyper responsiveness
Airway remodeling
Corticosteroid-resistance

Airway smooth muscle cells play a key role in modulating airway caliber in patients with asthma. Airway remodeling in asthmatic airways is characterized by hyperplasia and hypertrophy of ASM cells which contribute to severe airway obstruction. Additionally, ASM cells from patient with asthma are dysfunctional. They display plasticity, and take on the hypercontractile, proliferative, and secretory phenotype upon priming by inflammatory mediators [4-6]. Activated ASM cells release proinflammatory cytokines, chemokines, adhesion molecules, and lay down Extracellular Matrix (ECM) proteins, which amplify the inflammatory responses, and perpetuate airway hyperresponsiveness, and airway remodeling [7-10]. The ASM cells produce chemokines, such as CXCL10 which is a potent chemoattractant for mast cells, and T lymphocytes. CRCL10 *via* its receptor CXCR3 and other chemokines promote migration of mast cells into ASM bundles, here after, activated mast cells release a plethora of granule preformed and newly synthesized mediators, cytokines, chemokines, growth factors, and enzymes [10-12]. The mast cell-derived inflammatory mediators further orchestrate airway inflammation, AHR, and airway remodeling, resulting in severe asthma.

Goblet cells hyperplasia, and mucus hypersecretion is a prominent feature of asthma. Patients with asthma secrete pathological mucus composed of mostly MUC5AC mucin which is tenacious, and sticky to the mucus secreting cells. Excessive mucilaginous mucus leads to airways mucus plugging, and is associated with severe asthma, and fatal asthma [13].

Angiogenesis and expansion of the bronchial vasculature with vasodilated permeable blood vessels accompanies airway remodeling in asthma. It is associated with mucosal edema, and airway inflammation due to leakage of cytokines and chemokines; and diapedesis of inflammatory cells from the dilated blood vessels.

Treatment of severe asthma due to ASM dysfunction and airway remodeling is challenging. The Standard of Care (SoC) treatment, including high-dose Inhaled Corticosteroids (ICS), and most biologics do not ameliorate airway remodeling, especially due to ASM cells hyperplasia and hypertrophy, and subepithelial fibrosis. The therapeutic option for severe asthma associated with severe remodeling is probably to administer biologics which target the IL-4/IL-13 and IL-4Rα immunological pathway, and "alarmin" monoclonal Antibodies (mAb), or bronchial thermoplasty to remove excessive ASM mass [14].

Airway Remodeling in Severe Asthma

Severe asthma is characterized by active airway inflammation, Airway Hyperresponsiveness (AHR), and remodeling. Airway remodeling is a complex pathophysiological process involving structural changes, such as ASM cells hypertrophy and migration, reticular basement membrane thickening and subepithelial fibrosis submucous gland and goblet cells hyperplasia thickening and shedding of the airway epithelium, and epithelial cells apoptosis [15-30]. Airway remodeling is also accompanied by neovascularization, and expansion of the airway vascular bed, vasodilatation, and mucosal oedema [31,32]. All of the above structural changes lead to airway narrowing, excessive bronchoconstriction, and severe, uncontrolled asthma. Table 1 summarizes the pathophysiologic mechanisms of airway remodeling in patients with severe asthma.

Extracellular Matrix Proteins

Airway remodeling involves laying of Extracellular Matrix (ECM) proteins by structural cells, principally fibroblasts, and to a lesser extent myofibroblasts, and ASM cells. The ECM proteins are composed of several proteins and glycoproteins, such as collagens I, II, III, V, and XI; adhesion molecules including fibronectin and tenascin-C; proteoglycans (lumican and biglycan); and glycosaminoglycans [33-37]. The ECM protein is produced mostly by fibroblasts, and to lesser extent by myofibroblasts, and ASM cells [35,37,38-41]. The ECM proteins provide structural and mechanical support of the airways, and provide a conducive milieu for cell adhesion, migration, proliferation, and activation [24]. Nevertheless, the structural changes lead to narrow and stiff airways, and correlate with clinical and functional severity of asthma [21,42,43]. Airway remodeling is seen in early stages of asthma, but correlates with the duration of severe asthma, and is associated with corticosteroid resistance [44-46].

Airway Mucus Secretion in Asthma

Airway remodeling in asthma is accompanied by goblet cells, and submucous glands hypertrophy and hyperplasia, mucus hypersecretion, and abnormal mucus [47]. The epithelial dysfunction in asthma [48,49], leads to impaired mucociliary transport, accumulation of mucus, and mucus plugging of the airways [47,50,51]. Dysfunctional mucociliary escalator is even evident in mild asthma, and decreases further during acute exacerbations [52-54]. Failure to clear mucus expectoration has been associated with death due to asphyxiation from intraluminal airway obstruction due to mucus plugs [55-57].

Humans secrete five types of gel-forming mucins (MUC2, MUC6, MUC19, MUC5AC, and MUC5B [25], but the mucins secreted in large quantities, and responsible for the viscoelastic properties of mucus depend on MUC5AC, and MUC5B [50]. Genome World-Wide Studies (GWAS) have revealed that polymorphism of 11p15 MUC5B, and MUC5AC locus is associated with airway hyper responsiveness, and asthma [58]. Altered expression of the pathologic mucin MUC5AC potentially contributes to mucus plugging and airway obstruction [59]. Furthermore, many patients with asthma have increased MUC5AC mRNA levels, but decreased MUC5B levels, thus the composition of mucus contributes to the viscoelasticity, and mucilaginous nature of mucus [60].

One of the characteristics mucus secreted by asthmatic patients is the change in the relative proportion of MUC5AC and MUC5B, and the organization of airway mucus which is likely to affect its properties, and contribute to airways mucus plugging [47]. Asthmatic airways produce more MUC5AC than MUC5B. It appears that MUC5AC is the mucin which is responsible for the mucilaginous mucus which is difficult to clear, because of the tethering of MUC5AC-containing mucus domains to mucus-producing cells in the epithelium [61]. Accumulation of pertinacious mucus causes diffuse airway obstruction, and is an important feature of severe, near fatal, and fatal asthma [55,56,60].

Interleukin-13 (IL-13 is a Th2 cytokine, produced by Type 2 helper (Th2) cells, and Innate Lymphoid Group 2 Cells (ILC2). It plays a key role in the production and secretion of excessive mucus from goblet cells, and submucous glands in patients with asthma. IL-13 has been shown to induce significant increases in the expression of MUC5AC in human epithelial cells in vitro, and in murine asthma model

[62,63-66]. Additionally, IL-13 dramatically impairs mucociliary transport of mucus containing MUC5AS mucus domain, and is responsible for other immunopathological features of severe eosinophilic asthma, such as subepithelial fibrosis [67]. Theoretically, targeting IL-13 and its sub-receptor IL-4Rα is a potential therapeutic option to ameliorate mucus hypersecretion and plugging.

Epidermal Growth Factor Receptor (EGFR) signaling is required for mucus production in vitro and vivo [65,68-70]. It induces MUC5AC expression [69], and EGFR levels are significantly increased in patients with asthma, correlating with the severity of the disease [70].

Pathological mucus and dysfunctional mucus escalator can lead to mucus plugging, and airflow obstruction in severely bronchoconstrictor airways. Currently, there are no effective mucolytic or mucoregulator drugs for the treatment of airway obstruction due to sticky mucus in patients with asthma [71,72]. The role of biologics targeted against Th2 cytokines has not yet been established as mucolytic or mucoregulator agents. MUC5AC targeted therapies might offer the opportunity to ameliorate mucus plugging and airway obstruction in patients with asthma [47].

Airway Smooth Muscle Hyperplasia and Hypertrophy

Airway smooth muscle cell hyperplasia and hypertrophy is a cardinal feature of airway remodeling in asthma. It is a major determinant of bronchoconstriction in response to allergen, respiratory viral infections, pollutants, and environmental tobacco smoke. Increase in ASM mas occurs early in the development of asthma [73], and is present even in school children with asthma [74-76], and in patients with mild-to-moderate asthma [77]. The increase in ASM mass occurs in most of the phenotypes of asthma, including neutrophilic asthma, and paucigranulocytic asthma [14]. The degree of increase in ASM hyperplasia, and ASM cell structural and phenotypic change correlate with the severity of asthma [78-82], and the duration of severe asthma in older patients [83]. Furthermore, severe ASM cell hyperplasia and hypertrophy has been associated with status asthmaticus, and fatal asthma [25,83-87].

Airway smooth muscle cell hypertrophy and hyperplasia is mostly due to the profibrotic and proliferative effects of growth factors, such as TGF-β [88-90], and due to infiltration of the muscle bundles by myofibroblasts, and neighboring ASM cells migration from the submucosa compartment, or hematopoietic progenitor cells from the circulation [91-94]. TGF-β plays an important role in the increase in ASM mass and hypercontractility. It is responsible for activation of the Reactive Oxygen Species (ROS)-generating enzyme (NADPH oxidase 4 (Nox 4) that induces myofibroblasts differentiation [95], and is implicated in ASM cell proliferation, and hyper contractility [96,97]. The mechanisms by which myofibroblast transform to ASM cell is speculative but probably represent part of the spectrum of plasticity of mesenchymal cells through transition from fibroblast to myofibroblast, and finally into ASMS cells [98]. Wicks, et al. [99] have reported that TGF-β2 may enhance upregulation of ASM cell from asthmatic myofibroblasts.

Another possible source of increase in the ASM cell numbers would be from differentiation of tissue resident Mesenchymal Stem Cells (MSCs); or from Epithelial-Mesenchymal Transition (EMT) of epithelial cells [100]. Additionally, pericytes transformation and migration may also contribute to the increase in ASM mass [98]. However, in order to transfer to functional ASM cells or myofibroblasts, all these cells require loss of their non-mesenchymal markers and acquire mesenchymal characteristics, such increase in mesenchymal proteins, including α-smooth muscle actin (α-ASMA), N-cadherin, and vimentin expression [98]. Not with standing, fibroblasts, myofibroblasts, and ASM cells from asthmatic patients display tremendous plasticity.

Migration of ASM cells from the submucosa and from other ASM bundles, may partly explain the increase in ASM mass in patients with asthma. Multiple lipid mediators, such as leukotrienes (LTE4, and LTB4), and prostaglandins (PGD2) [92] have been show to stimulate ASM cell migration into muscle bundles. Similarly multiple cytokines, such as IL-8, IL-13, IL-17, IL-25, IL-33, TSLP, and TNF-α [101-104], chemokines (CXCL2, CXCL3, CXCL8, CCL19, eatoxins,

and RANTES) [101,105-107], and growth factor, including platelet-derived growth factor, TGF-β [92,93] stimulate ASM cells migration. Chemokines, cytokines, and growth factors synergize with other chemo attractants, such as CXCL8 (IL-8), eotaxins, and RANTES in order to promote ASM cells migration. Notably, activated ASM cells in vitro are capable of releasing cytokines, such as IL-5, IL-6, and IL-8, and chemokines, including CCL5, CXCL8, and eotaxins [108-109], which may act in a positive feedback autocrine fashion to enhance ASM cells migration and contraction [106,108,110]. Inflammatory mediators which promote ASM cells proliferation and migration are shown in Table 2.

Table 2: Airway smooth muscle cells proliferative and migratory mediators in asthma.

Cytokines	Chemokines
Interleukin (IL) IL-1β	CCL2 (MCP-1, 3, 5)
IL-2	CCL5 (RANTES)
Il-5	CCL11 (eotaxin)
CCL10	CXCL10
IL-6	CX_3CL1 (Fraktalkine)
IL-8	CXCL8 (IL-8)
IL-10	Growth factors
IL-11	TGF-β1
IL-12	bFGF-1
TSLP	PDGF-BB
Lipid mediators	
Leukotriene D4 (LTD4)	VEGF
Thromboxane A2	SCF
Enzymes	TNF-α
Tryptase	CTGF
β-Hexasaminidase	IGF-1, IGF-2
Lysosomal hydroxylase	
MMP-9, MMP-12	Neuropeptide transmitters
Thrombin	Bradykinin
Small-molecule transmitters	Angiotensin II
Histamine	Endothelin-1
Serotonin	

Angiogenesis in Asthma

Angiogenesis is a prominent feature of airway remodeling in patients with asthma. It is a complex process of formation of new blood vessels, and enlargement and expansion of the existing vessels, induced by angiogenic factors and counteracted by angiostatin factors [51,111]. The sub-epithelial submucosa of the airways in asthmatic patients is characterized by an increase in the vascular density [112-115]. The total number of blood vessels, and vascular area is increased about two- to three-folds compared to healthy control subjects [116,117]. The blood vessels are dilated and more permeable leading to airway mucosal oedema [118], and inflammation due to leakage of pro-inflammatory mediators, and diapedesis of inflammatory cells through the capillary pores [119]. The increase in airway vasculature has been shown to correlate with airflow obstruction [112,120,121], and airway hyper responsiveness [122].

Angiogenesis is a complex tightly regulated process mediated by a balance between multiple proangiogenic factors and antiangiogenic cytokine, chemokines, growth factors, and enzymes [31,32,123-126]. The proangiogenic factors include growth factors, such as Vascular Endothelial Growth Factor (VEGF), Basic Fibroblast Growth Factor (bFGF), Epidermal Growth Factor (EGF), Insulin-Like Growth Factor (IGF-1), Amphiregulin, Angiopoitein-1, and 2 (Ang-1, Ang-2), and angiogenin [124]. The cytokines involved in angiogenesis include IL-6, IL-8 [122], and IL-25 [126]. The most potent profibrotic growth factor is VEGF, which has six splice-variants [127]. VEGF promotes enlargement of existing vascular structures from existing ones, by causing endothelial cell proliferation and migration [127,128]. It also stimulates formation of new capillaries, and blood vessels [127,128]. Additionally, VEGF significantly increases the permeability of blood vessel, almost about 50,000 times more potent than histamine [129]. VEGF concentration in sputum and in lung tissue is elevated, and correlates with the severity of asthma [130].

Co-expression of VEGF with Ang-1, and Ang-2 has been shown to induce proliferation and migration of endothelial cells, and sprouting of new capillaries, and enlargement of existing capillaries [130]. Ang-1 stimulates migration of pericytes and ASM cells and therefore stabilizes the new

capillary tubes during angiogenesis [131]. Angiogenesis is further enhanced by secretion of proangiogenic factors by activated ASM cells, such as VEGF, angiogenin, and angiopoietin-1 [111,132], thus perpetuating neovascularization.

Airway angiogenesis is counterchecked by multiple antiangiogenic factors, such as arrestin tumstatin, canstatin, endostatin, and arrestin [124]. However, in patients with asthma, the proangiogenesis mechanisms override antiangiogenic factors in the vascular remodeling process. Other asthma-associated stimuli, such as polymorphism in the ADAM33 gene [133], environmental tobacco smoke [134], and rhinovirus infection also promote angiogenesis [134].

Neovascularization and vasodilatation lead to increased vascular permeability, and mucosal oedema which narrows the airway lumen. Furthermore, transmigration of inflammatory cells, and leakage of mediators result in more airway inflammation, AHR, and airway remodeling. Increase in the submucosal microvascular plexus, vasodilatation, and mucosal oedema correlate with asthma severity [112,116,123], and has been associated with fatal asthma [111, 135].

Treatment of Airway Remodeling in Severe Asthma

Treatment of airway remodeling in patients with severe asthma due to airway remodeling is challenging. Currently, there is no specific pharmacological treatment for airway remodeling, including biologics, with the potential exception of IL-4/IL-13 targeted therapies, such as dupilumab [136], and probably anti-TSLP, namely tezepelumab [137]. Dupilumab (Dupixent®) is a fully humanized IgG4 monoclonal antibody to the IL-4Rα, which mediates signaling to both IL-4 and IL-13, and blocks their immunological pathways and suppressing airway eosinophilic inflammation [138]. Dupilumab is the only biologic which has been approved for the treatment of eosinophilic asthma, allergic rhinitis, chronic rhinosinusitis and nasal polyposis, and atopic dermatitis [139,140], and eosinophilic oesophagitis [141], and is highly effective in treating these conditions. Patients with the above co-morbidities should be considered for the so called “magic bullet’ biologic.

Tezepelumab is a first-in-class fully human IgGʎ2 monoclonal Antibody (mAb) that binds to TSLP, and prevents it to interact with its receptor TSLPR, thus inhibiting multiple downstream immunopathologic pathways, and production of cytokines, and chemokines [142]. Several clinical trials have shown that tezepelumab can reduced both the early and late asthmatic responses due to allergen challenges, and significantly reduce the AAER, and improve lung function and HLQoL in patients with eosinophilic asthma and non-eosinophilic asthma [143-146]. Furthermore, tezepelumab had been demonstrated to reduce eosinophil counts, and eosinophilic biomarkers of airway inflammation, such as serum IgE, and FeNO [144-146]. Due its pathophysiological roles in the pathophysiology of eosinophilic, and neutrophilic asthma, and airway remodeling, tezepelumab might prevent or ameliorate airway remodeling [147]. It is effective as add-on treatment of different phenotypes of asthma irrespective of the baseline biomarkers of airway inflammation.

Brochial Thermoplasty (BT) is a bronchoscopic therapeutic intervention which uses a special AlairTM catheter (Bronchial Thermoplasty System, Natick, MA, USA) to remove excessive ASM mass, ECM proteins, subepithelial fibrosis, sub mucus glands, and nerve endings [148,149]. The criteria for selection of patients for BT, and the procedure are discussed in great detail elsewhere [150-154]. Bronchial thermoplasty has been shown to be relatively safe, and result in significant improvement in asthma control, and HRQoL, and reduction in annual exacerbation rates compared with sham procedure [155]. BT was approved by the U.S. Food and Drug Administration (FDA) in 2010 [156], and is approved in several European Community countries, UK, Australia, Brazil, Canada, Japan, and South Korea for the treatment of severe persistent asthma in patients 18 years and older, that is not controlled by high-dose ICS, and LABA.

Conclusion

Airway remodeling is a complex structural change in the airways due to deposition of ECM proteins, thickening of

the reticular basement membrane, subepithelial fibrosis, goblet cell hyperplasia and mucus hypersecretion, and ASM hyperplasia and hypertrophy. Currently, there are no specific pharmacological agents, and biologics for the treatment of the increase in ASM mass, and airway remodeling in patients with severe asthma. Biologics targeting IL-4/IL-13 and IL-4Rα immunological pathway, such as dupilummab, and anti-TSLP, including tezepelumab might ameliorate airway remodeling. Bronchial thermoplasty which removes excessive ASM mass, matrix proteins, and subepithelial fibrosis is a treatment option for highly selected patients in experienced centers.

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